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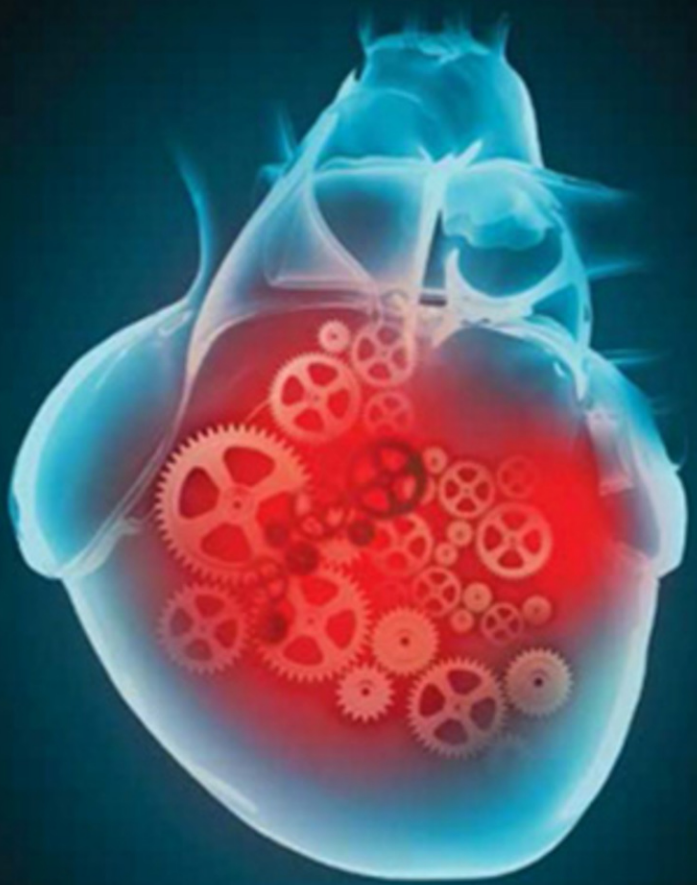
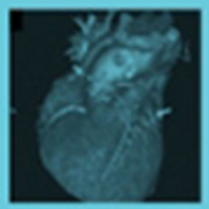
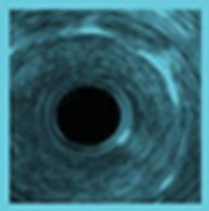
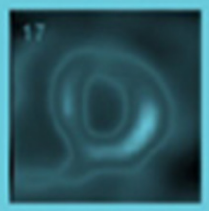
TEXTBOOK OF Interventional Cardiology

ERIC J. TOPOL | PAUL S. TEIRSTEIN









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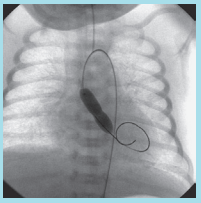
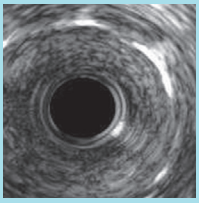
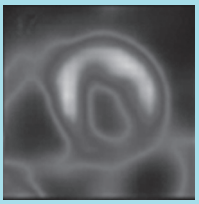
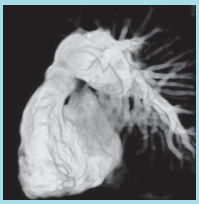
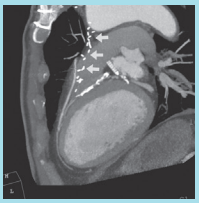

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To our many fellows who, over the years, have taught and inspired us so much.

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Preface

The seventh edition of *Textbook of Interventional Cardiology* has been more extensively updated than any previous edition. We have tried to fully capture the excitement and relentless maturation of the field of interventional cardiology. New chapters have been added to address radiation safety, interventions for heart failure, and (for many patients) the lack of need for hospitalization after interventions. Over the years, coronary intervention became increasingly predictable and, in many ways, routine, with the progressive maturation of stents and leaps forward in our adjunct pharmacologic therapies. In some ways, the field of interventional cardiology lost a bit of its pioneering spark that had so characterized this discipline from its inception in the 1980s. In those heady times, performing balloon angioplasty in the coronary artery was unpredictable. The predictability provided by stents was replaced with the upredictability of stent thrombosis. Interventional cardiologists and scientists had to not only rise to the challenge for each individual patient but also discover the vital innovations that would perpetuate the prominence and importance of the specialty.

Today, the challenges continue, but they have morphed considerably. The profile of patients who undergo coronary intervention has dramatically increased in complexity to include patients with advanced age and those with left main stem lesions, chronic occlusions, and what would formerly have been considered prohibitive complexity. Whatever happened to patients with Type A lesions? How can we break the maximal SYNTAX score barrier for percutaneous coronary intervention? At the same time, the crisis in health care economics has placed an undue burden on interventional cardiologists with respect to time, constraints in equipment selection, and fulfilling the responsibility of 24/7 coverage for such emergencies as acute myocardial infarction. There is also the incremental pressure from scorecarding initiatives and challenges to the appropriateness or overuse of procedures. But hopefully, all of these challenges are outweighed by the immense gratification of helping a symptomatic patient with limitations in quality of life get back to his or her baseline. Nowhere in medicine is this feeling more prevalent than in the transformative field of transcatheter aortic valve replacement.

This book is intended to serve as a resource for the interventional cardiology community, which not only includes practicing cardiologists but also the team involved in procedures, referring physicians, and those training or who have aspiration to train in this awe-inspiring field. We have changed authors for many chapters to provide a sense of newness and a fresh perspective, and in every chapter, we have sought the authors who are widely regarded as the true experts in the field. Going forward, we fully recognize that there needs to be increased cooperativity with cardiac surgeons—the rising popularity of hybrid and collaborative valve procedures that capitalize on the best parts of percutaneous and surgical approaches is clearly indicative of that collaboration.

We want to express our genuine and deep appreciation to the authors from all over the world who have graciously contributed to this new edition. They represent a remarkable brain trust from whom we have learned so much in the review of their input. We thank Taylor Ball and Dolores Meloni, both at Elsevier, for their first rate, professional support of this endeavor. And we are especially grateful to the interventional community of readers of this book who have supported it as the primary reference textbook source for nearly 30 years. That represents a large sense of responsibility for us to maintain, and we hope to have lived up to that, and perhaps exceeded expectations with the seventh edition.

Eric J. Topol, MD
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La Jolla, California, 2015

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Individualized Assessment for Percutaneous or Surgical Revascularization

1

VASIM FAROOQ | SCOT GARG | PATRICK W. SERRUYS

KEY POINTS

- Changes in the demographics of patients who present in need of revascularization, advances in percutaneous and surgical revascularization techniques, and results from contemporary studies of percutaneous versus surgical revascularization have made it essential that patients be assessed as individuals prior to selection of a treatment strategy.
- Risk stratification plays an important role in the assessment of patients undergoing revascularization.
- Clinical tools used to assist the heart team in risk stratifying patients and deciding the most appropriate revascularization modality can be broadly divided into assessments based on clinical comorbidities, coronary anatomy, or a combination of the two.
- Clinical tools based on the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial have evolved from purely anatomic factors (anatomic SYNTAX score) to anatomic factors augmented by clinical variables (culminating in the development of the SYNTAX Score II) and tools to assess a level of reasonable incomplete revascularization that would not have an adverse effect on long-term morbidity and mortality (residual SYNTAX score). Validation of many of these newly developed clinical tools is ongoing.
- Clinical and anatomic factors have an impact on short- and long-term morbidity and mortality following surgical or percutaneous revascularization and must be considered by the heart team in open dialogue with the patient during the decision-making process.

Revascularization of patients with coronary artery disease (CAD) has progressed exponentially since Andreas Grüntzig[1] performed the first balloon angioplasty in 1977. These developments, which have been fueled by new technology, have blurred the boundary between what was once considered exclusively surgical disease and what can be treated percutaneously. Consequently, there is a greater need than ever to tailor revascularization appropriately, taking into consideration a patient's comorbidities, coronary anatomy, personal preferences, and individual perception of risk. This chapter will explore the increasing requirement for a more individualized assessment of patients undergoing revascularization, and it will review the clinical tools currently available to assist in this decision-making process.

THE NEED FOR INDIVIDUALIZED PATIENT ASSESSMENT

A number of confounding factors have made it imperative that patients are assessed as individuals prior to the selection of revascularization strategy.

Patient Comorbidities

The demographics of patients presenting to tertiary care services in need of revascularization are constantly evolving. This has been largely the consequence of increased longevity of the general population, a lower threshold to investigate patients who present with symptoms suggestive of obstructive CAD, and increased resources that have made revascularization via by percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) more accessible. Together with increased age, patients in need of revascularization are now more likely to have comorbidities such as diabetes, hypertension, and hyerlipidemia.[2,3] These factors are all implicated in accelerating the progression of CAD, and consequently patients are more likely to present with more extensive CAD. The Arterial Revascularization Therapies Studies (ARTS) parts I and II were separated by a period of 5 years, and despite both studies having the same inclusion criteria, patients in ARTS-II had a significantly greater incidence of risk factors and overall increased disease complexity (Table 1-1).[4]

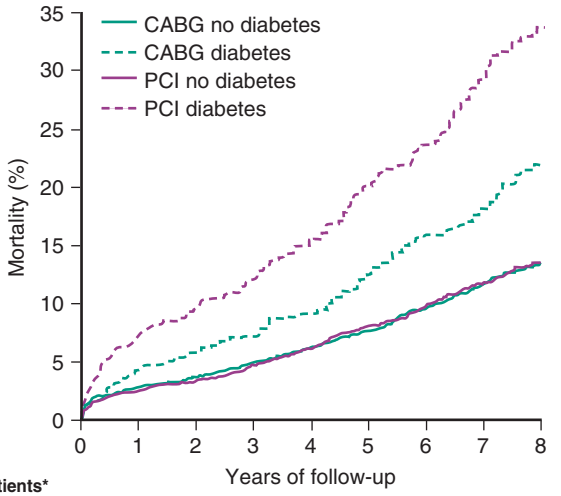
Patient comorbidities must be taken into consideration when assessing patients for revascularization because they have the potential to significantly influence patient outcomes; moreover, they may have a different impact depending on the underlying revascularization strategy selected. Notably, LeGrand and colleagues[5] demonstrated that patient age was a significant independent predictor of major adverse cardiovascular and cerebrovascular events (MACCEs) in patients enrolled in the ARTS-I and II studies who were treated with CABG but not PCI. More recently, in the randomized all-comers SYNTAX trial, increasing age was shown to favor PCI over CABG when adjustments were made for other anatomic and clinical factors.[6-8] In addition, other anatomic and clinical factors were shown to have an impact on long-term mortality, and thereby decision making between CABG and PCI (SYNTAX Score II[7,8]), and this topic is discussed later under "SYNTAX-Based Clinical Tools."

In a collaborative patient-level analysis of 10 randomized trials of patients with multivessel disease (MVD) treated with PCI using bare-metal stenting and CABG, Hlatky and coworkers[9] demonstrated comparable rates of 5-year mortality between both treatment groups in patients without diabetes. Notably, when patients with diabetes were viewed as a whole, mortality was significantly higher in those treated with PCI, even after multivariate adjustment (Fig. 1-1). In the Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial,[10,11] it was shown that in patients with diabetes and advanced CAD, CABG was superior to PCI in that it significantly reduced rates of death and myocardial infarction (MI) but at the expense of a higher rate of stroke (Fig. 1-2).[11] In addition, using the American College of Cardiology Foundation (ACCF) National Cardiovascular Data Registry (NCDR) and the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database, Weintraub and colleagues[12] found that subjects who had elective intervention for MVD had a long-term survival advantage

TABLE 1-1 The Changing Baseline Demographics of Patients Enrolled in Drug-Eluting Stent Trials

	ALL-COMERS STUDIES					
	SIRTAX[18]	LEADERS[19]	RESOLUTE[21]	ARTS-I[22]	ARTS-II[149]	SYNTAX[13]
Years of Enrollment	2003-2004	2006-2007	2008	1997-1998	2003	2005-2007
Stent Type	DES	DES	DES	BMS	DES	DES
Demographics						
Age, years (mean ± SD)	62 ± 11	65 ± 11	64.4 ± 10.9	61 ± 10	63 ± 10	65 ± 10
Diabetes, %	20	24	23.5	19	26	26
Hypertension, %	61	73	71.1	45	67	69
Hypercholesterolemia, %	59	67	63.9	58	74	78
Previous myocardial infarction, %	29	33	28.9	44	34	32
Left ventricular function, % (mean ± SD)	57 ± 12	56 ± 12		61 ± 12	60 ± 12	59 ± 13
Lesion Characteristics (Per Patient)						
Multivessel disease, %	59	23	58.4	96	100	92
Bifurcation lesions, %	8	22	16.9	35	34	72
Total occlusions, %	19	12	16.3	3	17	24
SYNTAX score (mean ± SD)	12 ± 7	14 ± 9	15 ± 9	–	21 ± 10	28 ± 12
Mean number of diseased lesions	1.4	1.5	1.5	2.8	3.6	3.6*
Procedural Characteristics (Per Patient)						
Mean number of stents	1.2 ± 0.5	1.3 ± 0.7†	11.9 ± 7.5	2.8 ± 1.3	3.7 ± 1.5	4.6 ± 2.3
Total stent length, mm (mean ± SD)	25.9 ± 15.5	24.7 ± 15.5†	34.4 ± 24.5	47.6 ± 21.7	72.5 ± 32.1	86.1 ± 47.9

*Treated lesions.
†Per lesion.
BMS, Bare-metal stent; *DES,* drug-eluting stent; *SD,* standard deviation; SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.



Number of patients*

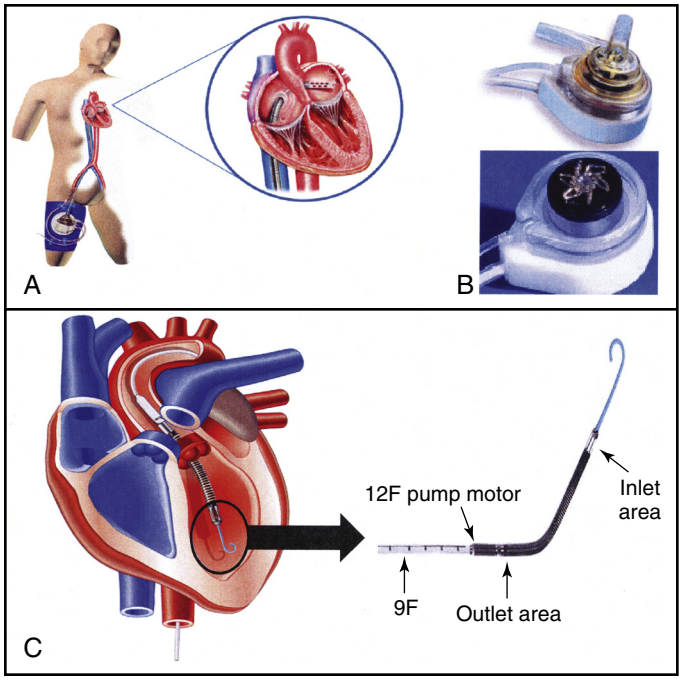
CABG no diabetes	3263	3169	3089	2877	2677	2267	1592	1380	1274
CABG diabetes	615	587	575	532	498	421	257	225	200
PCI no diabetes	3298	3217	3148	2918	2725	2281	1608	1393	1288
PCI diabetes	618	574	555	508	475	373	218	179	160

FIGURE 1-1 Cumulative survival curve of long-term mortality stratified according to diabetic status among patients with multivessel disease randomized to treatment with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The importance of diabetic status on outcomes are highlighted not only by the higher mortality among patients with diabetes compared with nondiabetics but also by the greater impact diabetic status had on patients treated with PCI compared with CABG. (From Hlatky MA, Boothroyd DB, Bravata DM, et al: Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 373[9670]: 1190-1197, 2009.)

among patients who underwent CABG compared with PCI (Fig. 1-3). Findings have been corroborated in the randomized, all-comers SYNTAX trial[13-16] as discussed later. Consequently, an urgent need exists for clinical tools that account for both anatomic and clinical factors and comorbidity to assist the heart team in decision making in regard to the most appropriate revascularization modality in patients with complex CAD.

TECHNOLOGICAL ADVANCES

The introduction in 2002 of drug-eluting stents (DESs) revolutionized the practice of interventional cardiology and was driven primarily through the dramatic reduction in rates of repeat revascularization.[17] The favorable results observed with DES use promptly resulted in an expansion of the indications for PCI, such that bifurcation lesions, chronic total occlusions, and MVD were no longer in the exclusive domain of surgical revascularization, and these were increasingly treated with PCI. Evidence of this expansion can be seen in the changing baseline lesion characteristics of patients enrolled in all-comers PCI trials such as the Sirolimus-Eluting and Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) trial,[18] the Limus Eluted From a Durable Versus Erodable Stent Coating Study (LEADERS),[19,20] the Clinical Evaluation of the Resolute Zotarolimus-Eluting Coronary Stent System in the Treatment of De Novo Lesions in Native Coronary Arteries (RESOLUTE),[21] and in studies of complex triple-vessel disease (3VD) and/or left main (LM) CAD, such as ARTS-I,[22] ARTS-II,[20] and the SYNTAX trial (see Table 1-1).[13-16] Further evidence in support of this change comes from assessments of real-world clinical practice, which indicate that approximately one third of patients with complex CAD are now treated with PCI.[23] This practice has been coupled with the expanding use of PCI, driven largely through advances in PCI technology, with more deliverable newer-generation drug-eluting stents, lower-profile balloons, new guidewires, adjunctive devices to aid stent delivery, crossing and reentry systems to aid total occlusion revascularization, functional assessment of lesions, intravascular ultrasound



E-FIGURE 1-1 Devices that are increasingly available to provide assistance during high-risk percutaneous coronary intervention (PCI) include percutaneous extracorporeal circulatory support devices such as **(A, B)** the TandemHeart and **(C)** the Impella device. **(A)** The TandemHeart removes oxygenated blood from the left atrium and returns this blood into the peripheral arterial circulation; with the **(B)** aid of a centrifugal pump. **C,** The Impella left ventricular assist device is a miniaturized rotary blood pump that is placed retrograde across the aortic valve, and it aspirates (inlet area) up to 2.5 L/min of blood from the left ventricular cavity and subsequently expels this blood (outlet area) into the ascending aorta. (From Valgimigli M, Steendijk P, Serruys PW, et al: Use of Impella Recover LP 2.5 left ventricular assist device during high-risk percutaneous coronary interventions; clinical, haemodynamic and biochemical findings. *EuroIntervention* 2[1]:91-100, 2006; and Vranckx P, Meliga E, De Jaegere PP, et al: The TandemHeart, percutaneous transseptal left ventricular assist device: a safeguard in high-risk percutaneous coronary interventions. The six-year Rotterdam experience. *EuroIntervention* 4:331, 2008.)

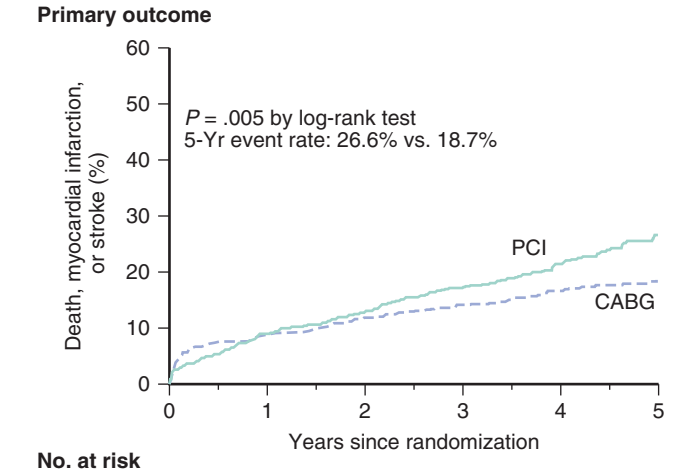


FIGURE 1-2 Kaplan-Meier Estimates of the Composite Primary Outcome of death, myocardial infarction (MI), or stroke **(A)** and death from any cause **(B)** truncated at 5 years after randomization in the FREEDOM trial. In FREEDOM, patients with diabetes and multivessel coronary artery disease were assigned to undergo either percutaneous coronary intervention (PCI) with first-generation drug-eluting stents or coronary artery bypass grafting (CABG). Patients were followed for a minimum of 2 years (median among survivors, 3.8 years), and CABG was shown to be superior to PCI with first-generation drug-eluting stents with significant reduced rates of death (10.9% vs. 16.3%, $P = .049$) and MI (6.0% vs. 13.9%, $P < .001$) but a higher rate of stroke (5.2% vs. 2.4%, $P = .03$). (From FREEDOM Trial Investigators: Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 367[25]:2375-2384, 2012.)

(IVUS) guidance to ensure adequate stent expansion, dedicated specialists for specific anatomic subsets, introduction of new adjunctive pharmacologic therapies, and the increasing availability of percutaneous extracorporeal circulatory support (E-Fig. 1-1).[24-30] From a technical perspective, a large subset of coronary lesions can now be addressed with PCI; however, it is important to emphasize that the percutaneous approach to revascularization requires individual patient selection to ensure that it is appropriate.

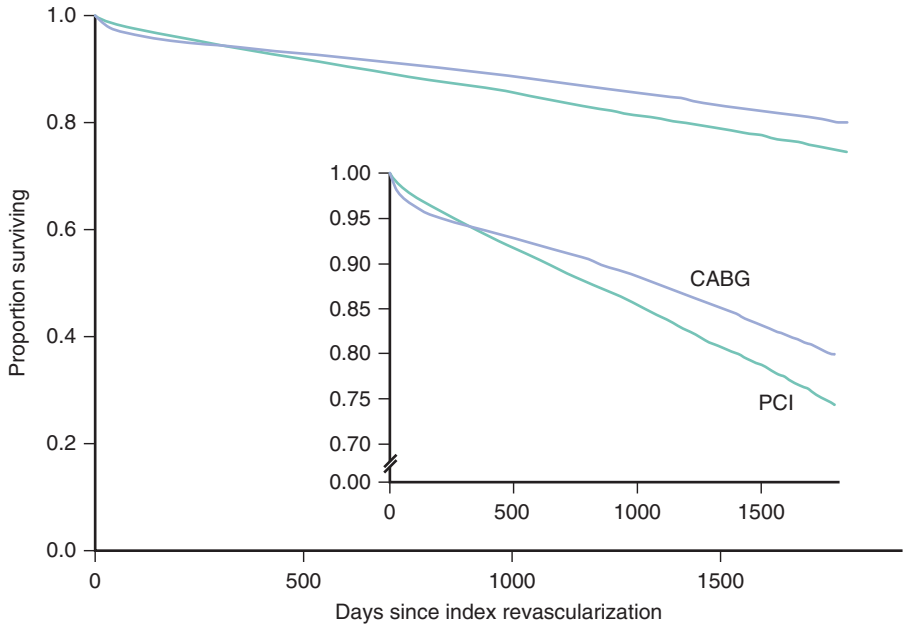
HISTORIC (PRE-SYNTAX) CLINICAL TRIAL RESULTS

Historically, and prior to the publication of the SYNTAX trial,[13-16] randomized trials to compare CABG and PCI centered on two major patient groups: either isolated proximal left anterior descending artery (LAD) lesions or complex CAD (3VD and/or LM disease). Although results of these studies suggest no differences were found in the hard clinical outcomes of death and MI between patients treated with PCI or CABG at short- and long-term follow-up (Table 1-2),[9,31-35] there was profound selection bias in enrollment of patients prior to randomization. Specifically between 2% to 12% of screened patients were randomized in most trials (Table 1-3), with patients with lesser comorbidities, such as impaired left ventricular function, or coronary anatomy (predominantly single- or double-vessel disease) often "cherry-picked" prior to randomization.[36-38] Consequently, interpreting and extrapolating these results to routine clinical practice has been difficult.

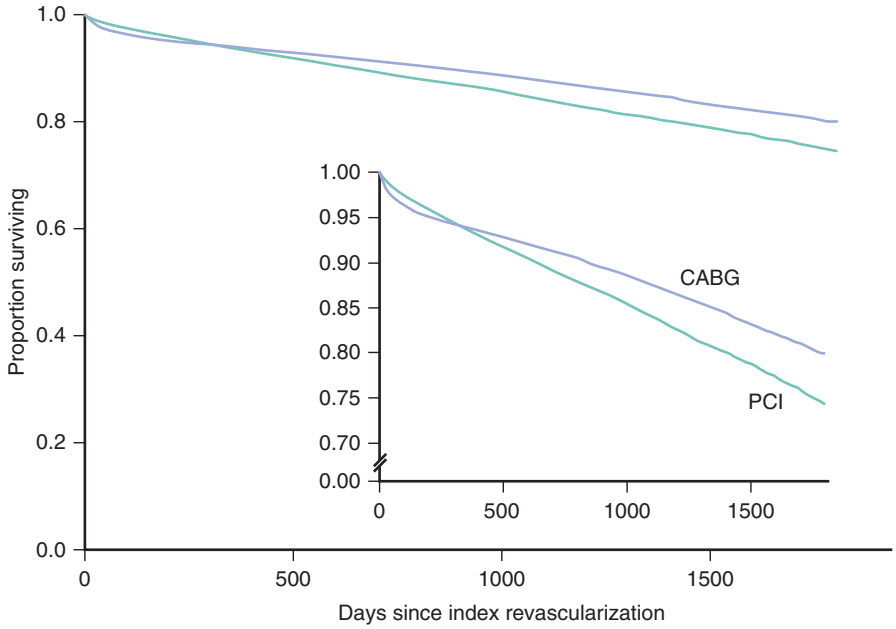
SYNTAX Trial

The landmark SYNTAX trial[13-16] represents the largest (and only) assessment of revascularization with PCI or CABG in all-comers with complex CAD. SYNTAX aimed to supply evidence to support the somewhat established but not evidence-based practice of performing PCI in patients with complex CAD,[23] and it also sought to identify which patients should only be treated with CABG. Through an all-comers design, SYNTAX addressed the limitations of the earlier CABG versus PCI trials, which were plagued by profound selection bias as previously discussed (see Table 1-3),[37,38] and in doing so it was anticipated that the results would be more relevant to contemporary routine clinical practice. Specifically:

- To ensure results were applicable to routine practice, the study was designed as an all-comers trial such that there were no specific inclusion criteria other than the need to have revascularization of de novo 3VD or unprotected left main CAD (in isolation or with CAD). Exclusion criteria were limited to prior revascularization, ongoing MI, and patients requiring concomitant cardiac surgery.[16] In contrast to the earlier studies, 70.9% of eligible patients were enrolled.
- The previously indicated problem of reporting outcomes from all patients with complex CAD together, irrespective of disease severity, was addressed in the SYNTAX trial through the utilization of the anatomic SYNTAX score (http://www.syntaxscore.com; Fig. 1-4),[13,39-43] which enabled CAD complexity to be objectively and prospectively quantified.
- To ensure assessment of patients on an individual level, all patients eligible for enrollment were discussed by the heart team.[44] An interventional cardiologist and cardiac surgeon carried out a careful and comprehensive review of the patient in terms of their anginal status, comorbidities, and coronary anatomy using the respective Braunwald score, European System for Cardiac Operative Risk Evaluation (EuroSCORE), and SYNTAX score (discussed under "SYNTAX-Based Clinical Tools"). The consensus reached from this meeting was subsequently used to allocate the patient into one of the three arms of the trial. In total 3075 patients were enrolled into one of the following:
  1. Randomized group ($n = 1800$ [58.5%]; 897 CABG, 903 PCI): These patients had CAD and were equally suitable for revascularization with PCI or CABG. The mean SYNTAX score for this group was 26.1 and 28.8 in patients treated with CABG and PCI, respectively.
  2. Nested CABG registry ($n = 1077$ [35.0%]): These patients had CAD that was considered unsuitable for PCI, clearly reflected in the high mean SYNTAX score (37.8) for this group.
  3. Nested PCI registry ($n = 198$ [6.4%]): These patients were deemed unsuitable for CABG. The commonest reason for this decision was the presence of multiple comorbidities[13] reflected in the mean EuroSCORE, which was 2 points higher in this group than the mean in the randomized group (5.8 vs. 3.8).



		30-Day	1-Yr	2-Yr	3-Yr	4-Yr
	Mortality after CABG, % (95% CI)	2.07 (1.98–2.17)	6.00 (5.58–6.17)	8.76 (8.56–8.94)	12.1 (11.9–12.4)	16.0 (15.7–16.3)
	Mortality after PCI, % (95% CI)	1.21 (1.14–1.27)	6.36 (6.22–6.51)	11.2 (11.0–11.4)	16.0 (15.7–16.2)	20.9 (20.6–21.3)
A	Relative risk with CABG (95% CI)	1.72 (1.58–1.84)	0.94 (0.91–0.97)	0.78 (0.76–0.80)	0.76 (0.74–0.78)	0.76 (0.75–0.78)



		30-Day	1-Yr	2-Yr	3-Yr	4-Yr
	Mortality after CABG, % (95% CI)	2.25 (2.09–2.41)	6.24 (5.97–6.50)	8.98 (8.68–9.29)	12.4 (12.0–12.8)	16.4 (15.9–16.9)
	Mortality after PCI, % (95% CI)	1.31 (1.21–1.41)	6.55 (6.35–6.76)	11.3 (11.0–11.6)	15.9 (15.6–16.3)	20.8 (20.4–21.2)
B	Relative risk with CABG (95% CI)	1.72 (1.52–1.89)	0.95 (0.90–1.00)	0.79 (0.76–0.83)	0.78 (0.75–0.81)	0.79 (0.76–0.82)

FIGURE 1-3 Incidence of survival in the coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) cohorts, from unadjusted (*upper*) and adjusted (*lower*) analyses. Cumulative mortality with CABG and PCI and the relative risk of CABG compared with PCI are shown. Data from the American College of Cardiology Foundation (ACCF) and Society of Thoracic Surgeons (STS) Database Collaboration on the Comparative Effectiveness of Revascularization Strategies (ASCERT) registry, the American College of Cardiology Foundation National Cardiovascular Data Registry, and the Society of Thoracic Surgeons Adult Cardiac Surgery Database from 2004 through 2008. (From Weintraub WS, Grau-Sepulveda MV, Weiss JM, et al: Comparative effectiveness of revascularization strategies. *N Engl J Med* 366[16]:1467-1476, 2012.)

TABLE 1-2 A Summary of Meta-Analyses Prior to Publication of the SYNTAX Trial Reporting Long-Term Outcomes in Patients With Isolated Proximal Left Anterior Descending Coronary Artery Disease or Multivessel Disease Randomized to Percutaneous or Surgical Revascularization

First Author	Number of Patients (PCI/CABG)	POBA/ BMS/ DES(%)	Follow-Up (Months)	Death (PCI vs. CABG)	MI (PCI vs. CABG)	Stroke (PCI vs. CABG)	Repeat Revasc. (PCI vs. CABG)	MACCEs (PCI vs. CABG)
Isolated Proximal LAD								
Aziz[31]	1952 (1300/652)	0/91/9	34	2.9% vs. 3.4%	2% vs. 1.1%	2.4% vs. 3.5%	14.3% vs. 4.4%*	21.4% vs. 11.1%*
Kapoor[32]	1210 (633/577)	22/59/19	60	9.4% vs. 7.2%	NA	NA	33.5% vs. 7.3%*	NA
Multivessel Disease								
Hlatky[9]	7812 (3923/3889)	63/37/0	5.9	10.0% vs. 8.4%	16.7% vs. 15.4%†	–	24.5% vs. 9.9%*†	36.4% vs. 20.1%*
Daemen[34]	3051 (1518/1533)	4/96/0	60	8.5% vs. 8.2%	2.5% vs. 2.9%	6.6% vs. 6.1%	25.0% vs. 6.3%*	34.2% vs. 19.6%*
Bravata[35]	9963 (5019/4944)	56/42/2	60	9.3% vs. 11.3%	0.6% vs. 1.2%*	11.9% vs. 10.9%	46.1% vs. 40.1% vs. 9.8%*‡	–

*$P < .001$.
†Composite with death.
‡Balloon angioplasty versus PCI versus CABG.
BMS, Bare-metal stent; *CABG,* coronary artery bypass grafting; *DES,* drug-eluting stent; *LAD,* left anterior descending coronary artery; *MACCE,* major adverse cardiovascular and cerebrovascular events (a composite of death, stroke, MI, and repeat revascularization); *MI,* myocardial infarction; *NA,* not available; *PCI,* percutaneous coronary intervention; *POBA,* plain old balloon angioplasty; *Revasc.,* revascularization.

TABLE 1-3 A Summary of 15 Randomized Control Trials Comparing Coronary Artery Bypass Grafting Against Percutaneous Coronary Intervention in the Pre–SYNTAX Era

Trial	Number of Patients Screened	% Randomized	Stent	% 3VD	Proximal LAD	EF >50%	% Diabetes
MASS[33]	142	69	–	–	100	100	21
ERACI[150]	127	9	–	45	–	100	11
EAST[151]	392	4	–	40	70	100	25
GABI[152]	359	4	–	18	–	–	10
CABRI[153]	1054	3	–	40	–	100	12
BARI[154]	1829	12	–	41	36	100	24
SIMA[155]	121	–	–	–	100	100	11
LAUSANNE[156]	134	3	–	0	100	–	12
RITA[157]	1011	4	–	12	–	–	6
TOULOSE[158]	152	3		29	–	–	14
AWESOME[159]	454	–	+	45	–	–	–
ERACI-II[160]	450	2	+	56	–	–	17
ARTS[161]	1205	5	+	32	–	100	19
SOS[162]	988	5	+	38	45	100	14
MASS II[163]	408	2	+	41	–	–	–
Summary	**8826**	**5**		**35**	**41**	**100**	**16**

From Soran O, Manchanda A, Schueler, S: Percutaneous coronary intervention versus coronary artery bypass surgery in multivessel disease: a current perspective. *Interact Cardiovasc Thorac Surg* 8(6):666-671, 2009.
3VD, Three-vessel disease; *CABG,* coronary artery bypass grafting; *EF,* ejection fraction; *LAD,* left anterior descending artery; *PCI,* percutaneous coronary intervention.

Overall, SYNTAX failed to meet the prespecified primary end point of noninferiority in terms of 12-month MACCEs, a composite of death, stroke, MI, and repeat revascularization (17.8% vs. 12.4%, $P = .002$). Final 5-year reporting of SYNTAX demonstrated significantly higher incidence of MACCE with PCI compared with CABG (26.9% vs. 37.3%, $P < .0001$; Fig. 1-5).[15]

As indicated earlier, analyses of all patients irrespective of disease severity does not provide adequate information for clinicians, who are faced daily with patients who display a wide variety of CAD complexity. To address this limitation of earlier studies, patient outcomes in SYNTAX were stratified according to tertiles of the anatomic SYNTAX score. As shown in Figure 1-6, clinical outcomes between patients treated with PCI and CABG in SYNTAX differed according to the presence of 3VD or unprotected left main CAD. With 3VD, a low SYNTAX score (<23) allowed for similar outcomes between CABG and PCI, whereas higher SYNTAX scores (particularly in the high SYNTAX score [>32] group) clearly favored CABG. With unprotected left main CAD, a low-intermediate SYNTAX score (<33) allowed for similar outcomes between CABG and PCI, whereas a high SYNTAX score (>32) clearly favored CABG. Furthermore, the SYNTAX Score II,[7,8] essentially the anatomic SYNTAX score augmented with clinical variables shown directly to affect decision making between CABG and PCI, was developed in the randomized, all-comers SYNTAX trial and allowed for the identification of higher- and lower-risk subjects in all

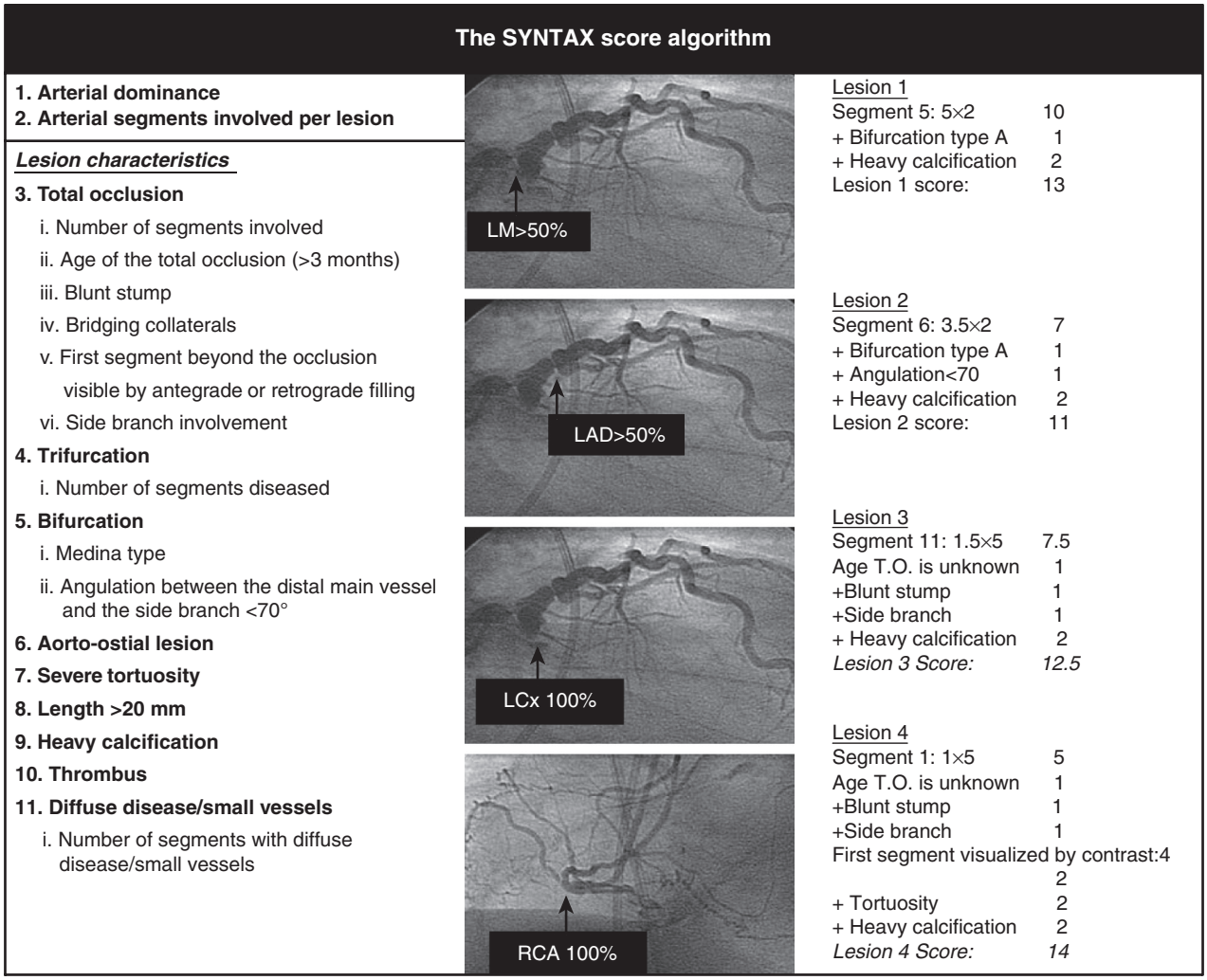


FIGURE 1-4 The SYNTAX score algorithm is applied to each individual coronary lesion in a vessel larger than 1.5 mm in diameter that has a stenosis diameter greater than 50%; the individual lesion scores are added together to give the final SYNTAX score.[16,39-41] (Modified from Serruys PW, Onuma Y, Garg S, et al: Assessment of the SYNTAX score in the SYNTAX study. *EuroIntervention* 5:50-56, 2009.)

tertiles of the anatomic SYNTAX score who had a long-term mortality that favored either CABG, PCI, or both revascularization modalities (discussed under "SYNTAX-Based Clinical Tools").[7,8,13-16]

The results of SYNTAX reiterate the importance of assessing patients when selecting a revascularization strategy. SYNTAX was able to identify those patients in whom either CABG or PCI was appropriate or in whom CABG or PCI was the optimal treatment. Considering the distribution of CAD in SYNTAX, overall one third of patients with 3VD/LM disease were deemed to have CAD that could be treated safely and effectively with PCI or CABG, whereas in the remaining two thirds, CABG remained the standard of care. Although these results helped further delineate the boundaries between a percutaneous and surgical revascularization approach in patients with complex CAD, the validation of the anatomic SYNTAX score and development of the SYNTAX Score II notably facilitated a more objective assessment of patients by the heart team as discussed later under "SYNTAX-Based Clinical Tools."

INDIVIDUAL ASSESSMENT FROM A PHYSICIAN'S PERSPECTIVE

There is no disputing the need for and potential benefits of selecting a revascularization strategy following an individualized patient assessment or risk stratification. Risk stratification is performed routinely and subconsciously by physicians in everyday clinical practice and is in essence behind all clinical decisions made by a physician. Stratification of risk is vital when assessing patients for revascularization because this treatment is only considered appropriate when "*the expected benefits, in terms of survival or health outcomes (symptoms, functional status, and/or quality of life) exceed the expected negative consequences of the procedure.*"[45] It should, however, be emphasized that the SYNTAX-pioneered heart team approach, consisting of at least an interventional/clinical cardiologist and a cardiac surgeon,[44] carries a class I recommendation in international guidelines for assessing risk and is subsequently the most appropriate revascularization modality in patients with complex CAD.[46-49]

Qualitative Versus Quantitative Risk Assessment

Qualitative risk stratification is subjective and relies on a clinician's experience. This subjective qualitative assessment also allows risk to be calculated and tailored to the expertise of the physician performing the procedure, as opposed to a clinician in another region who may use different techniques and who may have different equipment available. In addition, assessments of patient frailty can be made that are frequently not captured by conventional risk-scoring systems.[50] Finally, this assessment does not require a calculator or computer and can be "computed" subconsciously very quickly. The major disadvantages of

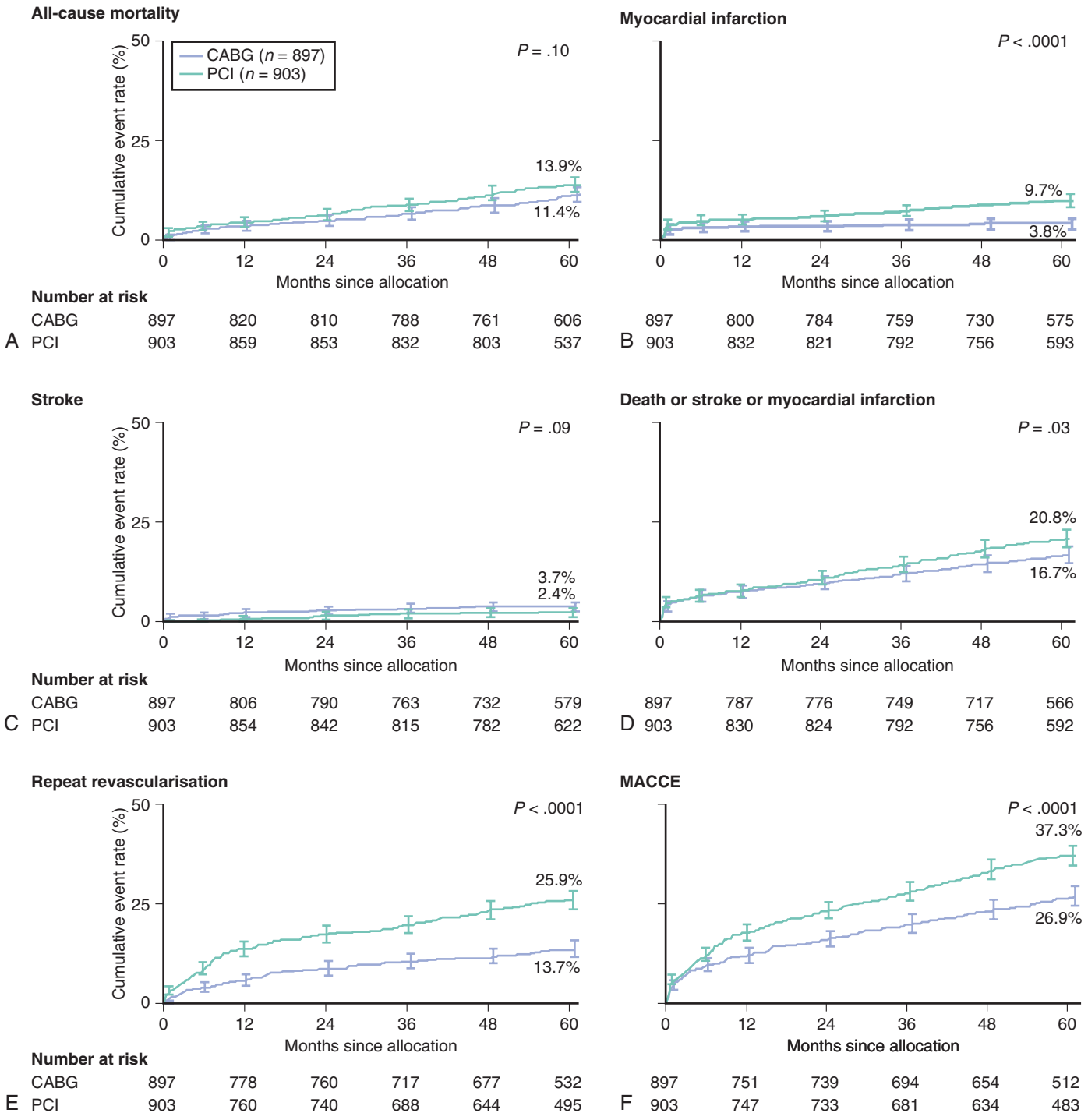


FIGURE 1-5 Five-year Kaplan-Meier cumulative event curves of major adverse cardiovascular and cerebrovascular events (a composite of death, stroke, myocardial infarction and repeat revascularization) and its components among the 1800 patients randomized to PCI or CABG in the SYNTAX Trial. *CABG,* Coronary artery bypass graft surgery; *PCI,* percutaneous coronary intervention; *MACCE,* major adverse cardiac and cerebrovascular events. (From Mohr FW, Morice MC, Kappetein AP, et al: Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 381[9867]:629-638, 2013.)

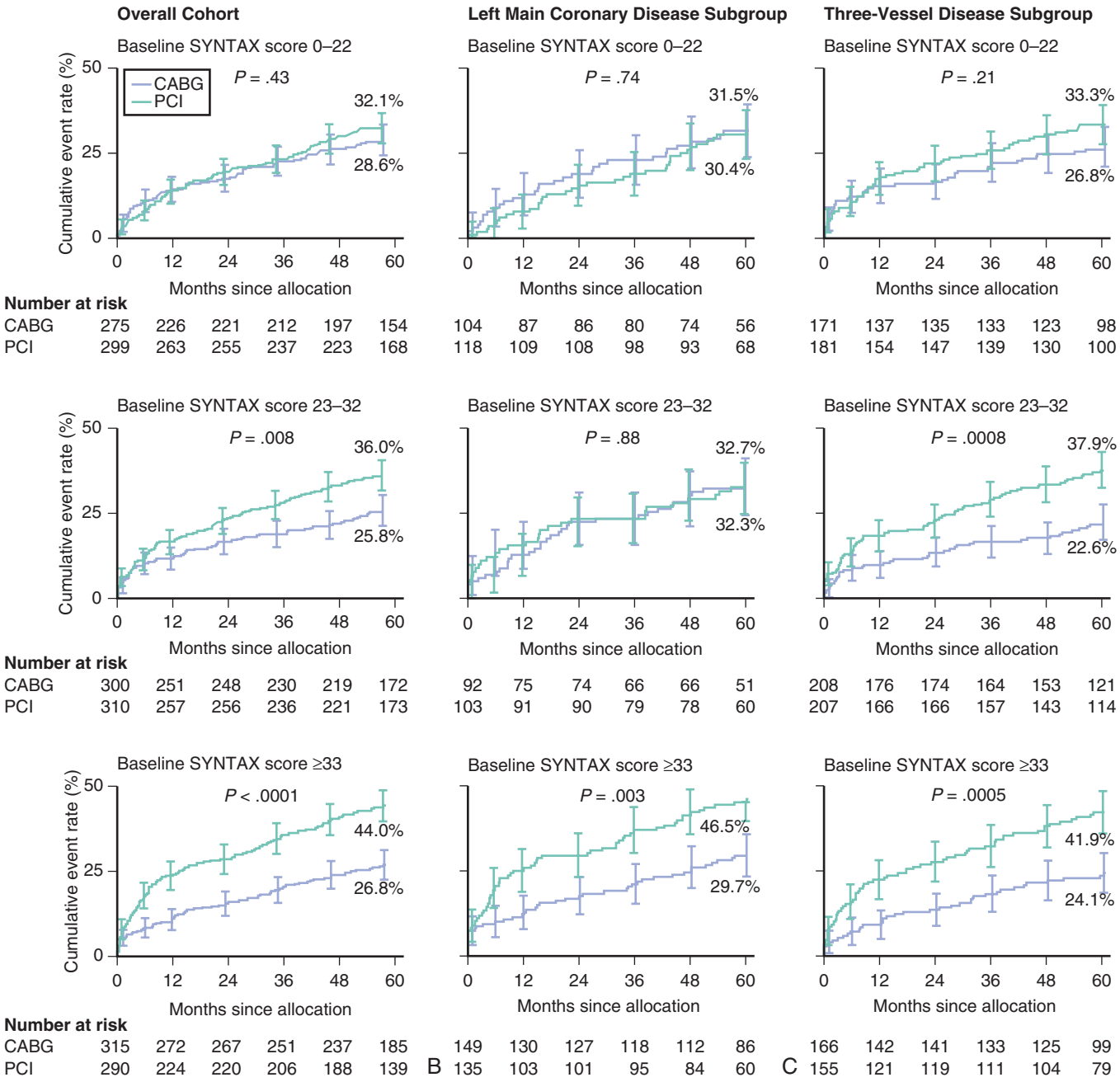


FIGURE 1-6 The evidence supporting the use of the SYNTAX score as a tool to assist in revascularization decisions. Five-year Kaplan-Meier cumulative event curves of major adverse cardiovascular and cerebrovascular events (MACCEs, a composite of death, stroke, myocardial infarction and repeat revascularization) among the 1800 patients randomized to percutaneous coronary (PCI) or coronary artery bypass graft surgery (CABG) in the SYNTAX Trial **(A)** and stratified by the presence of unprotected left main coronary artery disease **(B)** or de novo three vessel disease **(C).** In patients with three-vessel disease **(C),** the incidence of MACCEs at 5-year follow-up was similar among patients treated with PCI and CABG for low SYNTAX scores (≤22); for all other SYNTAX scores (>22), outcomes were significantly better following CABG. **B,** In patients with unprotected left main coronary artery disease, clinical outcomes were similar among patients treated by PCI or CABG for all low to intermediate SYNTAX scores (<33), whereas more complex disease (SYNTAX score >32) fared significantly better with CABG. (From Mohr FW, Morice MC, Kappetein AP, et al: Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 381[9867]:629-638, 2013.)

this method of risk assessment are its dependence on the operator's prior experience, potential personal bias to undertake or withhold potential revascularization, and its high interobserver variability.

Quantitative risk stratification can be performed using a variety of risk scores that frequently incorporate clinical variables sourced from large patient registries,[51-58] with the exception of the SYNTAX Score II,[7,8] which was developed in the all-comers randomized SYNTAX trial to reduce unavoidable (but often appropriate) selection bias inherent to all registries no matter their size. These risk scores largely incorporate objective variables to ensure adequate reproducibility of the score; however, those risk scores—such as the American College of Cardiology/American Heart Association (ACC/AHA) lesion score[59] or the anatomic SYNTAX score/newly developed SYNTAX Score II,[7,8,40] which include angiographic variables—continue to have documented intraobserver and interobserver variability.[41,60] These tools do, however, provide a more objective assessment of the patient risk and suitability for the most appropriate revascularization modality, which may be modified by the heart team consensus. In addition to their role in the risk stratification of individual patients, these quantitative risk scores have increasing use in the wider context of overall health care. They can provide a vital measure of overall patient care and can help identify future directions to further improve outcomes. Clinical governance and the increasing requirement to publically report clinical performance and complications have also propelled the need to risk stratify patients, thereby allowing a useful comparison of performance to be made between clinicians and institutions against the standards dictated by regulatory authorities.[61] In addition, calculation of risk using accepted risk scores may aid clinicians faced with an increasing need to be able to justify their clinical decisions to peers, regulatory bodies, and patients.

In comparison with the qualitative risk scores, the use of a finite number of variables results in these risk scores lacking the sensitivity to accurately predict risk in an individual, such that they are more apt at predicting risk for a population of patients with similar comorbidities. The number of variables included in the score must strike a balance between sufficient numbers to enable a meaningful prediction of risk to be calculated; however, the number must not be excessive so as to prevent use in routine practice. In addition, a minimal number of variables reduces the chances of colinearity between independent variables, which can result in redundant information being collected[56] while also increasing the chances of "overfitting" the score, and thereby reducing the overall accuracy of the results.[62]

The applicability of a risk score to contemporary practice must also take into consideration the time when the score was developed. Risk scores rely on large patient databases to derive appropriate weighting factors for variables in the score to enable the final calculation of risk. It follows that they are developed using retrospective information that may no longer be relevant in the era when the risk score is being used. The European System for Cardiac Operative Risk Evaluation (EuroSCORE), for example, was developed in 1999; however, there have been calls for its recalibration because repeated evaluations indicate that it overestimates risk by a factor of two to three, which has largely been attributed to improvements in surgical techniques and lower perioperative mortality in the decade following its construction.[63,64] The updated EuroSCORE II now addresses many of the limitations of the original EuroSCORE.[65-67] The Society of Thoracic Surgeons (STS) score is also derived from a large patient database and is periodically recalibrated to ensure its results are applicable to contemporary practice.[68]

Risk Scores in Contemporary Practice

Numerous risk scores are available to assist clinicians in stratifying risk among patients undergoing revascularization. Some scores are appropriate for patients prior to the selection of a revascularization strategy, whereas some have only been validated in patients undergoing one form of revascularization. Nevertheless, the various risk scores can largely be categorized according to the variables—clinical, angiographic, or a combination of both—used in the overall estimation of risk. Tables 1-4 and 1-5 summarize the different risk scores used in contemporary CABG and PCI practice (excluding SYNTAX-based tools), and Table 1-6 summarizes SYNTAX-based clinical tools. A selection of these is described in more detail below.

Clinical Scores

These risk scores only incorporate clinical variables and do not require any data from the angiogram. They offer the advantage of being able to be computed relatively quickly, usually at the bedside, and principally include variables that are not subject to user interpretation, thereby ensuring excellent reproducibility.

The EuroSCORE and EuroSCORE II

The EuroSCORE is an established risk model that utilizes 17 clinical variables used in cardiothoracic surgical practice for predicting operative mortality, and it has been validated in many populations around the world.[52,69-71] In use since 1999, the model was derived from almost 20,000 consecutive patients from 128 hospitals in eight European countries. The additive EuroSCORE assigns an individual score to 17 clinical variables (Table 1-7) with a low-risk tertile that ranges from 1 to 2, an intermediate-risk tertile from 3 to 5, and a high-risk tertile of 6 and higher. Early validation studies, however, suggested that the additive EuroSCORE underestimated risk in those at highest risk; this led to the development of the logistic EuroSCORE, which uses the same clinical variables and requires use of an online calculator (available at www.euroscore.org) to quantify risk.[52,53,64,71] However, the logistic EuroSCORE has been shown to potentially overestimate observed mortality, and its accuracy at predicting risk varies in different surgical subgroups.[64,72]

In addition to the EuroSCORE's assessment and validation in patients undergoing surgical revascularization, Kim and colleagues[73] first demonstrated that the high-risk tertile of the additive EuroSCORE was an independent predictor of death/MI after unprotected LM

TABLE 1-4 Summary of Contemporary Risk Scores for Assessment of Risk in Patients Undergoing Surgical Revascularization With the Exception of the Anatomic SYNTAX Score*

	NUMBER OF VARIABLES USED TO CALCULATE SCORE		VALIDATED IN PCI/CABG	
Risk Model	Clinical	Angiographic	PCI	CABG
EuroSCORE[13,51-53,69,70,74-78]	17	0	+	+
EuroSCORE II[65-67]	18	0	–	+
ACEF[56]	3	0	–	+
Society of Thoracic Surgery score[58,68,81,98]	40	2	–	+
Anatomic SYNTAX score[4,13,41,75,78,88,89,164-171]	0	11 (per lesion)	+	+

ACEF, Age, creatinine and ejection fraction; *AHA/ACC,* American Heart Association/American College of Cardiology; *CABG,* coronary artery bypass grafting; *PCI,* percutaneous coronary intervention.
*SYNTAX-based tools are shown in Table 1-6.

TABLE 1-5 Summary of a Selection of Established and Contemporary Risk Scores Categorized by Anatomic, Clinical, or Combined Types for the Assessment of Risk in Patients Proposing to Undergo Percutaneous Coronary Intervention

Clinical Risk Score	NUMBER OF VARIABLES USED TO CALCULATE RISK: Clinical	Angiographic	PCI Outcomes (Surgical Outcomes in Italics)
Anatomic Scores			
ACC/AHA lesion classification*	0	11 (per lesion)	Pre-DES era: predictive of angiographic success of PCI and prognostic effect on early and late clinical outcomes. Conflicting results were yielded in the DES era.[87,89,172-174]
Myocardial Jeopardy Scores			
Duke Jeopardy Score	0	Coronary tree divided into six segments: LAD, diagonal, septal perforating branches, LCx, OM, and PDA; a segment distal to ≥70% is considered at risk. Each segment is assigned 2 points with a maximum of 12 points.[90,91†]	
Myocardial Jeopardy Index (BARI)	0	Distal terminating portions of LAD, LCx, RCA, and major branch vessels (diagonals, OM, ramus, PDA and LV branches) assigned units of 1, 2, or 3 on the basis of length and vessel size. Septal perforators are arbitrarily assigned a maximum of 3 units. Extent of jeopardy defined by units jeopardized by ≥50% stenosis summated and divided by total LV territory.[91,92†]	
APPROACH lesion score	0	Based on principle from autopsy studies that the LAD generally subtends 41% of the LV, with the LCx and RCA supplying the remainder, dependent on vessel dominance. Score is calculated by percent of myocardium supplied by a vessel or its branches and jeopardized territories supplied by vessels with ≥70% stenosis (≥50% in the LMS); the maximum score is 100.[91†]	
Clinical Scores			
New Mayo Clinic Risk Score*	7	0	Procedural death and MACEs for PCI; model has been externally validated for death[56,57] (in-hospital death with CABG).[81]
Parsonnet Score	14	0	Independent predictor of long-term MACEs after LMS PCI in two registry populations[175,176] (Operative mortality after open-heart surgery)[177]
EuroSCORE (additive or logistic)	17	0	Evidence for predicting death or MACCEs in high-risk tertiles for PCI[73,74,77,178] (operative mortality for all forms of cardiothoracic surgery).[52,55]
NCDR CathPCI Risk Score*	8	0	Developed from 181,775 procedures performed in Medicare patients; incidence of in-hospital and 30-day mortality after all PCI patient types internally validated in two separate cohorts.[59]
ACEF score (age, creatinine, ejection fraction)	3	0	Predictor of cardiac death and MI at 1 year after PCI; inferior to the SYNTAX score at predicting overall MACEs and repeat revascularization in two separate populations[84,112] (operative mortality in elective cardiac operations).[56,82]
Combined (Anatomic AND Clinical) Risk Scores			
EuroHeart PCI Score*	10	6	Developed from 46,000 patients from the Euro Heart Survey; in-hospital mortality in all PCI patient types; internally validated. The score has strong applicability for European practice.[99]
New Risk Classification Score (NERS)	17	Angiographic: 33 Procedural: 4‡	6-month cardiac death and cumulative MACEs after unprotected LMS PCI; although internally validated, application to larger all-comers population is required (see text).[100]
New York PCI Risk Score†	8	1	In-hospital death after PCI; developed based on data from 46,090 procedures in 2002 and validated from 50,046 procedures in 2003[179]; excellent predictive ability in validation cohort (c-statistic 0.905).
The Texas Heart Institute Risk Score*	8	Angiographic: 2 Procedural: 1§	Predictors of in-hospital MACEs after PCI or CABG; developed in 9494 patients (BMS era) and validated in 5545 patients (DES era).[180]
Mayo Clinic Risk Score*	6	2	In-hospital death, Q-wave myocardial infarction, emergent or urgent CABG or CVA after PCI; validated using the NHLBI registry.[181]

*Risk scores that include prediction of in-hospital mortality or MACEs. SYNTAX-based tools are shown in Table 1-6.
†All myocardial jeopardy scores were validated in one population-based cohort consisting of more than 20,000 patients and were predictive of 1-year mortality in patients treated with PCI or medically.[90-92]
‡Need of intraaortic balloon pump, two-stent technique, intravascular ultrasound guidance.
§Number of stents.
ACC/AHA, American College of Cardiology/American Heart Association; *BMS,* bare-metal stent; *CABG,* coronary artery bypass grafting; *CVA,* cerebrovascular accident; *DES,* drug-eluting stent; *LAD,* left anterior descending artery; *LCx,* left circumflex artery; *LMS,* left main stem; *LV,* left ventricular; *MACCE,* major adverse cardiovascular and cerebrovascular event; *MACE,* major adverse cardiovascular event; *NCDR,* National Cardiovascular Data Registry; *OM,* obtuse marginal artery; *PCI,* percutaneous coronary intervention; *PDA,* posterior descending artery; *NHLBI,* National Heart, Lung, and Blood Institute; *RCA,* right coronary artery.

intervention with sirolimus-eluting stents. Subsequently, Romagnoli and coworkers[74] applied the additive EuroSCORE to predict in-hospital mortality in 1173 consecutive patients undergoing PCI in a single high-volume center and correlated the higher-risk tertiles of the EuroSCORE with in-hospital mortality; the study population also included patients who had undergone unprotected left main PCI. The EuroSCORE has since been evaluated in numerous studies of patients undergoing PCI, the majority of which specifically enrolled patients with LM disease.[13,73,75-77] Notably, all studies, irrespective of disease severity, have demonstrated the EuroSCORE to be an independent predictor of mortality[74,76] and/or MACCE at follow-up ranging from 1 to 3 years.[13,73,75-77] Importantly, those studies that also included a surgical control group—such as the SYNTAX study, the Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization (MAIN-COMPARE) study, and the registry by

TABLE 1-6 Outline of the Anatomic SYNTAX Score and the Progression of SYNTAX-Based Tools

	Year	Structure	Remarks
Anatomic SYNTAX Score[4,13-15,41,49,54,58-66,144]	2006	Score of angiographic variables (i.e., anatomic complexity); developed during the design of the SYNTAX trial[13,41] as a tool to force the heart team to systematically analyze the coronary angiogram and agree equivalent anatomic revascularization (CABG and PCI) could be achieved	First reported to be useful for decision making between CABG and PCI in the SYNTAX trial in 2009[13]; categories of anatomic complexity (low, intermediate, and high), no clinical variables, no individual predictions; adding a functional component shown to improve accuracy[13]; noninvasive multislice computed tomography anatomic SYNTAX score in development,[30] with integration of a noninvasive functional component.[139]
Development Phase: Augmenting the Anatomic SYNTAX Score With Clinical Variables and the Move Toward Individualized Decision Making			
ACEF[140]	2009	Age, creatinine, ejection fraction	Predicted individual in-hospital operative mortality post CABG; shown to be at least comparable to the EuroSCORE (composed of 17 variables) in predicting operative risk[56,82,83]; shown to aid in long-term predictions of mortality after PCI or CABG.[56,83]
Clinical SYNTAX Score[117]	2010	Amalgamation of SYNTAX score with modified ACEF score (creatinine replaced with CrCl shown to be more predictive of mortality[111])	Similar to the SYNTAX score; categorized patient risk; could only identify a high-risk group in PCI-treated patients; provided little help in decision making between CABG and PCI; not individualized.
Global Risk[82,113]	2010	Amalgamation of SYNTAX score with surgical EuroSCORE (composed of 17 variables)	Similar to the SYNTAX score; categorized patient risk; could identify a low-risk group with comparable outcomes with CABG and PCI in LM and 3VD patients; not individualized; patients with a high EuroSCORE were found to have a prognostic benefit in undergoing CABG compared with PCI irrespective of the SYNTAX score provided an acceptable threshold of operative risk was not exceeded.
Logistic Clinical SYNTAX Score[116,117]	2011	Combination of age, SYNTAX score, CrCl, and LVEF shown to contain most of the prognostic data for 1-year mortality predictions after PCI	Individual 1-year mortality predictions in all PCI patients (STEMI, NSTEMI) irrespective of clinical presentation (except cardiogenic shock); not designed to help decision making between CABG and PCI; cross-validated in seven contemporary stent trials and more than 6000 patients and further externally validated.[113]
End Result of This Process Leading to the Development of the SYNTAX Score II			
SYNTAX Score II[114]	2012	Augmenting SYNTAX score with clinical variables; based on the principle that age, CrCl, LVEF, and SYNTAX score contain most of the long-term prognostic data in CABG and PCI patients; additional variables added that directly influenced decision making between CABG and PCI	Individualized approach; threshold of the SYNTAX score in guiding decision making between CABG and PCI shown to alter based on the presence of other risk factors; validated in the DELTA Registry[7,8] containing LM and 3VD (25% of the population) with almost a third (30%) with highly complex disease (SYNTAX scores ≥33); prospective validation studies are underway in the EXCEL trial (LM), and SYNTAX II trial is ongoing (de novo three vessel disease).
Use of the SYNTAX Score as an Objective Marker of Completeness of Revascularization			
Residual SYNTAX Score[119]	2012	Recalculation of the SYNTAX score after PCI	Developed and validated in the ACUITY[129,130] and SYNTAX[129] trials; a residual SYNTAX score greater than 8 was shown to have an adverse effect on long-term prognosis at up to 5 years follow-up; further, prospectively run validation studies are awaited.
Post-CABG SYNTAX Score[130]	2013	Recalculation of the SYNTAX score after CABG with points deducted based on the importance of the diseased coronary artery segment (Leaman score[132,133]) that has a functioning bypass graft anastomosed distally	Pilot study in angiographic substudy of the SYNTAX trial demonstrated the feasibility of this approach in identifying subjects post CABG with an adverse long-term (5-year) prognosis[103]; validation studies are awaited.

3VD, Triple-vessel disease; *CABG,* coronary artery bypass grafting; *CrCl,* creatinine clearance; *LM,* left main; *LVEF,* left ventricular ejection fraction; *NSTEMI,* non–ST-elevation myocardial infarction; *PCI,* percutaneous coronary intervention; *STEMI,* non–ST-elevation myocardial infarction.

Rodés-Cabau and colleagues[77]—also demonstrated the EuroSCORE to be an independent predictor of MACCE in surgical patients.[75,78] Only one study has examined the logistic EuroSCORE in PCI patients, however, little differences were found in stratifying risk when compared with the additive EuroSCORE.[74]

Specifically in the SYNTAX trial, which represents the only randomized study to assess the EuroSCORE, the additive EuroSCORE was shown to be an independent predictor of MACCE at 1-year follow-up irrespective of the method of revascularization (odds ratio [OR] 1.21; 95% confidence interval [CI], 1.12 to 1.32; $P < .001$) in 705 patients undergoing LM revascularization.[75] Similarly, at intermediate follow-up of 23 months, Rodés-Cabau and colleagues[77] identified a EuroSCORE of 9 or higher as the best predictor of MACCE after PCI and CABG among 249 octogenarians with LM disease. In the MAIN-COMPARE registry, which enrolled over 1500 patients with LM disease followed up for a median of 3.1 years, the EuroSCORE has been identified as an independent predictor of death, MI, and stroke irrespective of revascularization strategy.[78] In addition, in the same registry, a EuroSCORE of 6 or higher has been shown to be an independent predictor of mortality following either PCI or CABG.[76]

More recently, the EuroSCORE II (Table 1-8) was developed to improve the risk-prediction model of the original EuroSCORE. EuroSCORE II was developed on newer data to reflect more contemporary surgical practice given that cardiac surgical mortality has decreased significantly in the last 15 years, despite patients being older and sicker, and that the previous additive and logistic EuroSCORE models were suggested to be representative of outdated surgical practices.[65-67,79]

The EuroSCORE II was shown to be better calibrated (actual mortality 4.18%, predicted 3.95%) compared with the original EuroSCORE model (actual 3.9%, additive predicted 5.8%, logistic predicted 7.57%) while preserving discrimination (area under the receiver operating

TABLE 1-7 The Components of the EuroSCORE and Relevant Weighting Factors of the Additive and Logistic EuroSCOREs

Patient Characteristics	Additive		Logistic β Coefficient
Age	Per 5 years or part thereof over the age of 60 years	1	0.07
Sex	Female	1	0.33
Chronic pulmonary disease	Long-term use of bronchodilators or steroids for respiratory disease	1	0.49
Peripheral arteriopathy	*Claudication, carotid stenosis >50%, previous or planned intervention on the abdominal aorta, limb arteries, or carotids	2	0.66
Neurologic dysfunction	Severely affected mobility or day-to-day function	2	0.84
Previous cardiac surgery	Previous opening of the pericardium	3	1.00
Serum creatinine	Preoperatively greater than 200 μmol/L	2	0.65
Active endocarditis	Antibiotic therapy at time of surgery	3	1.10
Critical preoperative state	*Preoperative cardiac arrest, ventilation, renal failure, inotropic support, intraaortic balloon pump use, ventricular arrhythmia	3	0.91
Cardiac-Related Factors			
Unstable angina	Rest pain that requires IV nitrates	2	0.57
Left ventricular function	Moderate (30% to 50%) Poor (<30%)	1 3	0.42 1.09
Recent MI	Within 90 days	2	0.55
Pulmonary hypertension	Systolic pulmonary pressure greater than 60 mm Hg	2	0.77
Operation-Related Factors			
Emergency	Operation performed before the start of next working day	2	0.71
Other than isolated CABG	Major cardiac procedure other than or in addition to CABG	2	0.54
Surgery on thoracic aorta		3	1.16
Postinfarct septal rupture		4	1.46
Constant β_0			–4.79

From Singh M, Rihal CS, Lennon RJ, et al: Bedside estimation of risk from percutaneous coronary intervention: the new Mayo Clinic Risk Scores. *Mayo Clinic Proc* 82:701-708, 2007; and Singh M, Peterson ED, Milford-Beland S, et al: Validation of the Mayo Clinic risk score for in-hospital mortality after percutaneous coronary interventions using the National Cardiovascular Data Registry, *Circ Cardiovasc Interv* 1:36-44, 2008.
*Any of these.
The logistic EuroSCORE can be calculated at www.euroscore.org.
CABG, Coronary artery bypass grafting; *IV,* intravenous; *MI,* myocardial infarction.

TABLE 1-8 Final Risk Factors by Mutivariate Regression for the EuroSCORE II Model

Risk Factor	Coefficient	Standard Error	*z*	$P \geq \|z\|$	[95% Confidence Interval]
New York Hospital Association (NYHA)					
II	0.1070545	0.1463849	0.73	0.465	[–0.1798547 to 0.3939637]
III	0.2958358	0.141466	2.09	0.037	[0.0185674 to 0.5731042]
IV	0.5597929	0.1697565	3.30	0.001	[0.2270763 to 0.8925095]
CCS4	0.2226147	0.1462888	1.52	0.128	[–0.0641061 to 0.5093356]
IDDM	0.3542749	0.145863	2.43	0.015	[0.0683887 to 0.6401611]
Age	0.0285181	0.0065954	4.32	0.000	[0.0155914 to 0.0414448]
Female	0.2196434	0.0953505	2.30	0.021	[0.0327599 to 0.4065269]
ECA	0.5360268	0.1106046	4.85	0.000	[0.3192458 to 0.7528079]
CPD	0.1886564	0.1232126	1.53	0.126	[–0.0528358 to 0.4301486]
N/M mob	0.2407181	0.1729494	1.39	0.164	[–0.0982564 to 0.5796927]
Redo	1.118599	0.1226272	9.12	0.000	[0.8782539 to 1.3589440]
Renal Dysfunction					
On dialysis	0.6421508	0.3083468	2.08	0.037	[0.0378021 to 1.2464990]
CC ≤ 50	0.8592256	0.1446758	5.94	0.000	[0.5756663 to 1.1427850]
CC 50 to 85	0.303553	0.1240518	2.45	0.014	[0.0604159 to 0.5466901]
Active endocarditis	0.6194522	0.2046001	3.03	0.002	[0.2184433 to 1.0204610]
Critical	1.086517	0.147657	7.36	0.000	[0.797115 to 1.3759200]
Left Ventricular Function					
Moderate	0.3150652	0.1036182	3.04	0.002	[0.1119773 to 0.5181530]
Poor	0.8084096	0.1498233	5.40	0.000	[0.5147614 to 1.1020580]
Very poor	0.9346919	0.2917754	3.20	0.001	[0.3628227 to 1.5065610]
Recent MI	0.1528943	0.136257	1.12	0.262	[–0.1141646 to 0.4199531]

TABLE 1-8 Final Risk Factors by Mutivariate Regression for the EuroSCORE II Model—cont'd

Risk Factor	Coefficient	Standard Error	*z*	*P* ≥ |z|	[95% Confidence Interval]
Pulmonary Artery Systolic Pressure					
31 to 55 mm Hg	0.1788899	0.1266713	1.41	0.158	[–0.0693812 to 0.4271611]
≥55	0.3491475	0.1676641	2.08	0.037	[0.0205318 to 0.6777632]
Urgency					
Urgent	0.3174673	0.1174178	2.70	0.007	[0.0873326 to 0.5476020]
Emergency	0.7039121	0.1719835	4.09	0.000	[0.3668306 to 1.0409940]
Salvage	1.362947	0.33706	4.04	0.000	[0.7023221 to 2.0235730]
Weight of Procedure					
1 non-CABG	0.0062118	0.1463574	0.04	0.966	[–0.2806434 to 0.2930670]
2	0.5521478	0.1268137	4.35	0.000	[0.3035975 to 0.8006980]
3+	0.9724533	0.1463969	6.64	0.000	[0.6855206 to 1.2593860]
Thoracic aorta	0.6527205	0.221183	2.95	0.003	[0.2192097 to 1.0862310]
Constant	–5.324537	0.1682446	–31.65	0.000	[–5.65429 to –4.9947830]

From Nashef SA, Roques F, Sharples LD, et al: EuroSCORE II. *Eur J Cardiothorac Surg* 41(4):734-744, 2012.
CABG, Coronary artery bypass grafting; *CC,* creatinine clearance; *CCS,* Canadian Cardiovascular Society; *IDDM,* insulin-dependent diabetes mellitus; *CPD,* chronic pulmonary dysfunction; *Critical,* critical preoperative state; *ECA,* extracardiac arteriopathy; *N/M mob,* neurologic or musculoskeletal dysfunction severely affecting mobility; *Redo,* previous cardiac surgery; *MI,* myocardial infarction.
Weight of procedure: 1, non-CABG, single major cardiac procedure (MCP) that is not isolated CABG; 2, two MCPs; 3+, three or more MCPs. For age, $X_i = 1$ if patient age is 60 or younger; X_i increases by one point per year thereafter (e.g., age 60 or less, $X_i = 1$; age 61, $X_i = 2$; age 62, $X_i = 3$, etc.).

characteristic [ROC] curve of 0.8095). It should be noted, however, that regular revalidation of the EuroSCORE II will need to be continued to identify calibration drift or clinical inconsistencies seen in previous versions.[79,80]

In summary, while acknowledging that most of these studies have been nonrandomized observational studies, the findings do suggest that the EuroSCORE and EuroSCORE II are valuable tools in the individual assessment of risk prior to the selection of a revascularization strategy.

New Mayo Clinic Risk Score

The new Mayo Clinic Risk Score (MCRS) was designed to replace the original MCRS by predominantly excluding angiographic variables, namely the presence of left main or multivessel disease, and a few of the interaction effects of specific clinical variables (see Table 1-5).

The new MCRS is based solely on baseline clinical and noninvasive assessments and incorporates seven preprocedural variables (age, serum creatinine, left ventricular ejection fraction [LVEF], MI within the past 24 hours, preprocedural shock, congestive heart failure, and peripheral vascular disease). The risk score had a c-statistic (area under ROC curve) of 0.74 and 0.89 for major adverse cardiovascular events (MACEs) and procedural death, respectively, in the population from whom the risk model was derived.[54,55] The risk score has since been validated for in-hospital mortality in the National Cardiovascular Data Registry (NCDR)[55]; however, it has not been validated for MACEs. The new MCRS has also been demonstrated to be predictive of in-hospital mortality after CABG surgery.[81]

Value of Age, Creatinine, and Ejection Fraction (ACEF) Score

Ranucci and colleagues[56,82] demonstrated in a relatively simple risk score consisting of only three clinical variables—age, preoperative serum creatinine value, and LVEF—a risk score for assessing operative mortality risk in elective cardiac operations. Notably, despite the simplicity of the score, the clinical performance of the ACEF score appeared to be comparable to either the additive or the logistic EuroSCORE.

The ACEF score is calculated using the following formula:

$$\text{ACEF} = [\text{Age}/\text{LVEF}\ (\%)] + [1\ (\text{if creatinine} > 2\ \text{mg/dL})]$$

From ACEF, a mortality risk can be calculated from a graphical relationship of ACEF with an operative risk or an equation (Fig. 1-7).[56,82] ACEF was developed from an initial dataset of 4557 patients and a subsequent validation series of 4091 patients from a single institution. The results demonstrated a similar accuracy and calibration for the prediction of in-hospital mortality with ACEF when compared with other more complicated surgical risk scores such as the EuroSCORE and the Cleveland Clinic Score. Subsequent validation studies have shown ACEF to have an accuracy level at least comparable to that of the EuroSCORE for operative mortality risk stratification in a series of 29,659 patients undergoing elective cardiac surgery.[82,83]

In addition, ACEF was applied to PCI patients from the all-comers LEADERS population at 1-year follow-up.[84] Despite ACEF being demonstrated to be superior to the SYNTAX score alone as a predictor of cardiac death and MI after PCI, ACEF was found to be inferior to the SYNTAX score at predicting overall MACE rates and the risk of repeat revascularization. This reflects the observation that anatomic and clinical variables appear to be necessary requirements for a comprehensive risk model in predicting clinical outcomes after PCI.

National Cardiovascular Database Registry CathPCI Risk-Prediction Score

The NCDR CathPCI risk-prediction score is the most contemporary clinical risk model currently available. It incorporates information from nine clinical variables (Table 1-9), which are assigned appropriate weighted values and are then added together to give a final score that can be translated into risk of in-hospital mortality (Fig. 1-8).[57] The score was developed using data from over 180,000 patients from the voluntary U.S. NCDR database and was validated in over 400,000 patients from the same database who underwent PCI between March 2006 and March 2007. Notably, the c-statistic for the prediction of in-hospital mortality was consistently above 0.90 for in-hospital mortality, whereas a lower but nevertheless adequate c-statistic of 0.83 was seen for 30-day mortality.

Angiography-Based Scores

Two major angiography-based scores have been developed, both of which are independent of patient clinical variables, calculated using only angiographic data. As alluded to earlier, this introduces a subjective element to the assessment of risk[41,60] and consequently introduces a degree of intraobserver and interobserver variability, which is notably absent from the clinical scores described above. Finally, these scores can only be computed after diagnostic coronary angiography has been

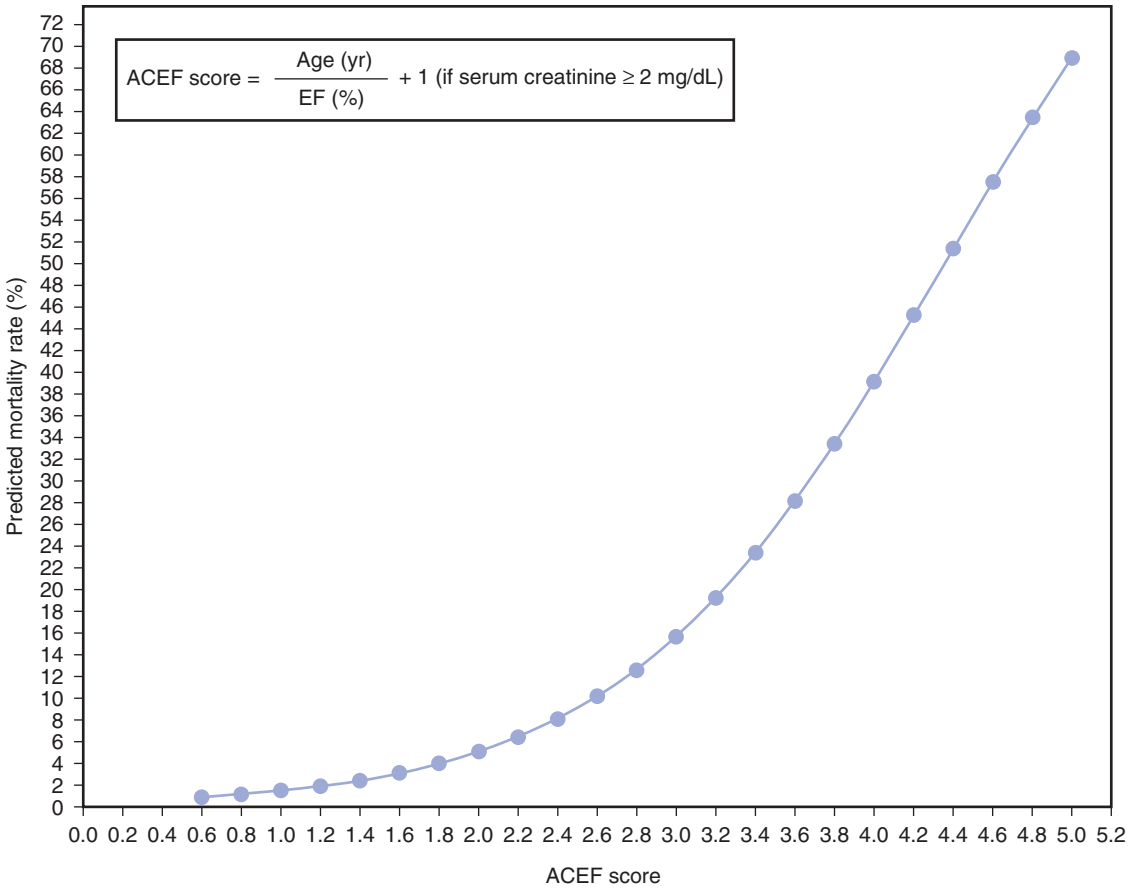


FIGURE 1-7 Univariate association (logistic regression) between ACEF score—the value of age, creatinine, and ejection fraction—and mortality risk. (From Ranucci M, Castelvecchio S, Menicanti L, et al: Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. *Circulation* 119[24]:3053-3061, 2009.)

TABLE 1-9 The National Cardiovascular Database

Variable	Scoring Response Categories			
Age	<60	≥60, <70	≥70, <80	≥80
Weighted score	0	4	8	14
Cardiogenic shock	No	Yes		
Weighted score	0	25		
Prior CHF	No	Yes		
Weighted score	0	5		
Peripheral vascular disease	No	Yes		
Weighted score	0	5		
Chronic lung disease	No	Yes		
Weighted score	0	4		
GFR (mL/min)	<30	30 to 60	60 to 90	>90
Weighted score	18	10	6	0
NYHA Class IV	No	Yes		
Weighted score	0	4		
PCI Status (STEMI)	Elective	Urgent	Emergent	Salvage
Weighted score	12	15	20	38
PCI Status (no STEMI)	Elective	Urgent	Emergent	Salvage
Weighted score	0	8	20	42

Registry risk model from Peterson ED, Dai D, DeLong ER, et al: Contemporary Mortality Risk Prediction for Percutaneous Coronary Intervention: Results From 588,398 Procedures in the National Cardiovascular Data Registry. *J Am Coll Cardiol* 55:1923-1932, 2010.
CHF, Congestive heart failure; *GFR,* glomerular filtration rate; *NYHA,* New York Heart Association; *PCI,* percutaneous coronary intervention; *STEMI,* ST-elevation myocardial infarction.
The risk of in-hospital mortality is derived using Figure 1-9.

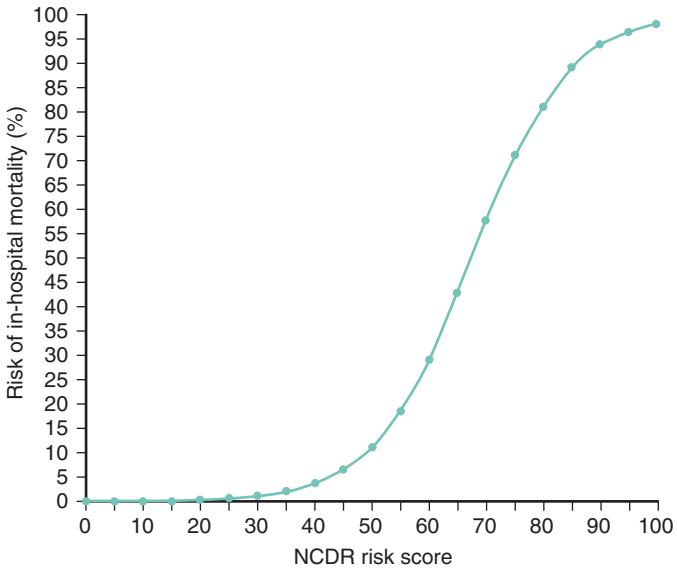


FIGURE 1-8 The predicted risk of in-hospital mortality using the National Cardiovascular Database Registry risk score. (From Peterson ED, Dai D, DeLong ER, et al: Contemporary Mortality Risk Prediction for Percutaneous Coronary Intervention: Results From 588,398 Procedures in the National Cardiovascular Data Registry. *J Am Coll Cardiol* 55:1923-1932, 2010.)

TABLE 1-10 American College of Cardiology/American Heart Association Characteristics of Type A, B, and C Lesions

Type A Lesions (high success, >85%; low risk)
Discrete (<10 mm length)
Concentric
Readily accessible
Nonangulated segment (<45 degrees)
Smooth contour
Little or no calcification
Less than totally occlusive
Not ostial in location
No major branch involvement
Absence of thrombus
Type B Lesions (moderate success, 60% to 85%; moderate risk)
Tubular (10 to 20 mm in length)
Eccentric
Moderate tortuosity of proximal segment
Moderately angulated segment, 45 to 90 degrees
Irregular contour
Moderate to heavy calcification
Ostial in location
Bifurcation lesions requiring double guidewires
Some thrombus present
Total occlusion less than 3 months old
Type B lesions are further subdivided into subtypes B1 (one type B characteristic) and B2 (two type B characteristics)
Type C Lesions (low success, <60%; high risk)
Diffuse (>2 cm length)
Excessive tortuosity of proximal segment
Extremely angulated segments (>90 degrees)
Inability to protect major side branches
Degenerated vein grafts with friable lesions
Total occlusion more than 3 months old

Krone RJ, Laskey WK, Johnson C, et al: A simplified lesion classification for predicting success and complications of coronary angioplasty. Registry Committee of the Society for Cardiac Angiography and Intervention. *Am J Cardiol* 85:1179-1184, 2000.

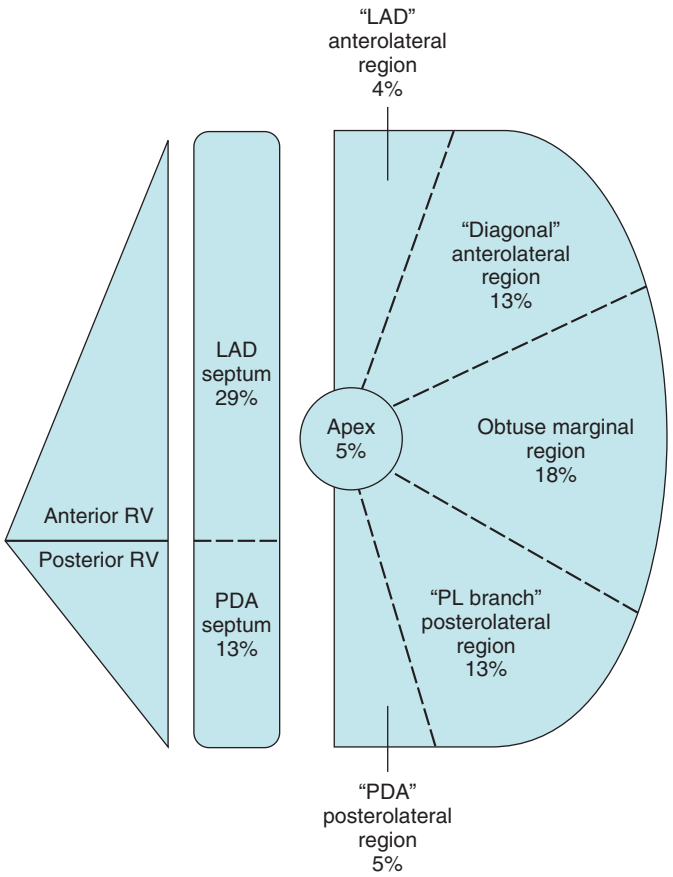


FIGURE 1-9 An example of a Myocardial Jeopardy Score. The APPROACH Lesion Score illustrating the weighting factors for myocardial regions is illustrated. *LAD,* Left anterior descending artery; *RV,* right ventricle; *PDA,* posterior descending artery; *PL,* posterolateral. (From Graham MM, Faris PD, Ghali WA, et al: Validation of three myocardial jeopardy scores in a population-based cardiac catheterization cohort. *Am Heart J* 142[2]:254-261, 2001.)

performed, thereby moving assessment further down the treatment pathway.

American College of Cardiology/American Heart Association Lesion Classification System

The ACC/AHA lesion classification system was one of the first angiographic scoring systems developed. Initially devised in 1986 and modified in 1990, it uses 11 angiographic variables to categorize lesions into four groups: types A, B1, B2, and C (Table 1-10). Historic studies prior to the arrival of drug-eluting stents indicated that that the ACC/AHA lesion classification did have a prognostic impact on early and late outcomes.[59,85,86]

However, registry data from the DES era has shown conflicting results. The German Cypher registry (n = 6755) failed to show any definite relationship between clinical outcomes and ACC/AHA lesion class at 6 months.[87] These results are at variance to the positive relationship identified between ACC/AHA lesion class and clinical outcomes in smaller studies of patients with more complex disease.[88,89]

Specifically, Valgimigli and colleagues[88] reported that a higher ACC/AHA lesion score (derived by assigning 1, 2, 3, and 4 points to type A, B1, B2, and C lesions, respectively) correlated with poor clinical outcomes among 306 patients with 3VD undergoing PCI with a DES. In addition, data from a small registry (n = 255) was potentially predictive of mortality and MACEs in unprotected left main stem PCI at 1-year follow-up.[89]

Anatomic SYNTAX Score

The SYNTAX score represents a comprehensive angiographic scoring system that allows the complexity of CAD to be objectively quantified. This is further discussed in the section on SYNTAX-based scoring tools.

Myocardial Jeopardy Scores

Myocardial jeopardy scores are a method of estimating the amount of myocardium at risk based on the assessment of both the severity of the coronary artery lesion and the volume of myocardium it supplies. Examples of such scores include the Duke Jeopardy Score, the Myocardial Jeopardy Index from the Bypass Angioplasty Revascularization Investigation (BARI) score, and the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) score (Fig. 1-9; see Table 1-5). The Duke and BARI scores were developed and validated in relatively small populations. All three models have since been validated in one population-based cohort consisting of more than 20,000 patients and were predictive of 1-year mortality in patients treated with PCI or treated medically; within this population, all three scores also had similar risk-model performance measures with only minor differences in C statistics evident.[90-92]

It has since been shown that the Duke Jeopardy Score is an independent predictor of adverse clinical outcomes, namely death and MI, in medically treated patients with acute coronary syndromes (ACSs) at up to 1 year in a post hoc study of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial.[93]

The BCIS-1 Myocardial Jeopardy Score, a variant of the Duke Jeopardy Score that has been reported to be simpler to use, has

recently been shown to have a strong correlation with the myocardial ischemic burden as assessed by cardiac magnetic resonance perfusion imaging.[94,95] A BCIS-1 Jeopardy Score of 10 to 12 and a revascularization index (preprocedural minus postprocedural jeopardy scores divided by preprocedural jeopardy score, with 1 indicating complete revascularization) of 0 to 0.33 were both shown to be highly predictive of mortality after contemporary PCI in a single U.K. center experience that involved over 600 patients.[96]

SYNTAX-based tools to assess completeness of revascularization (see Table 1-6) after CABG and PCI have been developed and are discussed in the section on SYNTAX-based tools.

Combined Risk Scores

The previous discussion has reviewed risk scores that rely on either clinical or angiographic variables (with the exception of SYNAX-based clinical tools). There is no disputing that for a complete individualized patient assessment, both factors must be taken into consideration. Moreover, current evidence indicates that clinical and angiography-based risk scores may be better suited to predict different patient outcomes. Clinical scores appear to be better at predicting clinical end points such as death or MI, whereas angiography-based scores appear to be superior for the prediction of angiographic success and the risk of repeat revascularization. Of note, Peterson and coworkers[57] observed only a minimal improvement in the ability of the NCDR CathPCI risk score to predict in-hospital mortality following the inclusion of angiographic variables. These findings are in line with previous reports, which demonstrated that the MCRS was superior to the ACC/AHA lesion classification in the prediction of death, stroke, MI, and emergent CABG but was inferior for the prediction of angiographic failure.[97]

According to the variables assessed in the risk score, these differential outcomes have raised interest in combined risk scores, which assess risk by considering both clinical and angiographic variables. In view of this, several combined clinical and angiographic risk scores have been developed. Other than the STS score, the newer combined scores have yet to be validated in large patient populations, such that outcome data are currently confined to small, retrospective studies with limited follow-up. The most prominent combined risk scores are discussed here.

Society of Thoracic Surgery Score

The STS score predicts the risk of operative mortality and morbidity after cardiac surgery and is calculated by means of an online calculator (www.STS.org) that requests information on 40 clinical and two angiographic variables (presence of LM lesion and number of vessels diseased).[58,68] As alluded to earlier, the STS score undergoes periodic recalibration, which is vital to ensure that its results remain applicable to contemporary practice. In comparison with other clinical models in patients undergoing CABG, the STS score has been shown to be superior to both the MCRS[81] and the EuroSCORE.[98] Notably, however, no evaluation has been done of the STS score in patients undergoing PCI, nor has any comparison been made between the STS score and angiography-based scores. Consequently, the role of the STS score in the assessment of patients undergoing revascularization is confined to those in whom surgical revascularization has already been selected.

EuroHeart Score

A logistic regression model comprising 10 clinical variables and 6 anatomic variables was developed based on the Euro Heart Survey, a European PCI registry consisting of over 46,000 patients from 176 European centers who underwent PCI for differing indications (Fig. 1-10).[99] The risk score was shown to be highly predictive of in-hospital mortality (C statistic 0.91); the strengths of the risk model were that it

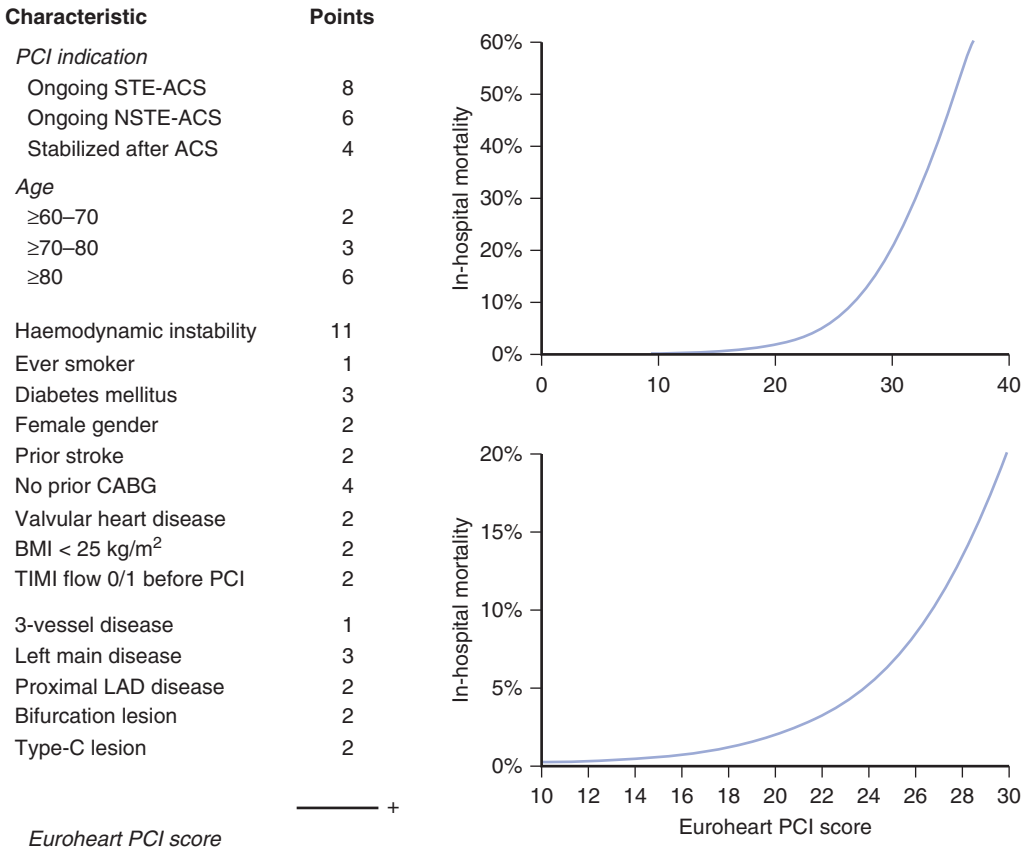


FIGURE 1-10 EuroHeart PCI Score–assigned integer scores. (From de Mulder M, Gitt A, van Domburg R, et al: EuroHeart score for the evaluation of in-hospital mortality in patients undergoing percutaneous coronary intervention. *Eur Heart J* 32[11]:1398-1408, 2011.)

was internally validated within the registry population and that it retained its discriminatory power (C statistic 0.90); the model was also sufficiently calibrated for the study and validation populations.

New Risk Classification Score

The New Risk Classification Score (NERS)[100] is a risk score developed to predict outcomes for unprotected left main stem PCI from four centers in China (n = 260). Reflecting the long time frame of this registry (~10 yr), the patients included either had bare-metal or drug-eluting stents implanted. The NERS was subsequently validated in a different consecutive group of patients within the same registry, all treated with drug-eluting stents (n = 337). The NERS consists of 54 variables (17 clinical, 4 procedural, and 33 angiographic features). A substantially higher C statistic was evident for the NERS compared with the anatomic SYNTAX score (NERS 0.89 vs. SYNTAX score 0.69), indicating that it had an excellent discriminatory ability. When the NERS score was separated into two groups of risk (high and low) and clinical outcomes were assessed, the high-risk group was demonstrated to be significantly more predictive of MACEs compared with the intermediate or high SYNTAX score tertiles (Fig. 1-11). However, in the low-risk NERS group, outcomes were similar to the low SYNTAX score group, suggesting at least from this study that anatomic variables alone may be sufficient to be predictive of clinical outcomes in the low-risk group. One of the main limitations of NERS is that patient comorbidity was significantly less prevalent compared with that of the all-comers SYNTAX population,[13,16] the latter of which was designed to overcome many of the limitations and selection bias inherent in small registries. A more simplified NERS II score consisting of 16 variables (seven clinical and nine angiographic) has recently been reported to have a predictive accuracy similar to that of the original NERS in a multicenter, prospective registry study in China.[101]

SYNTAX-Based Tools

The augmentation of the anatomic SYNTAX score with clinical variables, culminating in the development and validation of SYNTAX Score II—in which objective and tailored decision making could be made for the individual patient—is detailed in next section.

SYNTAX-BASED CLINICAL TOOLS

In this section we systematically examine the widening applications of tools for clinical decision making that are based on the SYNTAX score.

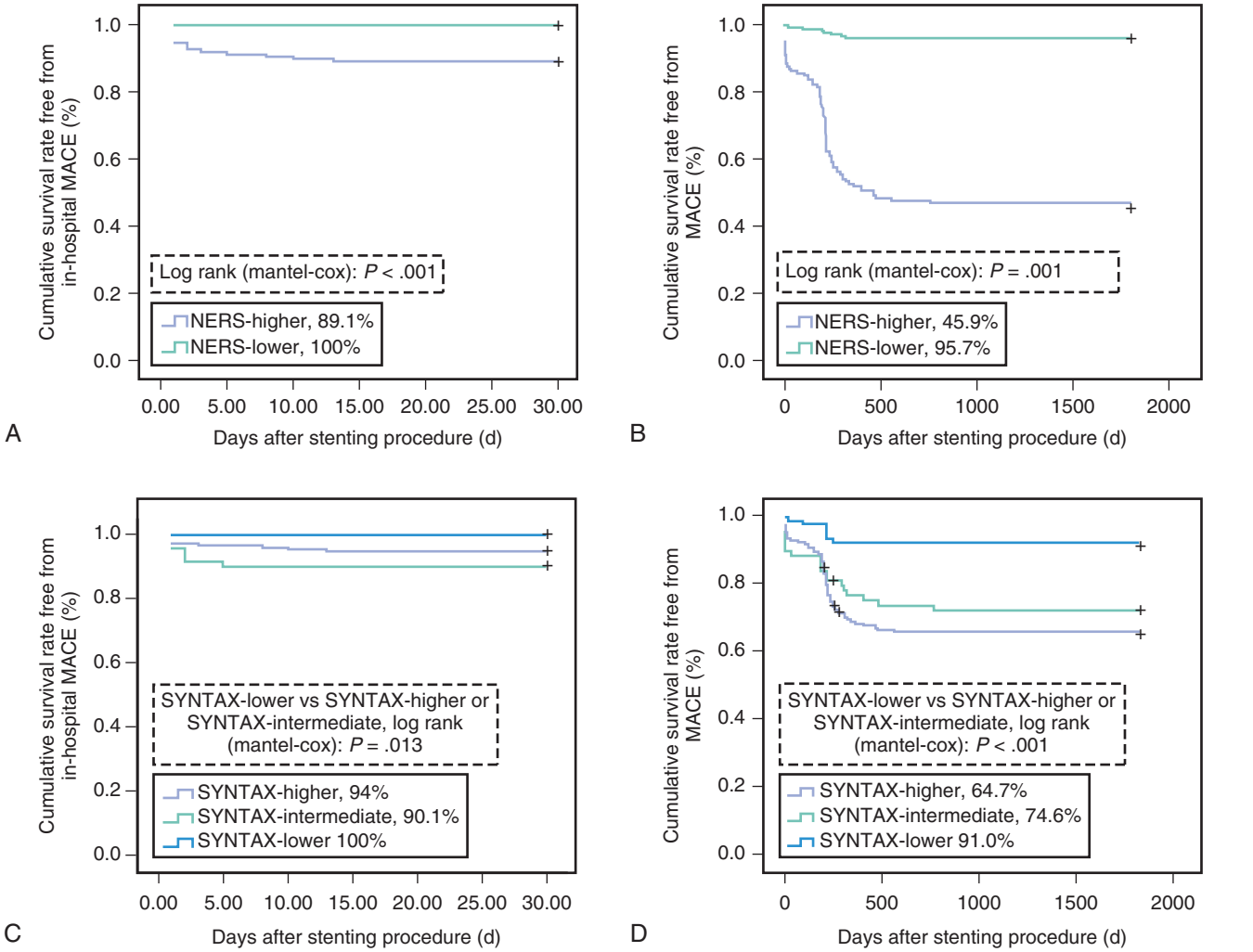


FIGURE 1-11 Comparison of freedom from in-hospital **(A)** and overall major adverse cardiac events (MACEs, **B**) survival between New Risk Stratification (NERS) groups and in-hospital **(C)** and overall MACEs **(D)** survival among SYNTAX groups. (From Chen SL, Chen JP, Mintz G, et al: Comparison between the NERS [New Risk Stratification] score and the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score in outcome prediction for unprotected left main stenting. *JACC Cardiovasc Interv* 3[6]:632-641, 2010.)

Anatomic SYNTAX Score

The anatomic SYNTAX score (http://www.syntaxscore.com) has emerged as an anatomic-based tool to objectively determine the complexity of CAD and to guide decision making between CABG and PCI.[39-42] Since the landmark SYNTAX trial[13-15] to compare CABG with PCI in patients with complex CAD (unprotected left main coronary artery [ULMCA] or de novo three- 3VD), numerous validation studies have confirmed the clinical validity of the SYNTAX score to identify higher-risk subjects and aid decision making between CABG and PCI in a broad range of patient types.[42,43] The SYNTAX score is now advocated in both the European and U.S. revascularization guidelines[46,48,49] as part of the SYNTAX-pioneered heart team approach.[44] In addition, the U.S. Food and Drug Association (FDA) mandates the SYNTAX score as entry criteria in ongoing contemporary stent and structural heart disease trials. Namely, the Evaluation of XIENCE PRIME or XIENCE V Everolimus-Eluting Stent System Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial (ClinicalTrials.gov ID# NCT01205776),[102] and Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate-Risk Subjects Who Need Aortic Valve Replacement (SURTAVI) trial (ID# NCT01586910).

The anatomic SYNTAX score was developed during the design of the SYNTAX trial as a tool to force the interventional cardiologist and cardiac surgeon to systematically analyze the coronary angiogram and to specify the number of coronary lesions that require treatment and assess their angiographic location and anatomic complexity.[13,39-43] The SYNTAX score combines the importance of a diseased coronary artery segment in terms of its severity (i.e., obstructive or occlusive), anatomic location, and importance in supplying blood to the myocardium (*vessel-segment weighting* based on the Leaman Score[103]), adverse lesion characteristics (ACC/AHA lesion classification),[104] bifurcation lesion characteristics (Medina classification[105]), and total occlusion characteristics from Recanalization of Total Coronary Occlusions Using a Laser Guidewire (the European TOTAL Surveillance Study).[106] Each vessel segment 1.5 mm in diameter or greater (Fig. 1-12, labeled 1 through 16) with a 50% or more diameter stenosis by visual estimation is awarded a multiplication factor related to coronary lesion location and severity (see Fig. 1-12, *left*). Further characterization of the coronary lesions leads to the addition of more points (see Fig. 1-12, *right*), which includes features of total occlusions (duration, length, blunt stumps, presence of bridging collaterals or side branch), bifurcation (Medina classification[105]) or trifurcation (number of diseased branches involved), side-branch angulation, aortoostial lesions, severe tortuosity, lesion length greater than 20 mm, heavy calcification, thrombus, and diffuse or small-vessel disease. An online SYNTAX score algorithm[39] automatically summates each of these features to calculate the total SYNTAX score.

Within the SYNTAX trial,[13] the distribution of the SYNTAX score was found to be normal (gaussian) in the randomized PCI and CABG populations with the curves almost being superimposable on each other (E-Fig. 1-2). When the scores of the randomized SYNTAX population were divided into tertiles, the upper boundary of the lowest tertile was 22 (low risk), the second tertile ranged from 23 to 32 (intermediate risk), and the lower boundary for the highest tertile was equal to or greater than 33 (high risk).

Based primarily on the results of the SYNTAX trial,[13-15] current European revascularization guidelines[46] give subjects with 3VD and low SYNTAX scores (0 to 22) a class I recommendation, level of evidence (LOE) A, for CABG and a class IIa LOE B recommendation for PCI. In subjects with ULMCA disease and low to intermediate SYNTAX scores (<33), a class I LOE A recommendation is given for CABG and IIb B for PCI. Furthermore, U.S. guidelines now give surgical revascularization for ULMCA disease a class I B recommendation[48,49] compared with a class I A recommendation in previous guidelines.[107]

Functional SYNTAX Score

PCI guided by the assessment of the functional significance of a lesion using fractional flow reserve (FFR) has been shown to improve clinical outcomes.[108] FFR requires the intravenous administration of adenosine to induce maximal hyperemia to allow measurement. The functional SYNTAX score uses the principle of the functional assessment of coronary lesions to determine the SYNTAX score, rather than the angiographic determination of the SYNTAX score based on visual assessment, as is undertaken in conventional SYNTAX score calculations. In a retrospective subanalysis of almost 500 patients (n = 497) from the FFR-guided arm of the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study, the primary benefit appeared in reclassifying higher-risk groups into lower-risk categories without any adverse sequelae in terms of MACEs and death or MI at 1 year.[30]

It should be emphasized that subjects in the FAME study had substantially less complex CAD (mean SYNTAX score 14.8 ± 6.0) compared with the PCI arm of the SYNTAX trial (mean SYNTAX score 28.4 ± 11.5), and that subjects with left main CAD were not investigated. Prospective validation studies of the functional SYNTAX score in complex CAD were ongoing at the time of this writing (SYNTAX II trial [NCT02015832] and FAME 3 [NCT02100722]).

Augmenting the Anatomic SYNTAX Score With Clinical Factors and the Personalization of Decision Making: Development of SYNTAX Score II

Since the SYNTAX score was developed, limitations of this scoring system to aid decision making between CABG and PCI became evident—namely, the lack of clinical variables and lack of a personalized approach to decision making. Below is a brief overview of the "development phase" leading to SYNTAX Score II, which was designed to overcome these limitations (see Table 1-6).

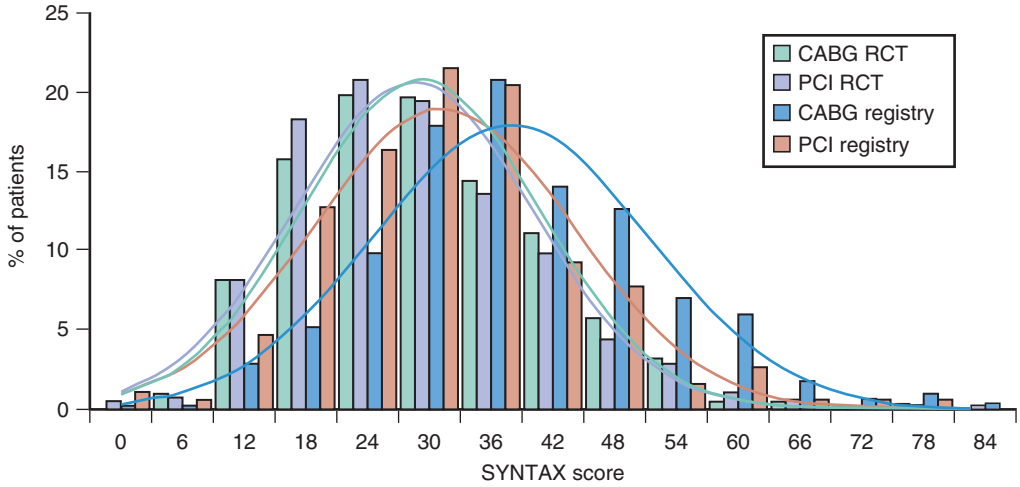
Age, Serum Creatinine, and Ejection Fraction

As described earlier, Ranucci and colleagues[56,82,83] developed a simple risk model that consisted of only three clinical variables—age, serum creatinine, and LVEF—for assessing operative mortality risk in elective cardiac operations (ACEF score, see Fig. 1-7). Based on the law of parsimony, or "Occam's razor," whereby a simple model can explain a phenomenon with the same level of accuracy as complex models, ACEF was shown to be least comparable to the EuroSCORE (composed of 17 variables)[52,53] in predicting in-hospital mortality after CABG.[56,83]

The three risk factors used in ACEF are natural continuous variables that are objectively defined and not subject to personal estimation (e.g., whether the patient has diabetes or extracardiac arteriopathy). In addition, the variables of ACEF were known independent risk factors for mortality, and it was subsequently shown that the end-organ manifestations of the risk factor as identified in ACEF were more important for predicting long-term prognosis rather than the actual presence of the risk factor.[6,82,109,110]

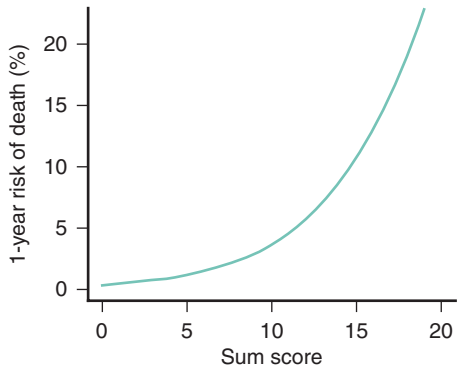
Clinical SYNTAX Score/Logistic Clinical SYNTAX Score

Based on the principle of ACEF, the clinical SYNTAX score,[84,111,112] and subsequently the logistic clinical SYNTAX score (E-Fig. 1-3)[113,114] were developed and validated. Both the clinical SYNTAX score and logistic clinical SYNTAX score combined ACEF with the SYNTAX score and were shown to improve mortality predictions, compared with the SYNTAX score alone, in subjects with complex CAD.[84,111-114] Similar to the conventional SYNTAX score, the clinical SYNTAX score relied on categorization of risk into low, intermediate, and high groups and was able to only identify a high-risk group after PCI.[84,111,112] The logistic clinical SYNTAX score was designed to individualize risk and provide 1-year mortality predictions in an all-comers PCI population irrespective of clinical presentation (except cardiogenic shock).[113,114]



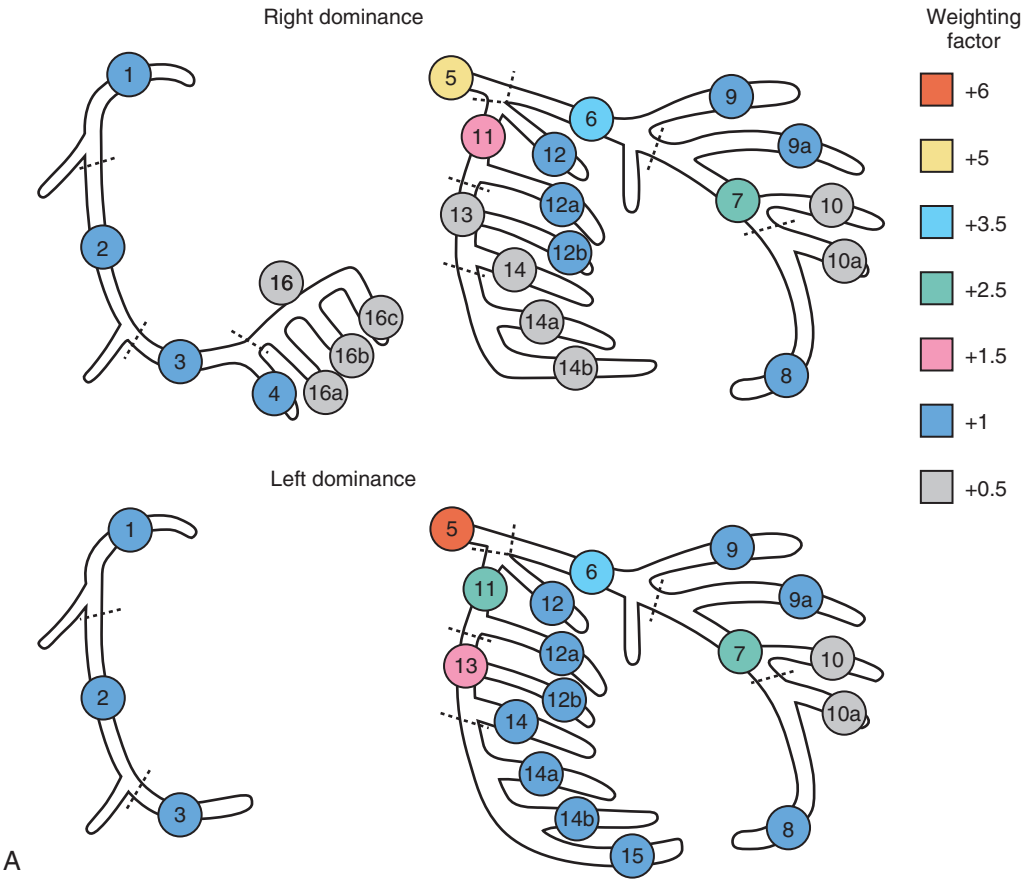
E-FIGURE 1-2 The distribution of the SYNTAX score in the randomized and nested registry percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) populations from the SYNTAX trial. Note how the distributions for both the randomized PCI and CABG populations are almost superimposable on each other, whereas the nested registries are shifted to the right.[13,42] (Reprinted with permission from Serruys PW, Onuma Y, Garg S, et al: Assessment of the SYNTAX score in the SYNTAX study. *EuroIntervention* 5[1]:50-56, 2009.)

	Points	Score
SYNTAX score	see below	
Age (years)	see below	
CrCl (mL/min)	see below	
LV ejection fraction	see below	
'SYNTAX-like' patient*	3	
	Sum score	



SYNTAX score	≤17	18–22	23–27	28–32	≥ 33			
	0	**1**	**2**	**3**	**4**			
Age (years)	<50	50–54	55–59	60–64	65–69	70–74	75–79	≥80
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
CrCl (mL/min)	<30	30–59	60–89	≥90				
	3	**2**	**1**	**0**				
LV ejection fraction (%)	<30	30–34	35–39	40–44	45–49	≥50		
	10	**8**	**6**	**4**	**2**	**0**		

E-FIGURE 1-3 The Logistic Clinical SYNTAX Score. (From Farooq V, Vergouwe Y, Généreux P, et al: Prediction of 1-year mortality in patients with acute coronary syndromes undergoing percutaneous coronary intervention: validation of the logistic clinical SYNTAX (Synergy Between Percutaneous Coronary Interventions With Taxus and Cardiac Surgery) score. *JACC Cardiovasc Interv* 6[7]:737-745, 2013.)



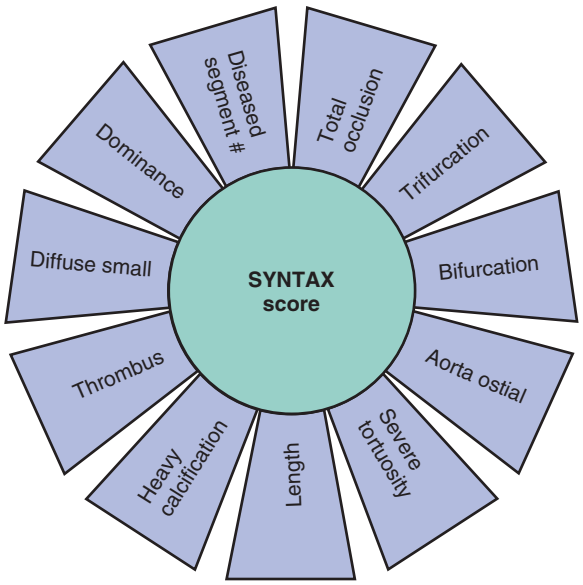


FIGURE 1-12 Coronary tree segments and their importance in supplying blood flow to the left ventricle (vessel segment weighting factors; Leaman score[132,133]) based on the presence of a right or left dominant system (*left image*).[103] A multiplication factor of two is used for nonocclusive lesions (50% to 99% diameter stenosis) and five for occlusive (100% diameter stenosis) lesions. For example, a nonocclusive stenotic proximal left anterior descending coronary artery (LAD) lesion (segment 6) would have a weighting factor of 3.5 × 2 (7 points) and an occlusive proximal LAD lesion a weighting factor of 3.5 × 5 (17.5 points). Other adverse lesion characteristics considered in the SYNTAX score have an additive value (*right image*). (Images courtesy the SYNTAX Trial Investigators.)

The logistic clinical SYNTAX score was developed and cross-validated (internal-external validation procedure[115]) in over 6000 subjects from seven contemporary coronary stent trials[113] and was further externally validated in 2627 subjects presenting with non–ST-elevation ACS and undergoing PCI from the ACUITY trial.[114] Notably, the addition of six clinical variables, including diabetes, to the logistic clinical SYNTAX score led to only a minor incremental benefit in improving risk predictions.[113,114] Thus the logistic clinical SYNTAX score was shown to follow the law of parsimony, as seen with the surgical ACEF model discussed previously,[56,82,83] and the end-organ manifestations of the risk factor were found to be more important for predicting prognosis than the actual presence of the risk factor.

Global Risk

In the SYNTAX trial, as well as the SYNTAX score in PCI subjects, it was shown that the EuroSCORE[52,53] is an independent predictor of

GLOBAL RISK

EuroSCORE	SYNTAX score		
	≤22	23–32	≥33
0–2	LOW	LOW	INT
3–5	LOW	LOW	INT
≥6	INT	INT	HIGH

LOW Global Risk: SYNTAX score <33 and EuroSCORE <6
Int Global Risk: SYNTAX score <33 and EuroSCORE ≥6
OR EuroSCORE <6 and SYNTAX score ≥33
High Global Risk: SYNTAX score ≥33 and EuroSCORE ≥6

FIGURE 1-13 The Global Risk matrix. (From Serruys PW, Farooq V, Vranckx P, et al: A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX Trial at 3 years. *JACC Cardiovasc Interv* 5[6]:606-617, 2012.)

MACEs in subjects undergoing surgical or percutaneous revascularization. Subsequently, it was hypothesized that the amalgamation of the anatomic SYNTAX score with the EuroSCORE could improve decision making between CABG and PCI (Fig. 1-13).[42] The feasibility of this "global risk" approach was demonstrated in a registry of 255 subjects with left main CAD using tertiles of the SYNTAX score and tertiles of the additive EuroSCORE that reflected the study population.[116] Subsequently, the global risk was validated in the SYNTAX trial using conventional tertiles of the SYNTAX score and EuroSCORE,[117] and compared with the SYNTAX score alone, it was shown to substantially enhance the identification of low-risk patients with ULMCA disease or de novo 3VD who could safely and efficaciously be treated with CABG or PCI.

One of the unexpected findings from the Global Risk was that higher-risk subjects (high additive EuroSCORE ≥6) in all tertiles of the SYNTAX score were shown to have a potential prognostic benefit from undergoing CABG compared with PCI irrespective of the baseline SYNTAX score, provided an acceptable threshold of operative risk was not exceeded.[117] For example, in the 3VD cohort of the SYNTAX trial, subjects with a low SYNTAX score (<23) and a high EuroSCORE (≥6) had a doubling of 3-year mortality when undergoing PCI (15.9%) compared with CABG (8.2%). Hypotheses to explain these findings included that the bypass graft would potentially "protect" the entire treated coronary vessel from future cardiac events for the life span of the graft in high-risk subjects compared with PCI, which would treat the individual lesion.[37] Based on these observations, it was hypothesized by the investigators that subjects of opposite risk concealed each other; for example, low-risk subjects were potentially concealed by high-risk subjects, and vice versa, in all tertiles of the SYNTAX score. This hypothesis is what prompted the investigators to develop a more individualized approach to decision making between CABG and PCI, and it is what subsequently led to the development of SYNTAX Score II,[7] as detailed below.

SYNTAX Score II

As previously discussed, the combination of the anatomic SYNTAX score with ACEF contained most of the prognostic information in predicting mortality after CABG (excluding the anatomic SYNTAX score[56,82,83,117]) or PCI (including the anatomic SYNTAX score[113]). SYNTAX Score II[7,8] augments the purely anatomic SYNTAX score with anatomic and clinical factors that were shown to alter the threshold value of the anatomic SYNTAX score in order for equipoise to be achieved between CABG and PCI for long-term mortality. This was accomplished through building SYNTAX Score II on the ACEF "skeleton" with the addition of risk factors that were shown to directly affect decision making between CABG and PCI through interaction effects (i.e., a risk factor being more predictive of mortality in patients undergoing PCI compared with CABG, or vice versa; Fig. 1-14). For example, the anatomic SYNTAX score aids decision making between CABG and PCI because it is more predictive of clinical outcomes in patients undergoing PCI, compared with patients undergoing CABG, in whom it is not predictive. Based on this principle, younger age, female sex, and reduced LVEF favored CABG compared with PCI on long-term prognostic grounds (E-Fig. 1-4). Thus in such patients a *lower* anatomic SYNTAX score would be required for the long-term mortality risk to be similar between CABG and PCI. By contrast, older age, chronic obstructive pulmonary disease (COPD), or ULMCA disease favored PCI compared with CABG (see E-Fig. 1-4) and thus, in this type of patient, a *higher* anatomic SYNTAX score would be needed for the long-term mortality risks to be similar.

By adopting the individualized approach of SYNTAX Score II, augmented by clinical variables, it was shown that subsets of patients existed in all tertiles of the SYNTAX score in which CABG or PCI would confer a mortality benefit or offer a similar long-term prognosis (Fig. 1-15).[7] A nomogram was developed (Fig. 1-16) that allowed for an accurate individualized prediction of 4-year mortality in patients proposing to undergo CABG or PCI to objectively aid decision making. For example, a 60-year-old man with an anatomic SYNTAX score of 30, ULMCA disease, a creatinine clearance of 60 mL/min, an LVEF of 50%, and COPD would have 41 points (predicted 4-year mortality 16.3%) and 33 points (predicted 4-year mortality 8.7%) to undergo CABG and PCI, respectively. The same example, without COPD included, would lead to identical points (29 points) and identical 4-year mortality predictions (6.3%) for CABG and PCI. An online version of SYNTAX Score II, version 2.11 using the 4-year data, is now available as a download along with the original SYNTAX score calculator (www.syntaxscore.com).

Diabetics

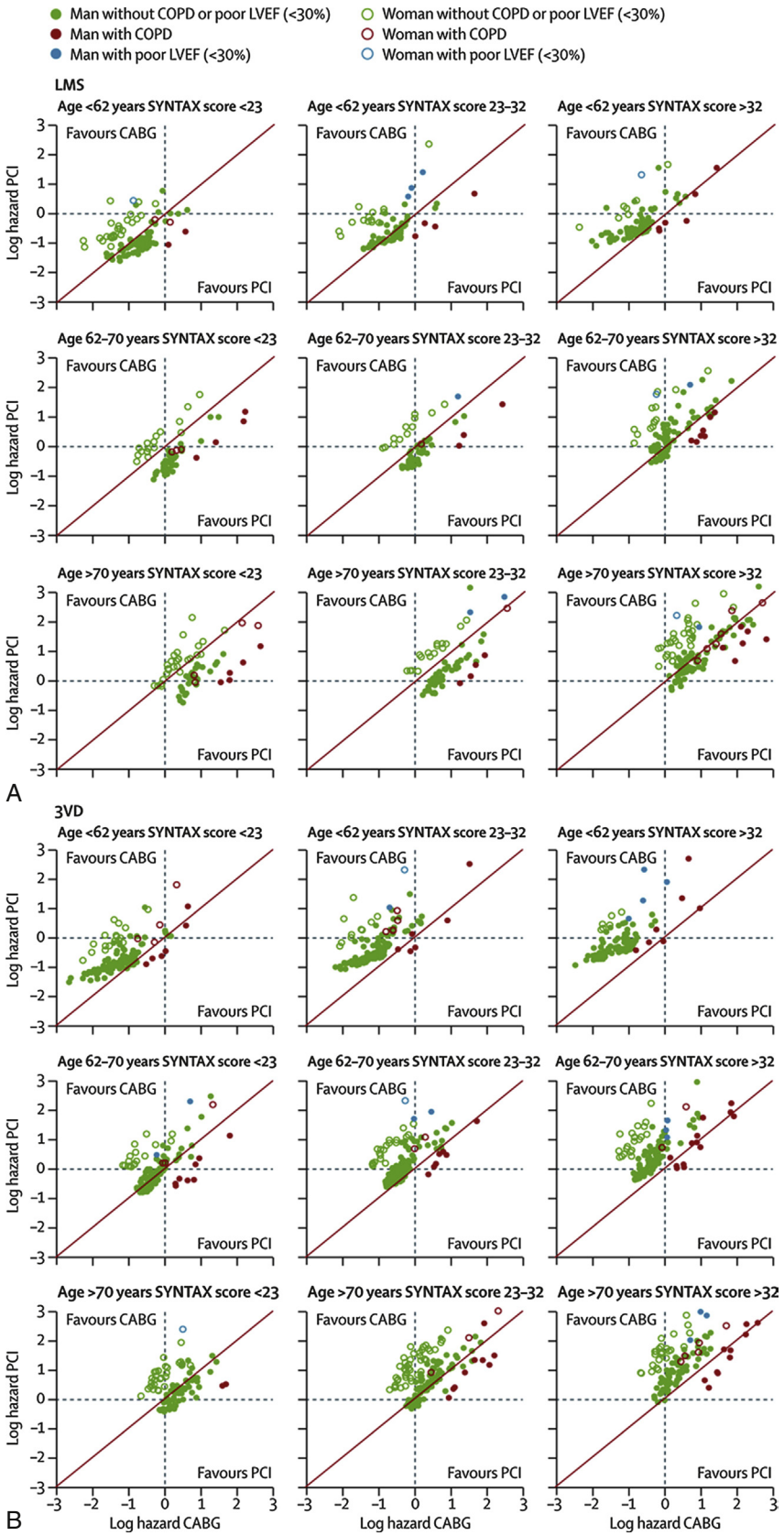
Notably, diabetes was not included in the final SYNTAX Score II despite medically treated diabetes being prestratified at randomization as a powered subgroup in the SYNTAX trial and present in over a quarter of the study patients (26%), this in spite of diabetes being perceived as a specific high-risk group potentially warranting a differing treatment strategy compared with that considering other risk factors.[11,46,48,49] The primary reason was that diabetes was shown not to be important for decision making between CABG and PCI because it lacked an interaction effect, that is, it was equally predictive of mortality in the CABG and PCI arms after adjustment for other risk factors (see Fig. 1-14). As previously discussed in ACEF, the end-organ manifestations of diabetes are what affected long-term mortality in CABG and PCI populations.[6,45,82,83,113] The findings of the lack of inclusion of diabetes in SYNTAX Score II are supported by epidemiologic data, in which nondiabetics with chronic kidney disease and proteinuria had a stronger association with risk of MI and a higher rate of mortality compared with diabetics, and that the relative risk of long-term mortality associated with chronic kidney disease was "much the same irrespective of the presence or absence of diabetes."[109,110]

Impaired Left Ventricular Ejection Fraction

Within SYNTAX Score II, impaired LVEF favored CABG over PCI on long-term prognostic grounds, findings supported by a recent subanalysis of the Surgical Treatment of Ischemic Heart Failure (STICH) trial[118]; namely, that in subjects with more advanced ischemic cardiomyopathy with more extensive CAD and worse myocardial dysfunction and remodeling, a net longer-term prognostic benefit was seen for CABG compared with optimal medical therapy despite the short-term (30-day) mortality risk being higher with CABG.

Validation of SYNTAX Score II

Compared with existing revascularization guidelines using the anatomic SYNTAX score,[46,48,49] it was shown that if CABG or PCI was



E-FIGURE 1-4 Collective effect of the anatomic SYNTAX score and other anatomic and clinical variables on mortality predictions in the left main stem (LMS, **A**) and three-vessel disease (3VD, **B**) cohorts of the SYNTAX Trial (SYNTAX Score II). Scatter plots are for illustrative purposes only. The diagonal line represents identical mortality predictions for coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). Individual predictions plotted to the left of the diagonal line favor CABG (actual percentages shown in top left corner) and to the right favor PCI (actual percentages shown in bottom right corner). (From Farooq V, van Klaveren D, Steyerberg EW, et al: Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 381[9867]:639-650, 2013.)

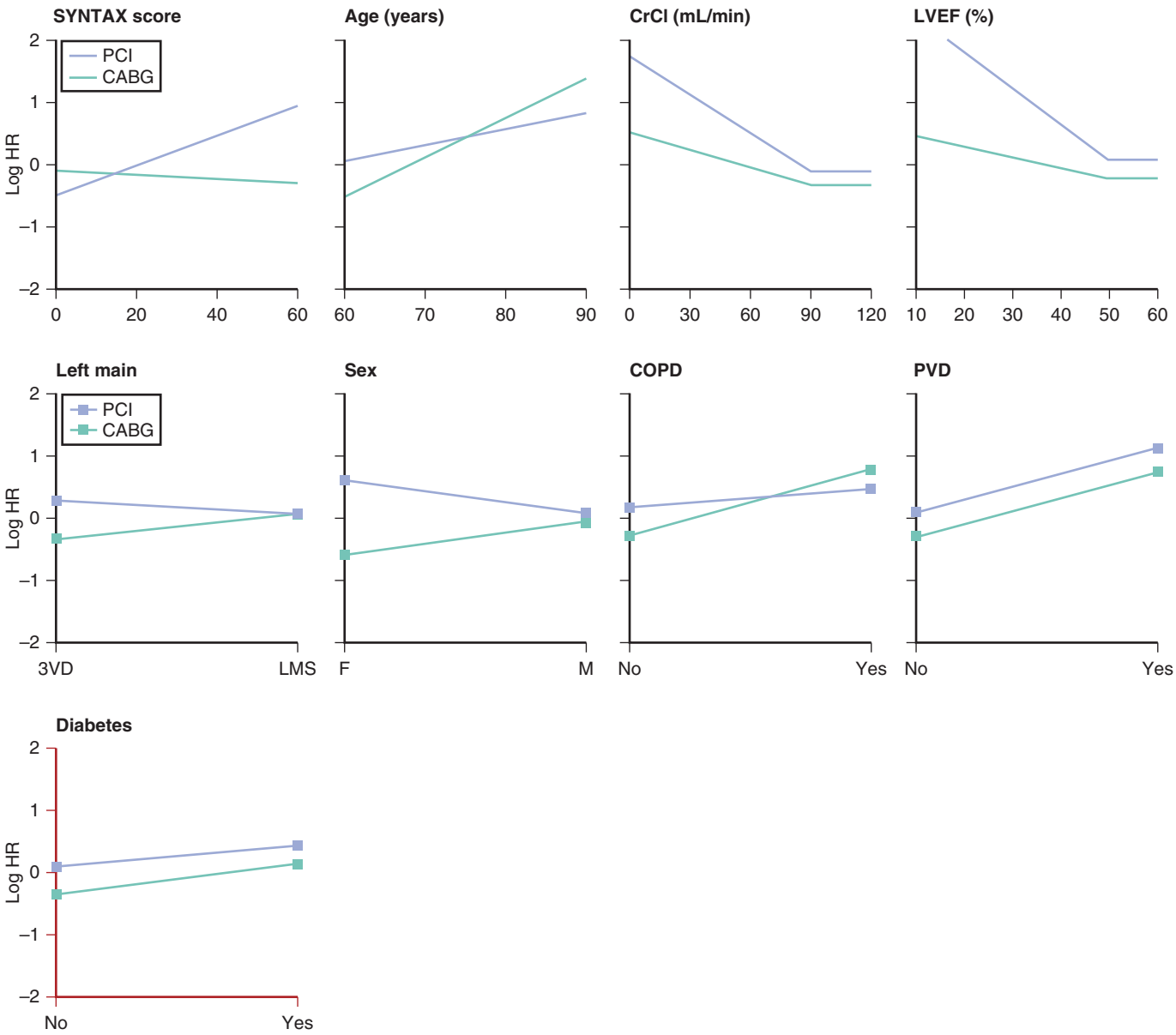


FIGURE 1-14 Predictor effects for coronary artery bypass surgery (CABG) and percutaneous coronary intervention (PCI) in the SYNTAX Score II. These are represented visually as a log hazard ratio (HR) for CABG and PCI on the y-axis for each predictor. Each predictor is expressed on the x-axis continuously (upper) or categorically (lower), for a person of mean baseline characteristics. Diabetes is included (*highlighted in red*) to illustrate its absence of interaction when included in the analyses. Note the differing gradients of the hazards for PCI and CABG, leading to the hazards crossing at an anatomic SYNTAX score of 15. At this crossover point of hazards, the mortality risk is comparable between CABG and PCI. This threshold of crossover of hazards will vary according to the level of other variables, namely, being *lower* for female sex, reduced left ventricular ejection fraction (LVEF) and younger age, and *higher* for chronic obstructive pulmonary disease (COPD), unprotected left main coronary artery (ULMCA) disease, and older age. As both peripheral vascular disease (PVD; $P = 1.00$) and diabetes ($P = .67$) lacked an interaction effect, as indicated by almost parallel HRs (i.e., a comparable increase in mortality risk), their presence would have no impact on decision making between CABG and PCI. (From Farooq V, van Klaveren D, Steyerberg EW, et al: Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 381[9867]:639-650, 2013.)

selected based on a higher or lower expected survival (irrespective of the margin of difference) with SYNTAX Score II in the SYNTAX trial, SYNTAX Score II would only need to be used in 110 patients to have one more patient alive at 4 years.[8]

External validation of SYNTAX Score II[7] was performed in the multinational Drug-Eluting Stent for Left Main Coronary Artery Disease (DELTA) registry (14 centers in Europe, the United States, and South Korea)[119] composed of subjects with ULMCA disease with or without multivessel disease (26% of the study population had 3VD). All variables in SYNTAX Score II interacted in a similar way and therefore influenced decision making between CABG and PCI in the SYNTAX trial and DELTA registry with the exception of age and LVEF,

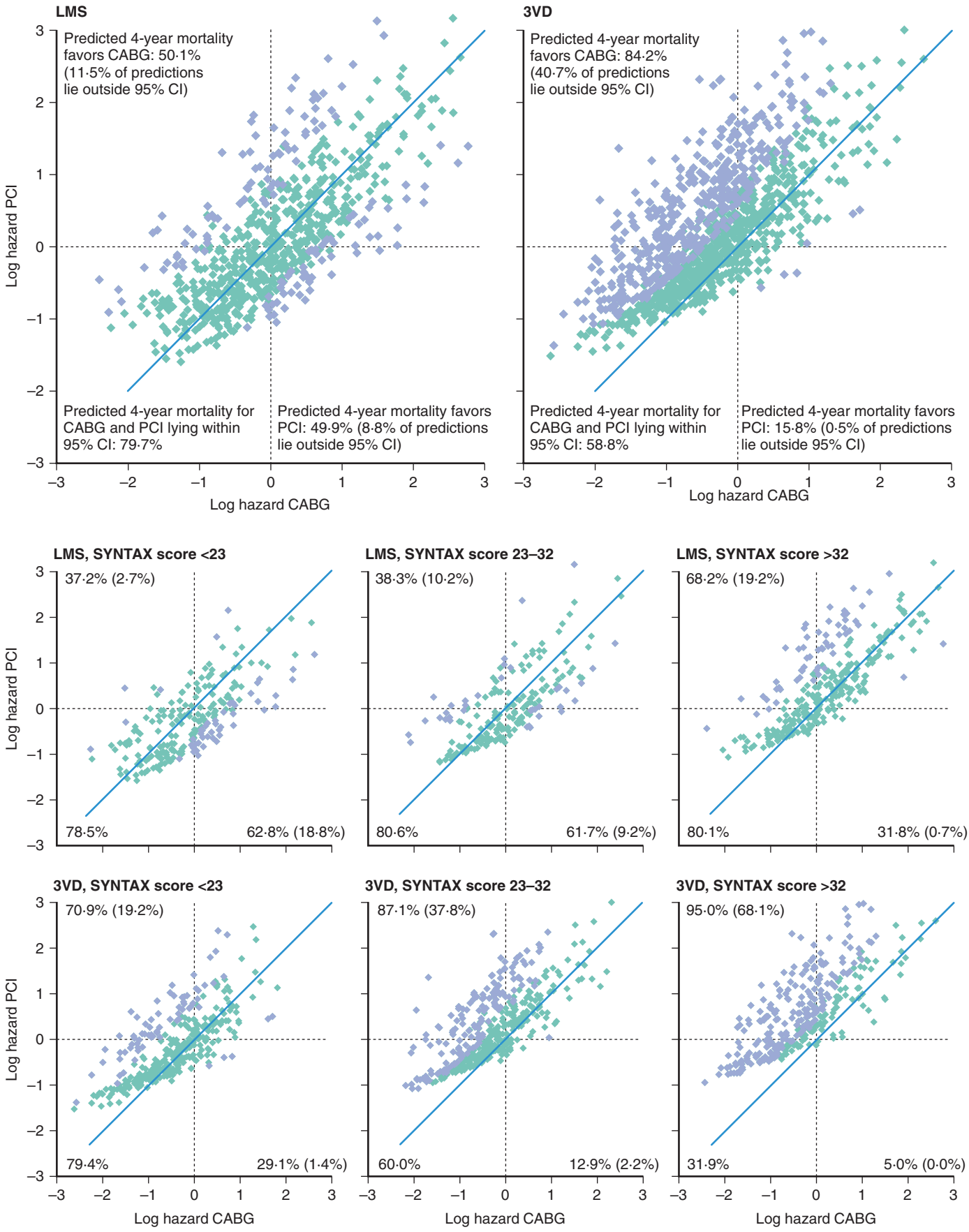

LMS
Predicted 4-year mortality favors CABG: 50·1% (11·5% of predictions lie outside 95% CI)
Predicted 4-year mortality for CABG and PCI lying within 95% CI: 79·7%
Predicted 4-year mortality favors PCI: 49·9% (8·8% of predictions lie outside 95% CI)
3VD
Predicted 4-year mortality favors CABG: 84·2% (40·7% of predictions lie outside 95% CI)
Predicted 4-year mortality for CABG and PCI lying within 95% CI: 58·8%
Predicted 4-year mortality favors PCI: 15·8% (0·5% of predictions lie outside 95% CI)
LMS, SYNTAX score <23
37·2% (2·7%)
78·5%
62·8% (18·8%)
LMS, SYNTAX score 23–32
38·3% (10·2%)
80·6%
61·7% (9·2%)
LMS, SYNTAX score >32
68·2% (19·2%)
80·1%
31·8% (0·7%)
3VD, SYNTAX score <23
70·9% (19·2%)
79·4%
29·1% (1·4%)
3VD, SYNTAX score 23–32
87·1% (37·8%)
60·0%
12·9% (2·2%)
3VD, SYNTAX score >32
95·0% (68·1%)
31·9%
5·0% (0·0%)
Log hazard PCI
Log hazard CABG
3
2
1
0
−1
−2
−3

FIGURE 1-15 Mortality predictions for coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) for each individual patient in the randomized SYNTAX trial. The SYNTAX trial included 1800 participants, separated into left main stem (LMS) cohort and three-vessel disease (3VD) cohort (*upper panels*), and by tertiles of the anatomic SYNTAX score (*lower panels*). The diagonal line represents identical mortality predictions for CABG and PCI. Individual predictions plotted to the left of the diagonal line favor CABG (actual percentages shown in top left corner), and to the right favor PCI (actual percentages shown in bottom right corner). Individual mortality predictions for CABG or PCI that could be separated with 95% confidence ($P < 0.05$) are colored blue (actual percentage shown in parentheses in respective corners). Mortality predictions that could not be separated with 95% confidence ($P > .05$) are highlighted in green and identify patients with similar 4-year mortality. Percentages of patients in each category are shown. (From Farooq V, van Klaveren D, Steyerberg EW, et al: Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 381[9867]:639-650, 2013.)

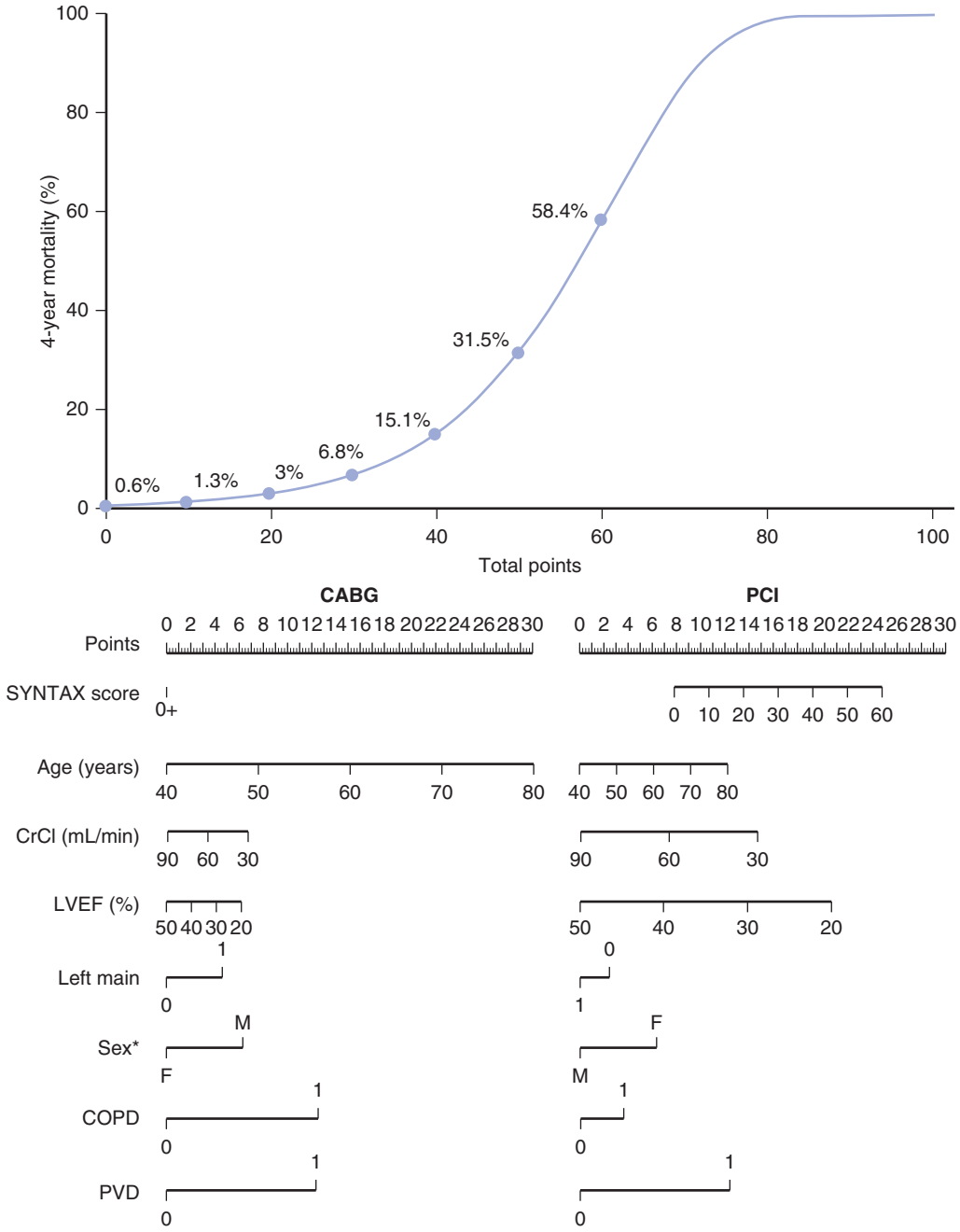


FIGURE 1-16 The SYNTAX Score II nomogram for bedside application. Total number of points for eight factors can be used to accurately predict 4-year mortality for the individual patient proposing to undergo for coronary artery bypass grafting (CABG) or percutaneous coronary artery intervention (PCI). (From Farooq V, van Klaveren D, Steyerberg EW, et al: Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 381[9867]:639-650, 2013.)

which had minimal interactions in the DELTA registry—findings that may relate to the unavoidable selection bias inherent to all registries because decision making between CABG and PCI has already been made and would be difficult to control for.[120] Even randomized trials that lack an all-comers design, with restrictive inclusion and exclusion criteria, can potentially make application to clinical practice questionable.[37,38,121] This was exemplified in a recent meta-analysis of randomized trials undertaken prior to SYNTAX that compared PCI against CABG, where in most trials, 2% to 12% (see Table 1-3) of screened subjects were randomized due to the highly restrictive inclusion and exclusion criteria.[122] In this meta-analysis, CABG was shown to be favored in older subjects, and PCI was favored in younger subjects,[122] findings that have since been directly contradicted by SYNTAX Score II in the all-comers SYNTAX trial in which the opposite was shown.[7] Hence "randomized" or prospective validation of SYNTAX Score II was proposed[7] in which further validation would be conducted in randomized controlled trials or prospectively run studies.

Further retrospective validation of SYNTAX Score II has recently been undertaken in 3896 patients with 3VD and/or ULMCA disease undergoing PCI (n = 2190) or CABG (n = 1796) from the Japanese Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) PCI/CABG multicenter registry.[123]

Prospective validation of SYNTAX Score II is ongoing in two separate studies. The international multicenter EXCEL trial recently completely recruitment of 1905 patients with ULMCA disease and investigator-reported SYNTAX scores less than 33, who were randomized to CABG (n = 957) or PCI with contemporary stents (n = 948). The primary end point is a composite measure of all-cause death, MI, or stroke at 3 years after revascularization.[102] As part of the prospective validation of SYNTAX Score II, it is currently being been used to forecast and compare 4-year mortality in the PCI and CABG arms of EXCEL. In the ongoing SYNTAX II trial (NCT02015832), SYNTAX Score II is being used as a tool to recruit subjects with de novo 3VD (without LM involvement) on the grounds of patient safety—that is, subjects with a similar long-term mortality between CABG and PCI—in conjunction with the heart team. Notably, subjects from all tertiles of the SYNTAX score are eligible. The PCI procedure will be guided by a functional assessment of all three vessels (functional SYNTAX score[7]), a newer-generation stent platform with a biodegradable polymer,[30] and IVUS-guided stent implantation.[124,125] The PCI and CABG arms of the SYNTAX trial[15,27] will act as control arms.

Tools for Assessment of Completeness of Revascularization

Interpreting the long-term prognostic impact of incomplete revascularization in patients with complex CAD has historically remained difficult.[126] The lack of standardized definitions of incomplete revascularization have confounded this issue and have made comparisons between studies difficult. In the SYNTAX trial, *complete revascularization* was defined as the treatment of any lesion with more than 50% diameter stenosis in vessels 1.5 mm or larger as estimated on the diagnostic angiogram during the local heart team conference and deemed appropriate for revascularization.[127,128] In SYNTAX, incomplete revascularization was shown to be linked to adverse long-term clinical outcomes, including mortality, in surgical and percutaneously treated patients (Fig. 1-17). The residual and post-CABG SYNTAX scores were designed to quantify the degree of incomplete revascularization and allow for a threshold of incomplete revascularization that would not have a negative impact on long-term clinical outcomes (i.e., reasonable incomplete revascularization).

Residual SYNTAX Score

The residual SYNTAX score is based on the principle of being a measure of the myocardial ischemic burden dependent on the location of the coronary disease, its importance in supplying blood to the myocardium, and the anatomic complexity (e.g., calcification, bifurcation, long lesion, etc.) associated with the obstructive disease. The residual SYNTAX score is essentially the SYNTAX score recalculated after the PCI procedure, and it provides an objective quantitative measure of the degree and complexity of residual stenosis after revascularization. More proximal CAD scores higher on the residual SYNTAX score because this is dependent on the vessel segment weighting as previously discussed (see Fig. 1-12), particularly if the obstructive disease is more complex.[129,130]

Généreux and colleagues[129] first demonstrated that a residual SYNTAX score greater than 8 after PCI was associated with adverse 1-year mortality in a post hoc analysis of the ACUITY trial, which consisted of subjects with moderate to high-risk ACS undergoing PCI and substantially less complex CAD (median SYNTAX score 9.0, interquartile range [IQR] 5.0 to 16.0) compared with those in the SYNTAX trial (median SYNTAX score 28, IQR 20.0 to 36.0).

The residual SYNTAX score was subsequently validated in the randomized, all-comers SYNTAX trial, which comprised subjects with complex CAD (ULMCA or de novo 3VD) at the final 5-year follow-up.[130] The previous findings, of residual SYNTAX score greater than 8 being associated with adverse long-term clinical outcomes in the ACUITY trial,[129] were found to be of equal importance in SYNTAX patients who underwent 5-year follow-up. Notably, as the baseline SYNTAX score increased, the frequency of a residual SYNTAX score greater than 8 increased in unison, with an associated increase in long-term mortality (Fig. 1-18). In addition, progressively higher residual SYNTAX scores were shown to be a surrogate marker of sicker patients,[128] with greater baseline clinical comorbidity and anatomic complexity and consequent adverse long-term clinical outcomes, including all-cause mortality.

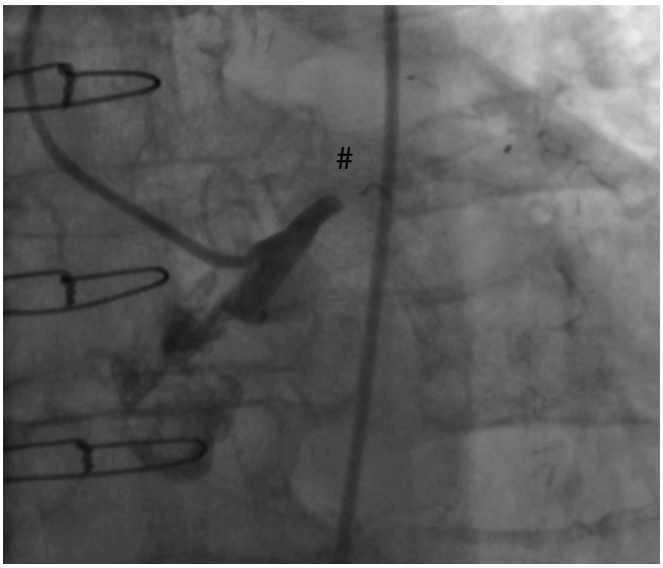
Stratified analyses in the powered subgroups of ULMCA disease and medically treated diabetes showed that a residual SYNTAX score greater than 8 was associated with adverse long-term clinical outcomes, including mortality. Stratified analyses in subjects with reduced LVEF also showed the results to be equally applicable, whereas in subjects with total occlusions, a more modest effect was shown that did not reach statistical significance. The latter perhaps implied that appropriate viability assessment was required to ensure that revascularization of the total occlusion was appropriate and clinically justified.[131]

In summary, the residual SYNTAX score allowed for the quantification of the degree of revascularization and for determination of an objective level of reasonable incomplete revascularization,[126] whereby a threshold value could be determined (≤8) that would not have a negative impact on long-term mortality and other clinical outcomes.

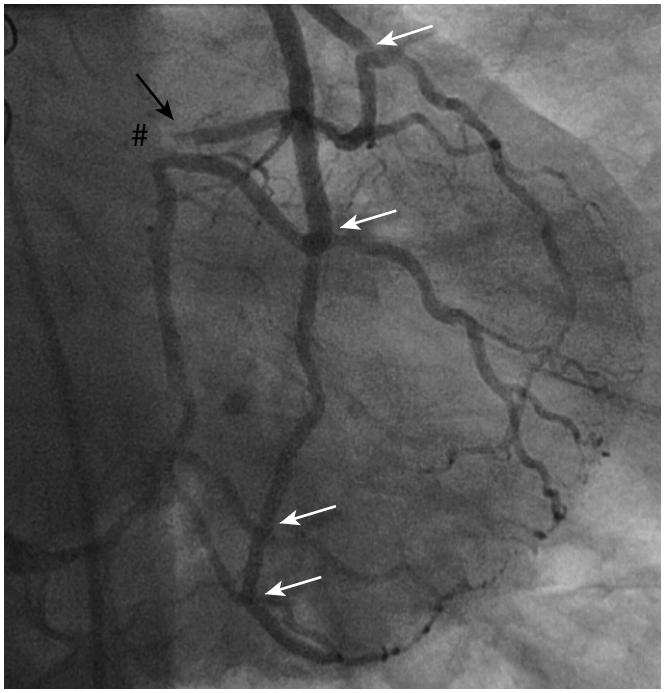
Post–Coronary Artery Bypass Grafting SYNTAX Score

The CABG equivalent of the residual SYNTAX score, the post-CABG SYNTAX score, has recently been shown to be linked to adverse 5-year clinical outcomes, including mortality, in the angiographic substudy of the SYNTAX trial (SYNTAX–LE MANS [Left Main Coronary Artery Stenting]; Fig. 1-19).[132,133] Because of the inherently differing mechanisms of treatment of CAD with CABG and PCI, calculation of the residual SYNTAX score (i.e., the burden of coronary disease removed by PCI) differs from that of the post-CABG SYNTAX score (i.e., coronary disease bypassed with a graft). The basic principle of the post-CABG SYNTAX score is that it deducts points from the "native" baseline SYNTAX score based on the level of "protection" conferred by the bypass grafts, through deduction of the vessel-segment weighting (Leaman Score,[103] see Fig. 1-12) that the bypass graft provides (E-Fig. 1-5). Because the post-CABG SYNTAX score is based on validated physiologic principles of blood flow (Leaman Score[103]), it does not arbitrarily deduct points for the type of bypass graft anastomosed. Points related to native coronary disease (e.g., bifurcation disease, calcification, total occlusions, long lesions, diffuse disease, etc.) remain unaltered.

Historical evidence to back the findings from the post-CABG SYNTAX score being linked to adverse long-term prognosis comes from the Coronary Artery Surgery Study (CASS)[134] and Rotterdam[135] registries. In both studies, more extensive preoperative CAD was linked to the higher prevalence and severity of other clinical risk factors and adverse long-term prognosis compared with subjects with



Native syntax score: 39



Inverse LIMA Y Graft LAD, OM 1-3:
deduct occluded segments 6 and 11
weighting: (3.5×5) + (2.5×5)= -30 points

CABG SYNTAX Score: 9

E-FIGURE 1-5 Application of noninvasive fractional flow reserve (FFR) technology during multislice computed tomography (MSCT) in subject with coronary artery disease. Figures shown are the noninvasive calculated FFR in all major epicardial vessels and side branches.

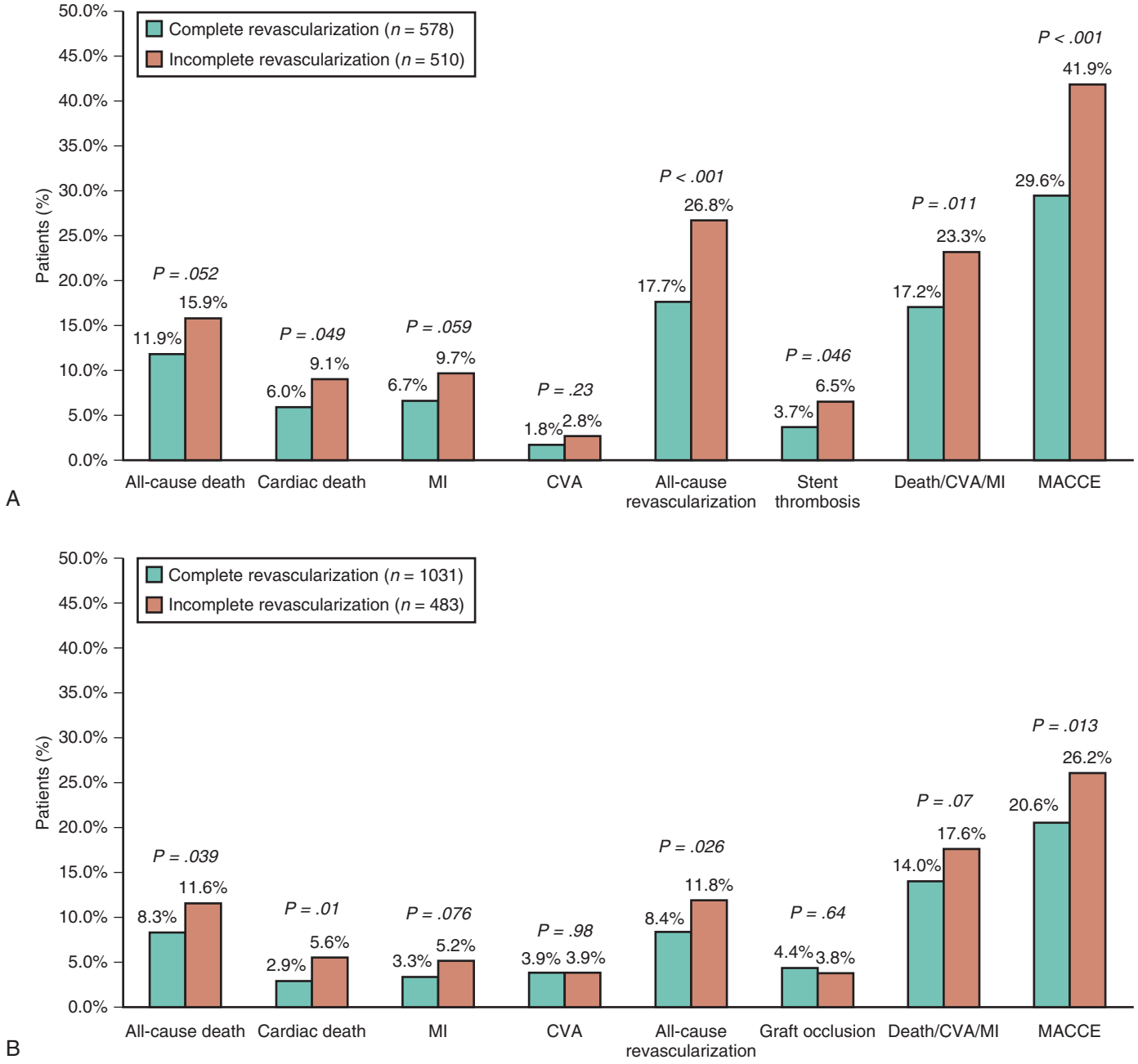


FIGURE 1-17 The residual SYNTAX score (SS) in the SYNTAX Trial. Complete (residual SS = 0) and incomplete (tertiles of the residual SS [residual SS >0]) revascularization, stratified according to tertiles of the baseline SS (*upper*). Kaplan-Meier curves show cumulative event rates through to 5 years, based on complete (residual SS = 0) and incomplete (tertiles of residual SS) revascularization, in the low (0 to 22), intermediate (23 to 32) and high (≥33) baseline SYNTAX scores (*lower*). Note the progressive increase in the frequency of a residual SS above 8 across the tertiles of the baseline SS (*upper*) and its association with adverse long-term mortality (*lower*). (From Farooq V, Serruys PW, Bourantas CV, et al: Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation* 128[2]:141-151, 2013.)

less complex CAD. Further, 5-year follow-up of the BARI trial demonstrated that native coronary disease progression, and not the extent of initial revascularization, was the predominant determinant of the recurrence of angina and jeopardized myocardium in percutaneous and surgically revascularized subjects.[136] Finally, coronary artery calcification has been linked to adverse all-cause mortality at 10 years independent of other risk factors.[137,138] Validation studies of the post-CABG SYNTAX score were anticipated at the time of this writing.

Future Directions

Papadopoulou and colleagues[139] first described the feasibility and reproducibility of a multislice computed tomography (MSCT)-derived SYNTAX score in 80 consecutive patients with symptomatic angina, using definitions of the angiographically defined SYNTAX score adapted for the MSCT capabilities. The underlying concept was to allow for the SYNTAX score to be calculated prior to the intervention to

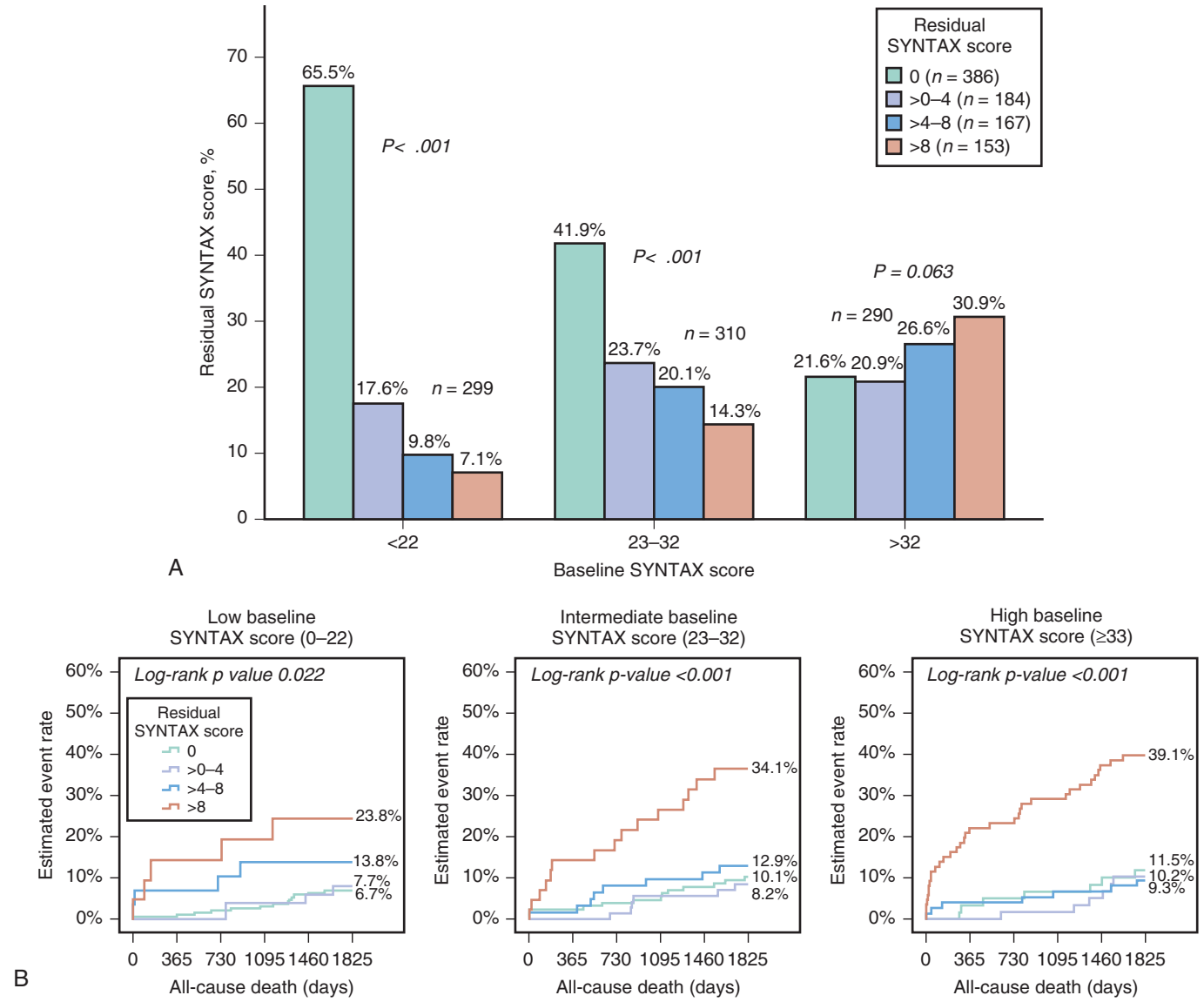
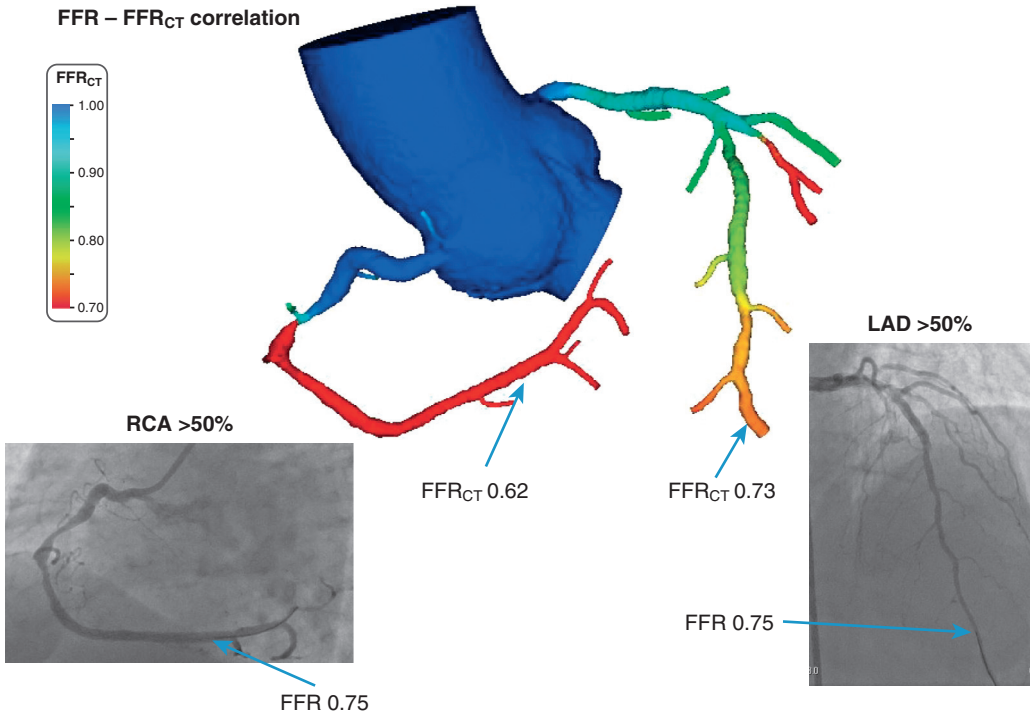


FIGURE 1-18 The post–coronary artery bypass grafting (CABG) SYNTAX score in the angiographic substudy of the SYNTAX trial (SYNTAX-LE MANS). Outcomes (Kaplan-Meier curves) separated by the median of the post-CABG SYNTAX score into low (0 to 21, $n = 58$) and high (≥22, $n = 55$) score groups. At 5 years, significantly greater rates of all-cause mortality (*left image*), all-cause death/cerebrovascular accident (CVA)/myocardial infarction (MI; *middle image*), and major adverse cardiovascular and cerebrovascular events (MACCEs; *right image*) were evident in the post-CABG high SYNTAX score group compared with the low post-CABG SYNTAX score group. Note the peak in MACCEs at approximately 18 months secondary to patients undergoing scheduled coronary angiography, the findings of which triggered repeat revascularization. (From Farooq V, Girasis C, Magro M, et al: The coronary artery bypass graft SYNTAX score: final five-year outcomes from the SYNTAX-LE MANS left main angiographic substudy, *EuroIntervention* 9[8]:1009-1010, 2013.)

potentially aid decision making and optimize patient management. The addition of a noninvasive FFR component (HeartFlow; HeartFlow Inc., Redwood City, CA) has the potential to allow for the noninvasive calculation of a functional MSCT SYNTAX score (E-Fig. 1-6). This technology is based on utilizing computational fluid-dynamic techniques applied to MSCT angiography.[139] Validation data of the noninvasive FFR MSCT has been reported in the Diagnosis of Ischemia-Causing Stenoses Obtained via Non-Invasive Fractional Flow Reserve (DISCOVER FLOW)[42,140] and multicenter Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO) trials.[141] Work is ongoing in deriving a noninvasive functional MSCT SYNTAX score using this technology.

INDIVIDUAL ASSESSMENT FROM A PATIENT'S PERSPECTIVE

The previous discussions have focused entirely on the factors physicians must take into account when making revascularization decisions. However, in the era of increased patient choice and transparency and greater patient involvement in decision making, it is vital to also consider aspects from a patient's perspective through the assessment of health-related quality of life (QoL). However, data on this key topic are limited to only a handful of studies that have assessed PCI in patients receiving DESs. Of note, early studies to compare PCI using a BMS with CABG have indicated a trend toward improved



E-FIGURE 1-6 Comparisons (Kaplan-Meier analyses) of 4-year clinical outcomes in the SYNTAX trial by completeness of revascularization in the All-Comers PCI **(A)** and All-Comers coronary artery bypass grafting **(B)** populations. *CVA,* Cerebrovascular accident; *MACCE,* major adverse cardiac and cerebrovascular event; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention. (From Farooq V, Serruys PW, Garcia-Garcia HM, et al: The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol* 61[3]:282-294, 2013.)

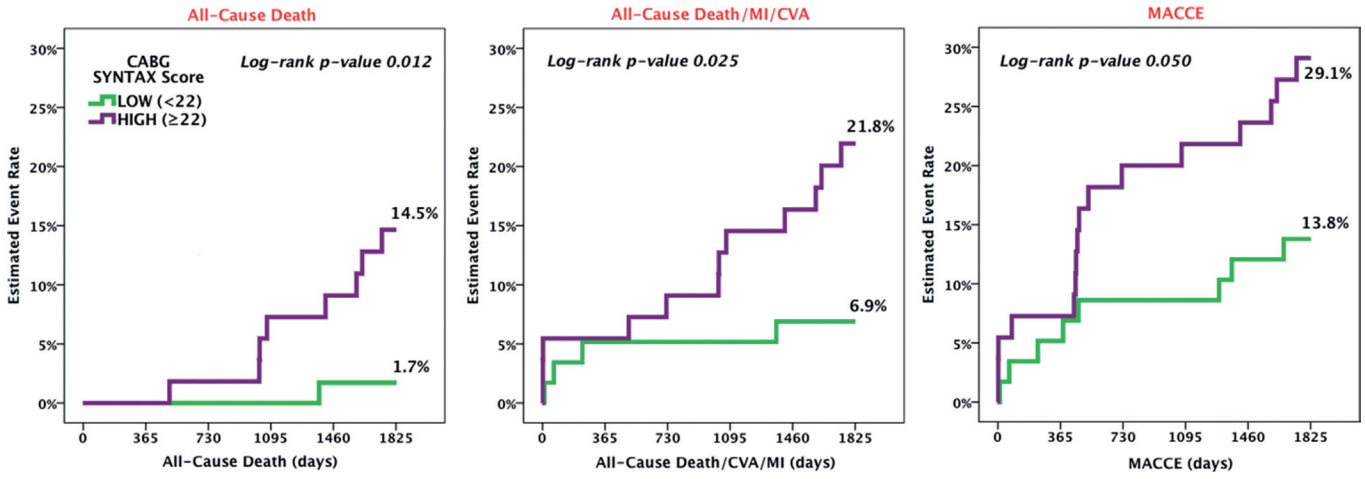


FIGURE 1-19 Example of the calculation of the post–coronary artery bypass grafting (CABG) SYNTAX score. Occluded left main (**#**) in a left dominant system gave a native SYNTAX score of 39 (*upper image*). A patent left internal mammary artery (LIMA) inverse Y graft anastomosed to the mid left anterior descending (LAD) coronary artery (*upper white arrow*), with sequential anastomoses to the first, second, and third obtuse marginal (OM) branches (lower three *white arrows*) are shown. Based on the vessel segment weighting (refer to Fig. 1-12 in text), 17.5 (occluded proximal LAD), and 12.5 (occluded proximal left circumflex artery [LCx]) points were deducted from the native SYNTAX score. Post-CABG SYNTAX score was therefore 39 – 17.5 – 12.5 = 9 points. (Reprinted with permission from Farooq V, Girasis C, Magro M, et al: The CABG SYNTAX Score: an angiographic tool to grade the complexity of coronary disease following coronary artery bypass graft surgery: from the SYNTAX Left Main Angiographic (SYNTAX-LE MANS) substudy, *EuroIntervention* 8[11]:1277-1285, 2013.)

QoL outcomes with CABG driven largely by higher rates of repeat revascularization with BMS use.[17] For example, the Stent or Surgery (SoS) study[142] reported favorable health-related QoL with CABG compared with PCI in terms of reduced angina frequency and physical limitation at 6 months, with the superior reduction in angina frequency maintained out to 12 months. Similarly, at 12-months follow-up in the Medicine, Angioplasty, or Surgery Study (MASS-II),[143] patients treated with CABG had a greater improvement in health-related QoL compared with those treated with PCI and medical therapy. As alluded to previously, analyses derived from data on randomized trials performed in the pre-SYNTAX era should be interpreted with caution, principally because of the profound selection bias in these studies (see Table 1-3) and that they now represent outdated revascularization practices.

Data on QoL from patients treated with a DES and CABG are limited to the 12-month results from the SYNTAX trial, 3-year results from the ARTS-II study, and a minimum follow-up of 2 years (median follow-up time of 3.8 years among survivors) from the FREEDOM trial.[144-146] Results from the 12-month follow-up of SYNTAX indicate that treatment with PCI or CABG leads to a significant improvement in QoL compared with baseline measures (Fig. 1-20). In addition, the greatest improvement in QoL was seen in those treated with CABG. It is noteworthy that the difference in the Seattle Angina Questionnaire (SAQ) angina frequency between both groups, which was 1.7 at 6 and 12 months, is less than that deemed to be clinically relevant (with differences of 8 to 10 points suggested to be clinically meaningful for each of the SAQ subscales[10,146,147]) and also less than that observed in other studies such as SoS, which showed a 3-point difference at 12 months, and Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE), which showed a 3- to 6-point difference (see Fig. 1-20).[147]

Similarly, data from the ARTS-II study indicated the absence of any significant difference in angina status between patients treated with DES and CABG from as early as 1 month after the index procedure through to the 3-year follow-up; of note, treatment with a BMS in ARTS-II led to consistently higher rates of angina.[145] More recently, in the FREEDOM trial at 2-year follow-up, CABG provided a small benefit compared with PCI using a DES (mean treatment benefit [MTB] 1.3; 95% CI, 0.3 to 2.2), with CABG and PCI providing similar

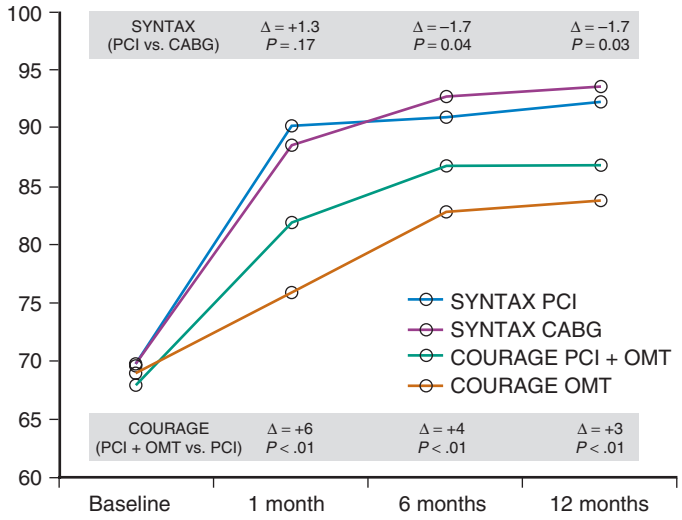
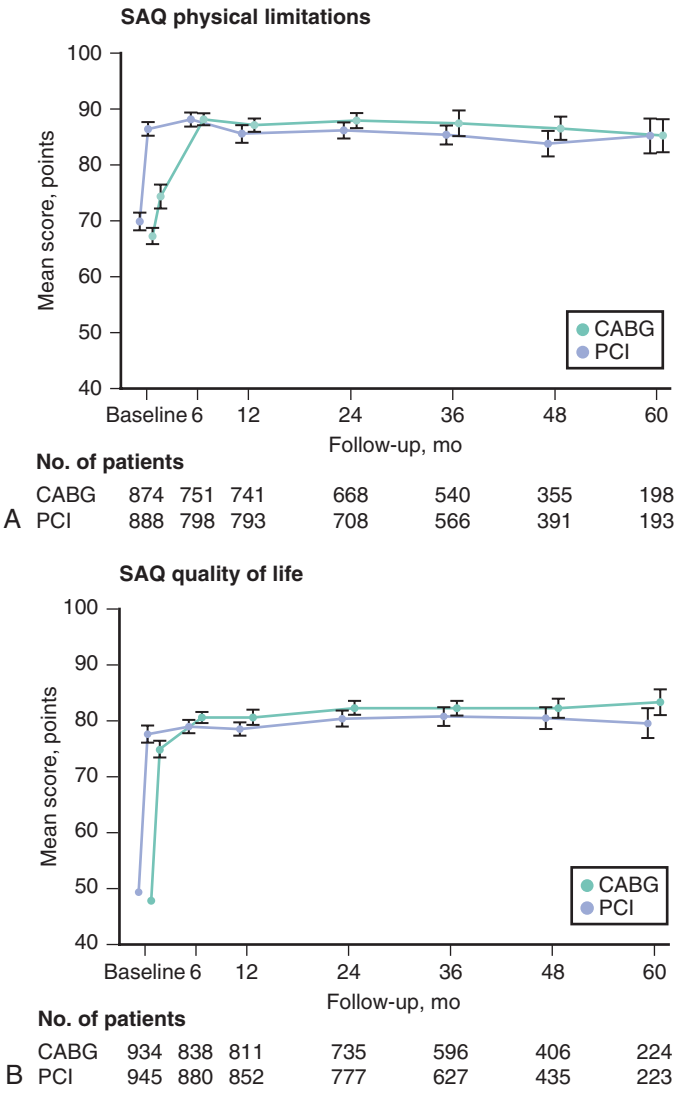


FIGURE 1-20 The change in Seattle Angina Questionnaire angina frequency during follow-up of the SYNTAX and COURAGE studies.[144,147] All therapies lead to a reduction in angina frequency; however, the improvement is greatest following surgical revascularization. It is important to note that the difference between percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in the SYNTAX study is not considered clinically significant; moreover, it is considerably less than the difference between PCI and optimal medical therapy (OMT) and OMT alone in the COURAGE study.

outcomes beyond 2 years (Fig. 1-21). It should, however, be emphasized that the minimum follow-up of FREEDOM was 2 years, with a median follow-up time of 3.8 years among survivors, and although the benefits of CABG in FREEDOM were driven by significant reductions in all-cause mortality (P = .049) and MI (P < .001), the mortality benefit did not emerge until 4 to 5 years after the initial treatment where analyses appeared underpowered (see Fig. 1-2).



E-FIGURE 1-7 Seattle Angina Questionnaire for physical limitations and quality-of-life in FREEDOM. Mean scores are reported (error bars indicate 95% confidence intervals [CIs]). Scores for each subscale range from 0 to 100 (reported by increments of 10) with higher scores representing better health status or quality of life. Note the short-term benefits for percutaneous coronary intervention (PCI; physical limitation up to 6 mo, quality of life up to 1 mo), and longer-term benefits for coronary artery bypass grafting (CABG) beyond 24 months. (From Abdallah MS, Wang K, Magnuson EA, et al: Quality of life after PCI vs CABG among patients with diabetes and multivessel coronary artery disease: a randomized clinical trial. *JAMA* 310[15]:1581-1590, 2013.)

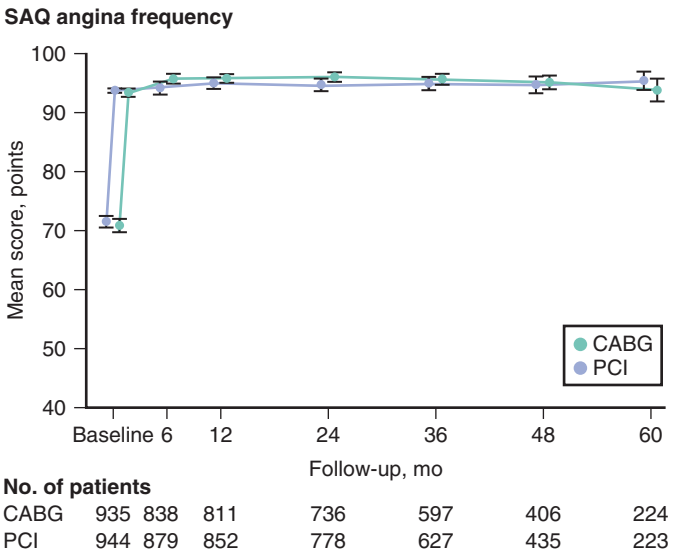


FIGURE 1-21 Seattle Angina Questionnaire for angina frequency in FREEDOM. Mean scores are reported (error bars indicate 95% confidence intervals [CIs]). Scores for each subscale range from 0 to 100 (reported by increments of 10) with higher scores representing better health status or quality of life. Note the benefits for coronary artery bypass grafting (CABG) at 12 to 24 months, without consistent differences beyond 24 months. (From Abdallah MS, Wang K, Magnuson EA, et al: Quality of life after PCI vs CABG among patients with diabetes and multivessel coronary artery disease: a randomized clinical trial. *JAMA* 310[15]:1581-1590, 2013.)

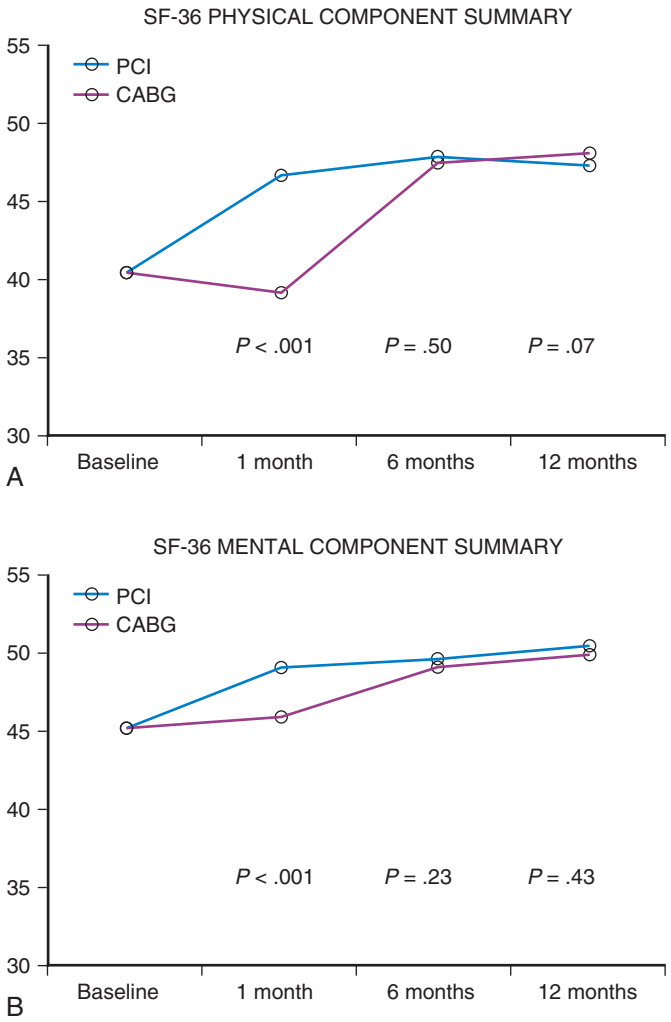


FIGURE 1-22 The temporal change in the SF-36 physical and mental component during follow-up after revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in the SYNTAX study. Of note, at 1-month, a significantly better outcome for both parameters was observed in those treated with PCI; however, by 12 months this difference had eroded such that both treatments were similar. (Cohen DJ, Van Hout B, Serruys PW, et al: Quality of life after PCI with drug-eluting stents or coronary-artery bypass surgery. *N Engl J Med* 364[11]:1016-1026, 2011.)

Although these results appear to indicate that CABG offers a small magnitude of benefit with regard to QoL, it must be stressed that these results are based on study populations, and as with the risk scores discussed previously, individual patients may have different concerns not captured in these evaluations of QoL. For example, some patients may be more willing to accept the increased chances of a repeat procedure with PCI because this treatment allows them to return to normal activity promptly after the procedure; conversely, others may be content with the longer convalescence from CABG because this offers a suitable trade-off with the subsequently lower risk of adverse clinical outcomes.[148] Of note, in the SYNTAX study, physical limitations, QoL, and treatment satisfaction were all significantly better with PCI compared with CABG at 1 month; however, by 6 months these differences were similar (Fig. 1-22). Similarly, in FREEDOM, measures of physical limitations and QoL outcomes were significantly better with PCI at 1 month (MTB, −8.1 [95% CI, −9.9 to −6.3] and −1.9 [95% CI, −3.6 to −0.2], respectively); in addition, measures of physical limitations were significantly better for PCI at 6 months (MTB, −2.3 [95% CI, −3.8 to −0.9] and 0.4 [95% CI, −1.1 to 1.8], respectively) and were slightly better with CABG at 2 years (MTB, 4.4 [95% CI, 2.7 to 6.1] and 2.2 [95% CI, 0.7 to 3.8], respectively; E-Fig. 1-7).

Clearly, an individual patient's views on these issues cannot be captured in a questionnaire but rather through frank discussions among the patient, the cardiologist, and the cardiac surgeon. Consequently, the patient's thoughts, concerns, and individual perception of risk must be considered before deciding on the optimal revascularization strategy.

CONCLUSIONS

The face of revascularization is changing as a result of greater numbers of patients with comorbidities presenting with more extensive CAD in need of revascularization. Concurrent with this have been the advances in percutaneous and surgical technology, which have led to a blurring of the classical divisions between which patients and which coronary lesions are suitable exclusively for PCI or CABG. This welcome change has increased the importance of assessing patients as individuals and taking into consideration their comorbidities, angiographic findings, and ultimately, their personal preferences and individual perceptions of risk prior to establishing a treatment strategy. Unquestionably, both SYNTAX and FREEDOM have helped delineate the boundaries on the appropriateness of each revascularization modality (CABG or PCI). To aid the heart team in quantifying levels of risk and to assist decision making between CABG and PCI, numerous risk scores have been developed, each of which incorporates different clinical and angiographic parameters. The importance of these clinical tools in contemporary practice is in part now emphasized by their inclusion in society guidelines on myocardial revascularization.

REFERENCES

1. Grüntzig A: Transluminal dilatation of coronary-artery stenosis. *Lancet* 1:263, 1978.
2. Hilliard AA, From AM, Lennon RJ, et al: Percutaneous revascularization for stable coronary artery disease temporal trends and impact of drug-eluting stents. *JACC Cardiovasc Interv* 3:172–179, 2010.
3. Vranckx P, Boersma E, Garg S, et al: Cardiovascular risk profile of patients included in stent trials: a pooled analysis of individual patient data from randomised clinical trials: insights from 33 prospective stent trials in Europe. *EuroIntervention* 7:859–871, 2011.
4. Serruys PW, Onuma Y, Garg S, et al: 5-Year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. *J Am Coll Cardiol* 55:1093–1101, 2010.
5. LeGrand VM, Garg S, Serruys PW, et al: Influence of age on the clinical outcomes of coronary revascularization for the treatment of patients with multivessel de novo coronary artery lesions: sirolimus-eluting stent vs. coronary artery bypass surgery and bare metal stent, insight from the multicentre randomised Arterial Revascularisation Therapy Study Part I (ARTS-I) and Part II (ARTS-II). *EuroIntervention* 6:838–845, 2011.
6. Farooq V, Serruys PW, Bourantas C, et al: Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial. *Eur Heart J* 33:3105–3113, 2012.
7. Farooq V, van Klaveren D, Steyerberg EW, et al: Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 381:639–650, 2013.
8. Farooq V, van Klaveren D, Steyerberg EW, Serruys PW: SYNTAX score II—Authors' reply. *Lancet* 381:1899–1900, 2013.
9. Hlatky MA, Boothroyd DB, Bravata DM, et al: Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 373: 1190–1197, 2009.
10. Farkouh ME, Dangas G, Leon MB, et al: Design of the Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) Trial. *Am Heart J* 155:215–223, 2008.
11. Farkouh ME, Domanski M, Sleeper LA, et al: Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 367:2375–2384, 2012.
12. Weintraub WS, Grau-Sepulveda MV, Weiss JM, et al: Comparative effectiveness of revascularization strategies. *N Engl J Med* 366:1467–1476, 2012.
13. Serruys PW, Morice MC, Kappetein AP, et al: Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 360:961–972, 2009.
14. Kappetein AP, Feldman TE, Mack MJ, et al: Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J* 32:2125–2134, 2011.
15. Mohr FW, Morice MC, Kappetein AP, et al: Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 381:629–638, 2013.
16. Ong AT, Serruys PW, Mohr FW, et al: The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J* 151:1194–1204, 2006.
17. Garg S, Serruys PW: Coronary stents: looking forward. *J Am Coll Cardiol* 56(10 Suppl):S43–S78, 2010.
18. Windecker S, Remondino A, Eberli FR, et al: Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med* 353:653–662, 2005.
19. Windecker S, Serruys PW, Wandel S, et al: Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 372:1163–1173, 2008.
20. Serruys PW, Farooq V, Kalesan B, et al: Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, noninferiority trial. *JACC Cardiovasc Interv* 6:777–789, 2013.
21. Serruys PW, Silber S, Garg S, et al: Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med* 363:136–146, 2010.
22. Serruys PW, Unger F, Sousa JE, et al: Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 344:1117–1124, 2001.
23. Kappetein AP, Dawkins KD, Mohr FW, et al: Current percutaneous coronary intervention and coronary artery bypass grafting practices for three-vessel and left main coronary artery disease. Insights from the SYNTAX run-in phase. *Eur J Cardiothorac Surg* 29:486–491, 2006.
24. Sjauw KD, Konorza T, Erbel R, et al: Supported high-risk percutaneous coronary intervention with the Impella 2.5 device the Europella registry. *J Am Coll Cardiol* 54:2430–2434, 2009.
25. Vranckx P, Schultz CJ, Valgimigli M, et al: Assisted circulation using the TandemHeart during very high-risk PCI of the unprotected left main coronary artery in patients declined for CABG. *Catheter Cardiovasc Interv* 74:302–310, 2009.
26. Stefanini GG, Holmes DR, Jr: Drug-eluting coronary-artery stents. *N Engl J Med* 368:254–265, 2013.
27. Zhang Y, Farooq V, Garcia-Garcia HM, et al: Comparison of intravascular ultrasound versus angiography-guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients. *EuroIntervention* 8:855–865, 2012.
28. Werner GS, Schofer J, Sievert H, et al: Multicentre experience with the BridgePoint devices to facilitate recanalisation of chronic total coronary occlusions through controlled subintimal re-entry. *EuroIntervention* 7:192–200, 2011.
29. Farooq V, Mamas MA, Fath-Ordoubadi F, Fraser DG: The use of a guide catheter extension system as an aid during transradial percutaneous coronary intervention of coronary artery bypass grafts. *Catheter Cardiovasc Interv* 78:847–863, 2011.
30. Nam CW, Mangiacapra F, Entjes R, et al: Functional SYNTAX score for risk assessment in multivessel coronary artery disease. *J Am Coll Cardiol* 58:1211–1218, 2011.

30a. Vranckx P, Meliga E, De Jaegere PP, et al: The TandemHeart, percutaneous transseptal left ventricular assist device: a safeguard in high-risk percutaneous coronary interventions. The six-year Rotterdam experience. *EuroIntervention* 4:331, 2008.

31. Aziz O, Rao C, Panesar SS, et al: Meta-analysis of minimally invasive internal thoracic artery bypass versus percutaneous revascularisation for isolated lesions of the left anterior descending artery. *BMJ* 334:617, 2007.
32. Kapoor JR, Gienger AL, Ardehali R, et al: Isolated disease of the proximal left anterior descending artery: comparing the effectiveness of percutaneous coronary interventions and coronary artery bypass surgery. *JACC Cardiovasc Interv* 1:483–491, 2008.
33. Thiele H, Neumann-Schniedewind P, Jacobs S, et al: Randomized comparison of minimally invasive direct coronary artery bypass surgery versus sirolimus-eluting stenting in isolated proximal left anterior descending coronary artery stenosis. *J Am Coll Cardiol* 53:2324–2331, 2009.
34. Daemen J, Boersma E, Flather M, et al: Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation* 118:1146–1154, 2008.
35. Bravata DM, Gienger AL, McDonald KM, et al: Systematic Review: The comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. *Ann Intern Med* 147:703, 2007.
36. Soran O, Manchanda A, Schueler S: Percutaneous coronary intervention versus coronary artery bypass surgery in multivessel disease: a current perspective. *Interact Cardiovasc Thorac Surg* 8:666–671, 2009.
37. Taggart DP, Thomas B: Ferguson Lecture. Coronary artery bypass grafting is still the best treatment for multivessel and left main disease, but patients need to know. *Ann Thorac Surg* 82:1966–1975, 2006.
38. Farooq V, Serruys PW: "Cherry-picking" patients for randomized, controlled trials—reliving the past. *J Am Coll Cardiol* 61:2492, 2013.
39. SYNTAX score calculator: http://www.syntaxscore.com, SYNTAX working-group, Launched 19th May 2009.
40. Sianos G, Morel MA, Kappetein AP, et al: The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 1:219–227, 2005.
41. Serruys PW, Onuma Y, Garg S, et al: Assessment of the SYNTAX score in the Syntax study. *EuroIntervention* 5:50–56, 2009.
42. Farooq V, Brugaletta S, Serruys PW: Contemporary and evolving risk scoring algorithms for percutaneous coronary intervention. *Heart* 97:1902–1913, 2011.
43. Head SJ, Farooq V, Serruys PW, Kappetein AP: The SYNTAX score and its clinical implications. *Heart* 100:169–177, 2014.
44. Head SJ, Kaul S, Mack MJ, et al: The rationale for Heart Team decision-making for patients with stable, complex coronary artery disease. *Eur Heart J* 34:2510–2518, 2013.
45. Patel MR, Dehmer GJ, Hirshfeld JW, et al: ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 53:530–553, 2009.
46. Wijns W, Kolh P, Danchin N, et al: Guidelines on myocardial revascularization. *Eur Heart J* 31:2501–2555, 2010.
47. Task Force Members: 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 34:2949–3003, 2013.
48. Levine GN, Bates ER, Blankenship JC, et al: 2011 ACCF/AHA/SCAI Guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 58:e44–e122, 2011.
49. Hillis LD, Smith PK, Anderson JL, et al: 2011 ACCF/AHA Guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 58:e123–e210, 2011.
50. Clegg A, Young J, Iliffe S, et al: Frailty in elderly people. *Lancet* 381:752–762, 2013.
51. Roques F, Nashef SA, Michel P, et al: Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg* 15:816–822, discussion 822-823, 1999.
52. Nashef SA, Roques F, Michel P, et al: European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 16:9–13, 1999.
53. Roques F, Michel P, Goldstone AR, Nashef SA: The logistic EuroSCORE. *Eur Heart J* 24:881–882, 2003.
54. Singh M, Rihal CS, Lennon RJ, et al: Bedside estimation of risk from percutaneous coronary intervention: the new Mayo Clinic Risk Scores. *Mayo Clin Proc* 82:701–708, 2007.
55. Singh M, Peterson ED, Milford-Beland S, et al: Validation of the Mayo Clinic risk score for in-hospital mortality after percutaneous coronary interventions using the National Cardiovascular Data Registry. *Circ Cardiovasc Interv* 1:36–44, 2008.
56. Ranucci M, Castelvecchio S, Menicanti L, et al: Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. *Circulation* 119:3053–3061, 2009.
57. Peterson ED, Dai D, DeLong ER, et al: Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. *J Am Coll Cardiol* 55:1923–1932, 2010.
58. Shroyer AL, Coombs LP, Peterson ED, et al: The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models. *Ann Thorac Surg* 75:1856–1864, discussion 1864–1865, 2003.
59. Ryan TJ, Bauman WB, Kennedy JW, et al: Guidelines for percutaneous transluminal coronary angioplasty: a report of the American Heart Association/American College of Cardiology Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Percutaneous Transluminal Coronary Angioplasty). *Circulation* 88:2987–3007, 1993.
60. Garg S, Girasis C, Sarno G, et al: The SYNTAX score revisited: a reassessment of the SYNTAX score reproducibility. *Catheter Cardiovasc Interv* 75:946–952, 2010.
61. Califf RM, Peterson ED, Gibbons RJ, et al: Integrating quality into the cycle of therapeutic development. *J Am Coll Cardiol* 40:1895–1901, 1993.
62. Concato J, Feinstein AR, Holford TR: The risk of determining risk with multivariable models. *Ann Intern Med* 118:201–210, 1993.
63. Choong CK, Sergeant P, Nashef SA, et al: The EuroSCORE risk stratification system in the current era: how accurate is it and what should be done if it is inaccurate? *Eur J Cardiothorac Surg* 35:59–61, 2009.
64. Bhatti F, Grayson AD, Grotte G, et al: The logistic EuroSCORE in cardiac surgery: how well does it predict operative risk? *Heart* 92:1817–1820, 2006.
65. Nashef SA, Roques F, Sharples LD, et al: EuroSCORE II. *Eur J Cardiothorac Surg* 41:734–744, discussion 744–745, 2012.
66. Nashef SA, Sharples LD: Editorial comment: pride without prejudice: EuroSCORE II, the STS score and the high-risk patient subset. *Eur J Cardiothorac Surg* 44:1012, 2013.
67. Nashef SA, Sharples LD, Roques F, Lockowandt U: EuroSCORE II and the art and science of risk modelling. *Eur J Cardiothorac Surg* 43:695–696, 2013.
68. Shahian DM, O'Brien SM, Filardo G, et al: The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1—coronary artery bypass grafting surgery. *Ann Thorac Surg* 88:S2–S22, 2009.
69. Toumpoulis IK, Anagnostopoulos CE, DeRose JJ, Swistel DG: European system for cardiac operative risk evaluation predicts long-term survival in patients with coronary artery bypass grafting. *Eur J Cardiothorac Surg* 25:51–58, 2004.
70. De Maria R, Mazzoni M, Parolini M, et al: Predictive value of EuroSCORE on long-term outcome in cardiac surgery patients: a single institution study. *Heart* 91:779–784, 2005.
71. Gogbashian A, Sedrakyan A, Treasure T: EuroSCORE: a systematic review of international performance. *Eur J Cardiothorac Surg* 25:695–700, 2004.
72. Grant SW, Grayson AD, Jackson M, et al: Does the choice of risk-adjustment model influence the outcome of surgeon-specific mortality analysis? A retrospective analysis of 14,637 patients under 31 surgeons. *Heart* 94:1044–1049, 2008.

73. Kim YH, Ahn JM, Park DW, et al: EuroSCORE as a predictor of death and myocardial infarction after unprotected left main coronary stenting. *Am J Cardiol* 98:1567–1570, 2006.
74. Romagnoli E, Burzotta F, Trani C, et al: EuroSCORE as predictor of in-hospital mortality after percutaneous coronary intervention. *Heart* 95:43–48, 2009.
75. Morice MC, Serruys PW, Kappetein AP, et al: Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation* 129: 2388–2394, 2014.
76. Min SY, Park DW, Yun SC, et al: Major predictors of long-term clinical outcomes after coronary revascularization in patients with unprotected left main coronary disease: analysis from the MAIN-COMPARE study. *Circ Cardiovasc Interv* 3:127–133, 2010.
77. Rodes-Cabau J, Deblois J, Bertrand OF, et al: Nonrandomized comparison of coronary artery bypass surgery and percutaneous coronary intervention for the treatment of unprotected left main coronary artery disease in octogenarians. *Circulation* 118:2374–2381, 2008.
78. Park SJ: Utility of the SYNTAX score in selecting left main patients for PCI vs. CABG. SYNTAX or EUROSCORE: Insight from the MAIN-COMPARE Registry. Presentation at Transcatheter Cardiovascular Therapeutics, San Francisco, 22 September 2009.
79. Guida P, Mastro F, Scrascia G, et al: Performance of the European System for Cardiac Operative Risk Evaluation II: a meta-analysis of 22 studies involving 145,592 cardiac surgery procedures. *J Thorac Cardiovasc Surg* 148:3049–3057, 2014.
80. Grant SW, Hickey GL, Dimarakis I, et al: How does EuroSCORE II perform in UK cardiac surgery; an analysis of 23 740 patients from the Society for Cardiothoracic Surgery in Great Britain and Ireland National Database. *Heart* 98:1568–1572, 2012.
81. Singh M, Gersh BJ, Li S, et al: Mayo Clinic Risk Score for percutaneous coronary intervention predicts in-hospital mortality in patients undergoing coronary artery bypass graft surgery. *Circulation* 117:356–362, 2008.
82. Ranucci M, Castelvecchio S: The ACEF score one year after: a skeleton waiting for muscles, skin, and internal organs. *EuroIntervention* 6:549–553, 2010.
83. Ranucci M, Castelvecchio S, Conte M, et al: The easier, the better: age, creatinine, ejection fraction score for operative mortality risk stratification in a series of 29,659 patients undergoing elective cardiac surgery. *J Thorac Cardiovasc Surg* 142:581–586, 2011.
84. Wykrzykowska JJ, Garg S, Onuma Y, et al: Value of age, creatinine, and ejection fraction (ACEF score) in assessing risk in patients undergoing percutaneous coronary interventions in the 'All-Comers' LEADERS trial. *Circ Cardiovasc Interv* 4:47–56, 2011.
85. Kastrati A, Schömig A, Elezi S, et al: Prognostic value of the modified American College of Cardiology/American Heart Association stenosis morphology classification for long-term angiographic and clinical outcome after coronary stent placement. *Circulation* 100:1285–1290, 1999.
86. Krone RJ, Laskey WK, Johnson C, et al: A simplified lesion classification for predicting success and complications of coronary angioplasty. Registry Committee of the Society for Cardiac Angiography and Intervention. *Am J Cardiol* 85:1179–1184, 2000.
87. Khattab AA, Hamm CW, Senges J, et al: Prognostic value of the modified American College of Cardiology/American Heart Association lesion morphology classification for clinical outcome after sirolimus-eluting stent placement (results of the prospective multicenter German Cypher Registry). *Am J Cardiol* 101:477–482, 2008.
88. Valgimigli M, Serruys PW, Tsuchida K, et al: Cyphering the complexity of coronary artery disease using the SYNTAX score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. *Am J Cardiol* 99:1072–1081, 2007.
89. Capodanno D, Di Salvo ME, Cincotta G, et al: Usefulness of the SYNTAX score for predicting clinical outcome after percutaneous coronary intervention of unprotected left main coronary artery disease. *Circ Cardiovasc Interv* 2:302–308, 2009.
90. Califf RM, Phillips HR, 3rd, Hindman MC, et al: Prognostic value of a coronary artery jeopardy score. *J Am Coll Cardiol* 5:1055–1063, 1985.
91. Graham MM, Faris PD, Ghali WA, et al: Validation of three myocardial jeopardy scores in a population-based cardiac catheterization cohort. *Am Heart J* 142:254–261, 2001.
92. Alderman EL, Stadius M: The angiographic definitions of the Bypass Angioplasty Revascularization Investigation. *Coron Artery Dis* 3:1189–1207, 1992.
93. Goto K, Lansky AJ, Fahy M, et al: Predictors of outcomes in medically treated patients with acute coronary syndromes after angiographic triage: an Acute Catheterization And Urgent Intervention Triage Strategy (ACUITY) substudy. *Circulation* 121:853–862, 2010.
94. Perera D, Stables R, Booth J, et al: The balloon pump-assisted coronary intervention study (BCIS-1): rationale and design. *Am Heart J* 158:910–916 e2, 2009.
95. Morton GD, De Silva K, Ishida M, et al: Validation of the BCIS-1 myocardial jeopardy score using cardiac magnetic perfusion imaging. *Clin Physiol Funct Imaging* 33:101–108, 2013.
96. TCT-170: The BCIS-1 Myocardial Jeopardy Score Predicts Mortality After Percutaneous Coronary Intervention. *J Am Coll Cardiol* 56:B40–b, 2010.
97. Singh M, Rihal CS, Lennon RJ, et al: Comparison of Mayo Clinic risk score and American College of Cardiology/American Heart Association lesion classification in the prediction of adverse cardiovascular outcome following percutaneous coronary interventions. *J Am Coll Cardiol* 44:357–361, 2004.
98. Ad N, Barnett SD, Speir AM: The performance of the EuroSCORE and the Society of Thoracic Surgeons mortality risk score: the gender factor. *Interact Cardiovasc Thorac Surg* 6:192–195, 2007.
99. de Mulder M, Gitt A, van Domburg R, et al: EuroHeart score for the evaluation of in-hospital mortality in patients undergoing percutaneous coronary intervention. *Eur Heart J* 32:1398–1408, 2011.
100. Chen S-L, Chen JP, Mintz G, et al: Comparison Between the NERS (New Risk Stratification) Score and the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) Score in Outcome Prediction for Unprotected Left Main Stenting. *JACC Cardiovasc Interv* 3:632–641, 2010.
101. Chen SL, Han YL, Zhang YJ, et al: The anatomic- and clinical-based NERS (new risk stratification) score II to predict clinical outcomes after stenting unprotected left main coronary artery disease: results from a multicenter, prospective, registry study. *JACC Cardiovasc Interv* 6:1233–1241, 2013.
102. Farooq V, Serruys PW, Stone GW, et al: Left main coronary artery disease. In *Percutaneous interventional cardiovascular medicine: the PCR-EAPCI textbook*, Part 3, Europa ed, Toulouse, France, 2012, PCR Publishing, pp 407–445.
103. Leaman DM, Brower RW, Meester GT, et al: Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. *Circulation* 63:285–299, 1981.
104. Smith SC, Jr, Feldman TE, Jr, Hirshfeld JW, et al: ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol* 47:e1–e121, 2006.
105. Medina A, Suárez de Lezo J, Pan M: [A new classification of coronary bifurcation lesions]. *Rev Esp Cardiol* (Article in Spanish) 59:183, 2006.
106. Hamburger JN, Serruys PW, Scabra-Gomes R, et al: Recanalization of total coronary occlusions using a laser guidewire (the European TOTAL Surveillance Study). *Am J Cardiol* 80:1419–1423, 1997.
107. Kushner FG, Hand M, Smith SC, Jr, et al: 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 54:2205–2241, 2009.
108. De Bruyne B, Pijls NH, Kalesan B, et al: Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 367:991–1001, 2012.
109. Tonelli M, Muntner P, Lloyd A, et al: Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet* 380:807–814, 2012.
110. Fox CS, Matsushita K, Woodward M, et al: Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 380:1662-1673, 2012.
111. Garg S, Sarno G, Garcia-Garcia HM, et al: A new tool for the risk stratification of patients with complex coronary artery disease: the Clinical SYNTAX Score. *Circ Cardiovasc Interv* 3:317–326, 2010.
112. Capodanno D, Caggegi A, Miano M, et al: Global Risk Classification and Clinical SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) Score in Patients Undergoing Percutaneous or Surgical Left Main Revascularization. *JACC Cardiovasc Interv* 4:287–297, 2011.
113. Farooq V, Vergouwe Y, Raber L, et al: Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the Logistic Clinical SYNTAX score. *Eur Heart J* 33:3098–3104, 2012.
114. Farooq V, Vergouwe Y, Généreux P, et al: Prediction of 1-year mortality in patients with acute coronary syndromes undergoing percutaneous coronary intervention: validation of the logistic clinical SYNTAX score. *JACC Cardiovasc Interv* 6:737–745, 2013.
115. Royston P, Parmar MK, Sylvester R: Construction and validation of a prognostic model across several studies, with an application in superficial bladder cancer. *Stat Med* 23:907–926, 2004.
116. Capodanno D, Miano M, Cincotta G, et al: EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. *Am Heart J* 159:103–109, 2010.
117. Serruys PW, Farooq V, Vranckx P, et al: A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX Trial at 3 years. *JACC Cardiovasc Interv* 5:606–617, 2012.
118. Panza JA, Velazquez EJ, She L, et al: Extent of Coronary and Myocardial Disease and Benefit From Surgical Revascularization in LV Dysfunction. *J Am Coll Cardiol* 64:553–561, 2014.
119. Chieffo A, Meliga E, Latib A, et al: Drug-eluting stent for left main coronary artery disease: the DELTA registry: a multicenter registry evaluating percutaneous coronary intervention versus coronary artery bypass grafting for left main treatment. *JACC Cardiovasc Interv* 5:718–727, 2012.
120. Farooq V, Serruys PW: Observations from the CREDO-Kyoto three-vessel disease registry: can one adjust for the unadjustable? *EuroIntervention* 9:419–421, 2013.
121. Hlatky MA, Boothroyd DB, Baker L, et al: Comparative effectiveness of multivessel coronary bypass surgery and multivessel percutaneous coronary intervention: a cohort study. *Ann Intern Med* 158:727–734, 2013.
122. Flather M, Rhee JW, Boothroyd DB, et al: The effect of age on outcomes of coronary artery bypass surgery compared with balloon angioplasty or bare-metal stent implantation among patients with multivessel coronary disease. A collaborative analysis of individual patient data from 10 randomized trials. *J Am Coll Cardiol* 60:2150–2157, 2012.
123. Campos CM, van Klaveren D, Iqbal J, et al: Predictive Performance of SYNTAX Score II in Patients With Left Main and Multivessel Coronary Artery Disease. *Circ J* 78:1942–1949, 2014.
124. Wilson GJ, Huibregtse BA, Pennington DE, Dawkins KD: Comparison of the SYNERGY with the PROMUS (XIENCE V) and bare metal and polymer-only Element control stents in porcine coronary arteries. *EuroIntervention* 8:250–257, 2012.
125. Meredith IT, Verheye S, Dubois CL, et al: Primary endpoint results of the EVOLVE trial: a randomized evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent. *J Am Coll Cardiol* 59:1362–1370, 2012.
126. De Bruyne B: Multivessel disease: from reasonably incomplete to functionally complete revascularization. *Circulation* 125: 2557–2559, 2012.
127. Head SJ, Mack MJ, Holmes DR, Jr, et al: Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. *Eur J Cardiothorac Surg* 41:535–541, 2012.
128. Farooq V, Serruys PW, Garcia-Garcia HM, et al: The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol* 61:282–294, 2013.
129. Genereux P, Palmerini T, Caixeta A, et al: Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. *J Am Coll Cardiol* 59:2165–2174, 2012.
130. Farooq V, Serruys PW, Bourantas CV, et al: Quantification of incomplete revascularization and its association with five-year mortality in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation* 128:141–151, 2013.
131. Fiocchi F, Sgura F, Di Girolamo A, et al: Chronic total coronary occlusion in patients with intermediate viability: value of low-dose dobutamine and contrast-enhanced 3-T MRI in predicting functional recovery in patients undergoing percutaneous revascularisation with drug-eluting stent. *Radiol Med* 114:692–704, 2009.
132. Farooq V, Girasis C, Magro M, et al: The CABG SYNTAX Score—an angiographic tool to grade the complexity of coronary disease following coronary artery bypass graft surgery: from the SYNTAX Left Main Angiographic (SYNTAX-LE MANS) substudy. *EuroIntervention* 8:1277–1285, 2013.
133. Farooq V, Girasis C, Magro M, et al: The coronary artery bypass graft SYNTAX Score: final five-year outcomes from the SYNTAX-LE MANS left main angiographic substudy. *EuroIntervention* 9:1009–1010, 2013.
134. Myers WO, Blackstone EH, Davis K, et al: CASS Registry long term surgical survival. Coronary Artery Surgery Study. *J Am Coll Cardiol* 33:488–498, 1999.
135. van Domburg RT, Kappetein AP, Bogers AJ: The clinical outcome after coronary bypass surgery: a 30-year follow-up study. *Eur Heart J* 30:453–458, 2009.
136. Alderman EL, Kip KE, Whitlow PL, et al: Native coronary disease progression exceeds failed revascularization as cause of angina after five years in the Bypass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol* 44:766–774, 2004.
137. Budoff MJ, Shaw LJ, Liu ST, et al: Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *J Am Coll Cardiol* 49:1860–1870, 2007.
138. Okwuosa TM, Greenland P, Ning H, et al: Distribution of coronary artery calcium scores by Framingham 10-year risk strata in the MESA (Multi-Ethnic Study of Atherosclerosis) potential implications for coronary risk assessment. *J Am Coll Cardiol* 57:1838–1845, 2011.
139. Papadopoulou SL, Girasis C, Dharampal A, et al: CT-SYNTAX score: a feasibility and reproducibility study. *JACC Cardiovasc Imaging* 6:413–415, 2013.

140. Serruys PW, Girasis C, Papadopoulou SL, Onuma Y: Non-invasive fractional flow reserve: scientific basis, methods and perspectives. *EuroIntervention* 8:511–519, 2012.
141. Koo BK, Erglis A, Doh JH, et al: Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. *J Am Coll Cardiol* 58: 1989–1997, 2011.
142. Zhang Z, Mahoney EM, Stables RH, et al: Disease-specific health status after stent-assisted percutaneous coronary intervention and coronary artery bypass surgery: one-year results from the Stent or Surgery trial. *Circulation* 108:1694-1700, 2003.
143. Favarato ME, Hueb W, Boden WE, et al: Quality of life in patients with symptomatic multivessel coronary artery disease: a comparative post hoc analyses of medical, angioplasty or surgical strategies-MASS II trial. *Int J Cardiol* 116:364–370, 2007.
144. Cohen DJ, Van Hout B, Serruys PW, et al: Quality of life after PCI with drug-eluting stents or coronary-artery bypass surgery. *N Engl J Med* 364(11):1016–1026, 2011.
145. van Domburg R, Daemen J, Morice M, et al: Short- and long-term health related quality-of-life and anginal status of the Arterial Revascularisation Therapies Study part II, ARTS-II; sirolimus-eluting stents for the treatment of patients with multivessel coronary artery disease. *EuroIntervention* 5:962–967, 2010.
146. Abdallah MS, Wang K, Magnuson EA, et al: Quality of life after PCI vs CABG among patients with diabetes and multivessel coronary artery disease: a randomized clinical trial. *JAMA* 310:1581–1590, 2013.
147. Weintraub WS, Spertus JA, Kolm P, et al: Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med* 359:677–687, 2008.
148. Federspiel JJ, Stearns SC, van Domburg RT, et al: Risk-benefit trade-offs in revascularization choices. *EuroIntervention* 6:936–941, 2011.
149. Serruys PW, Ong ATL, Morice M-C, et al: Arterial Revascularisation Therapies Study Part II—Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. *EuroIntervention* 1:147–156, 2005.
150. Bair TL, Muhlestein JB, May HT, et al: Surgical revascularization is associated with improved long-term outcomes compared with percutaneous stenting in most subgroups of patients with multivessel coronary artery disease: results from the Intermountain Heart Registry. *Circulation* 116:I226–I231, 2007.
151. King SB, 3rd, Lembo NJ, Weintraub WS, et al: A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST). *N Engl J Med* 331:1044–1050, 1994.
152. Hamm CW, Reimers J, Ischinger T, et al: A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. German Angioplasty Bypass Surgery Investigation (GABI). *N Engl J Med* 331: 1037–1043, 1994.
153. First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). CABRI Trial Participants. *Lancet* 346:1179–1184, 1995.
154. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. *N Engl J Med* 335:217–225, 1996.
155. Goy JJ, Kaufmann U, Hurni M, et al: 10-year follow-up of a prospective randomized trial comparing bare-metal stenting with internal mammary artery grafting for proximal, isolated de novo left anterior coronary artery stenosis the SIMA (Stenting versus Internal Mammary Artery grafting) trial. *J Am Coll Cardiol* 52:815–817, 2008.
156. Goy JJ, Eeckhout E, Moret C, et al: Five-year outcome in patients with isolated proximal left anterior descending coronary artery stenosis treated by angioplasty or left internal mammary artery grafting. A prospective trial. *Circulation* 99:3255–3259, 1999.
157. Coronary angioplasty versus coronary artery bypass surgery: the Randomized Intervention Treatment of Angina (RITA) trial. *Lancet* 341:573–580, 1993.
158. Carrie D, Elbaz M, Puel J, et al: Five-year outcome after coronary angioplasty versus bypass surgery in multivessel coronary artery disease: results from the French Monocentric Study. *Circulation* 96:II-1-6, 1997.
159. Morrison DA, Sethi G, Sacks J, et al: Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. Investigators of the Department of Veterans Affairs Cooperative Study #385, the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). *J Am Coll Cardiol* 38:143–149, 2001.
160. Rodriguez AE, Baldi J, Fernandez Pereira C, et al: Five-year follow-up of the Argentine randomized trial of coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple vessel disease (ERACI II). *J Am Coll Cardiol* 46:582–588, 2005.
161. Serruys PW, Ong AT, van Herwerden LA, et al: Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol* 46:575–581, 2005.
162. SoS Investigators: Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial. *Lancet* 360:965–970, 2002.
163. Hueb W, Lopes NH, Gersh BJ, et al: Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 115:1082–1089, 2007.
164. Capodanno D, Capranzano P, Di Salvo ME, et al: Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. *JACC Cardiovasc Interv* 2:731–738, 2009.
165. Onuma Y, Girasis C, Piazza N, et al: Long-term clinical results following stenting of the left main stem—insights from RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) Registries. *JACC Cardiovasc Interv* 3:584–594, 2010.
166. Wykrzykowska J, Garg S, Girasis C, et al: Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. *J Am Coll Cardiol* 56:272–277, 2010.
167. Girasis C, Garg S, Raber L, et al: Prediction of 5-year clinical outcomes using the SYNTAX score in patients undergoing PCI from the Sirolimus eluting stent compared with paclitaxel eluting stent for coronary revascularisation (SIRTAX) trial. Abstract at American College of Cardiology meeting, March 14-16th 2010, Atlanta GA.
168. Serruys PW: Left Main Lessons from SYNTAX (Early Results and 2 Year Follow-up): Interventional Perspectives. Presentation Transcatheter Cardiovascular Therapeutics, 21st September 2009. Available online: http://www.tctmd.com/txshow.aspx?tid=9390768&id=83938&trid=938634.%5D. Accessed September 2014.
169. Birim O, van Gameren M, Bogers AJ, et al: Complexity of coronary vasculature predicts outcome of surgery for left main disease. *Ann Thorac Surg* 87:1097–1104, discussion 1104-1105, 2009.
170. Lemesle G, Bonello L, de Labriolle A, et al: Prognostic value of the Syntax score in patients undergoing coronary artery bypass grafting for three-vessel coronary artery disease. *Catheter Cardiovasc Interv* 73:612–617, 2009.
171. Morice MC: Multivessel Disease Lessons From SYNTAX (Early Results and 2 Year Follow-Up): Interventional Perspectives. Presentation at Transcatheter Cardiovascular Therapeutics, San Francisco, 21st September 2009.
172. Escaned J, Serruys PW: *Coronary stenosis imaging, structure and physiology*, Toulouse, France, 2011, PCR Publishing.
173. Valgimigli M, Dawkins K, Macaya C, et al: Impact of stable versus unstable coronary artery disease on 1-year outcome in elective patients undergoing multivessel revascularization with sirolimus-eluting stents: a subanalysis of the ARTS II trial. *J Am Coll Cardiol* 49:431–441, 2007.
174. Topol EJ: *Textbook of interventional cardiology*, ed 3, Philadelphia, 1999, Saunders.
175. Valgimigli M, van Mieghem CAG, Ong ATL, et al: Short- and Long-Term Clinical Outcome After Drug-Eluting Stent Implantation for the Percutaneous Treatment of Left Main Coronary Artery Disease: Insights From the Rapamycin-Eluting and Taxus Stent Evaluated At Rotterdam Cardiology Hospital Registries (RESEARCH and T-SEARCH). *Circulation* 111:1383–1389, 2005.
176. Chakravarty T, Buch MH, Naik H, et al: Predictive accuracy of SYNTAX score for predicting long-term outcomes of unprotected left main coronary artery revascularization. *Am J Cardiol* 107:360–366, 2011.
177. Parsonnet V, Dean D, Bernstein AD: A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. *Circulation* 79:I3–12, 1989.
178. Kim Y-H, Park D-W, Kim W-J, et al: Validation of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) Score for Prediction of Outcomes After Unprotected Left Main Coronary Revascularization. *JACC Cardiovasc Interv* 3:612–623, 2010.
179. Wu C, Hannan EL, Walford G, et al: A risk score to predict in-hospital mortality for percutaneous coronary interventions. *J Am Coll Cardiol* 47:654–660, 2006.
180. Madan P, Elayda MA, Lee VV, Wilson JM: Predicting major adverse cardiac events after percutaneous coronary intervention. *Am Heart J* 155:1068–1074, 2008.
181. Singh M, Rihal CS, Selzer F, et al: Validation of Mayo Clinic risk adjustment model for in-hospital complications after percutaneous coronary interventions, using the National Heart, Lung, and Blood Institute dynamic registry. *J Am Coll Cardiol* 42:1722–1728, 2003.

2 Evidence-Based Interventional Practice

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KEY POINTS

- When coronary revascularization is considered, prognostic and symptomatic indications must be distinguished.
- In general, percutaneous coronary intervention (PCI) for single-vessel disease is justified only if an improvement of symptoms can be anticipated or ischemia that comprises more than 10% of the left ventricle can be relieved.
- With multivessel disease or left main coronary artery (LMCA) stenosis, the decision for PCI versus coronary artery bypass grafting (CABG) depends on the complexity of the coronary artery involvement, which can be gauged by the Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score and by the surgical risk.
- In patients with LMCA stenosis and a SYNTAX score below 33 or with multivessel disease and a SYNTAX score below 23 in the absence of LMCA stenosis, the 5-year outcome of PCI is similar to that after CABG, provided that complete revascularization can be achieved. Thus PCI is an acceptable alternative to bypass surgery in many cases with multivessel disease or LMCA stenosis.
- In patients with multivessel disease and diabetes mellitus, CABG is the treatment of choice. Nevertheless, PCI may be considered in selected patients with a low SYNTAX score.
- In many instances, individualized decisions must be made jointly by the cardiac surgeon and the interventional cardiologist at institutionalized meetings of the heart team.

OVERVIEW

Changing Paradigms of Coronary Revascularization

When the era of interventional cardiology began, with the pioneering work of Andreas Grüntzig on plain balloon angioplasty, PCI (for a list of abbreviations and acronyms, see Table 2-1) was a treatment option only for isolated proximal coronary lesions that did not involve the ostium or the LMCA stem. In the late 1980s, coronary stents were developed with the goal of reducing the risk of restenosis and achieving a more predictable acute result of angioplasty, thus avoiding the dreaded abrupt closure as a result of dissection. As shown subsequently, stents were successful in achieving this goal. Nevertheless, they created a new problem: subacute stent thrombosis. After intense research on periinterventional and postinterventional antithrombotic treatment, the concept of dual- or triple-antiplatelet therapy emerged, which significantly reduced the incidence of this complication. The use of coronary stents in conjunction with optimized antithrombotic treatment extended the spectrum of coronary lesions for which PCI was considered a reasonable treatment option and thereby led to a substantial expansion of interventional techniques. Because of the large number of patients who were being treated with coronary stents, restenosis as a result of to neointima formation became a serious problem. Although various studies demonstrated that compared with plain balloon angioplasty, stents reduced the need for reintervention, restenosis rates continued to be relevant and ranged from just above 10% in the simplest lesions to more than 50% with diffuse disease in patients with diabetes.

Thus it is not surprising that the community of interventional cardiologists celebrated the advent of drug-eluting stents (DESs) as a major breakthrough, given that the initial studies suggested restenosis rates of zero. In the meantime, it has become clear that compared with bare-metal stents (BMSs), DESs reduce the need for target-vessel reintervention by around 80%, thus largely reducing—but not eliminating—the problem of restenosis. Subsequently, DESs led to another massive expansion of the proportion of patients treated with PCI. With the widespread use of these stents for PCI, reports appeared that pointed to a new problem that had not been seen with BMSs: late stent thrombosis. Yet a thorough reevaluation of the data from randomized studies—with uniform application of definitions for *definite, probable,* and *possible* stent thrombosis—failed to confirm these alarming initial reports.[1] Nevertheless, a meta-analysis of studies with first-generation paclitaxel- and sirolimus-eluting stents suggested a slight increase in the risk of very late (>1 year) stent thrombosis after the placement of DESs compared with BMSs.[2] In the meantime, DESs with improved design have replaced the first-generation paclitaxel- and sirolimus-eluting stents. For the most part, these next-generation DESs are more efficacious and safer than first-generation DESs.[3,4] Specifically, a network meta-analysis based on 49 trials that included 50,844 randomly assigned patients showed a 2-year risk of stent thrombosis for the everolimus-eluting stents that was even lower than that for BMSs.[3,4]

Despite the remaining problems of PCI, its use has increased exponentially over the past few decades. Initially, this increase has come at the expense of lone medical therapy. More recently, however, with the advent of DESs, a shift has been seen in patients with multivessel disease and other complex coronary anatomies from CABG to PCI. This shift has been facilitated by both physician and patient preference for the supposedly easier approach to coronary revascularization, given the idea that the problem of restenosis has been largely solved. However, reasonable concern exists that this shift has led to the overuse of PCI and that in some patients, it may not yield the same outcome as CABG, which for a number of indications is an established treatment option with a well-documented survival benefit compared with that of medical therapy.

The Scope of This Chapter

In comparing PCI with medical treatment alone or with bypass surgery, it is important to scrutinize the available evidence that PCI offers at least as great a benefit as CABG on the one hand or a greater benefit than medical treatment alone on the other. This review summarizes and discusses the currently available evidence so as to present a rationale for clinical decision making.

Pharmacologic therapy and coronary revascularization, by either CABG or PCI, are the mainstays of treatment for coronary artery disease (CAD). The prime objective of such treatment is improved survival (prognostic indication); other reasonable treatment goals are relief of symptoms and improved quality of life (symptomatic indication). In pursuing these goals, the prevention of myocardial infarction (MI) is a key issue that pertains to both survival and quality of life. In deciding on the optimal revascularization strategy in a patient with CAD, it is necessary to determine first whether a prognostic

TABLE 2-1 List of Acronyms

ACIP: Asymptomatic Cardiac Ischemia Pilot study
ACME: Angioplasty Compared to Medicine
APPROACH: Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease
ARTS: Arterial Revascularization Therapies Study
AVERT: Atorvastatin Versus Revascularization Treatments
AWESOME: Angina With Extremely Serious Operative Mortality Evaluation
BARI: Bypass Angioplasty Revascularization Investigation
BARI 2D: Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes
CABRI: Coronary Angioplasty Versus Bypass Revascularization Investigation
CARDia: Coronary Artery Revascularization in Diabetes
CARDS: Collaborative Atorvastatin Diabetes Study
CASS: Coronary Artery Surgery Study
COMBAT: Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease
COURAGE: Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
CUSTOMIZE: Appraise a Customized Strategy for Left Main Revascularization
DELTA: Multicenter Registry Evaluating Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting for Left Main Treatment
EAST: Emory Angioplasty Versus Surgery Trial
ECSS: European Coronary Surgery Study
ERACI: Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty With Stenting Versus Coronary Artery Bypass Surgery in Multivessel Disease
EXCEL: Evaluation of Xience Prime Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization
FAME: Fractional Flow Reserve Versus Angiography for Multivessel Evaluation
FINESSE: Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events
FREEDOM: Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease
FRISC: Fragmin and Revascularization During Instability in Coronary Artery Disease
GABI: German Angioplasty Bypass Surgery Investigation
ICTUS: Invasive Versus Conservative Treatment in Unstable Coronary Syndromes
ISAR-SWEET: Intracoronary Stenting and Antithrombotic Regimen: Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics?
ISAR-LEFT-MAIN: Intracoronary Stenting and Antithrombotic Regimen: Drug-Eluting Stents for Unprotected Left Main Stem Disease
LE MANS: Left main coronary artery stenting
MAIN-COMPARE: Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization
MASS: Medicine, Angioplasty, or Surgery Study
PRECOMBAT: Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease
RITA: Randomized Intervention Trial of Unstable Angina
SIMA: Stenting Versus Internal Mammary Artery
SoS: Stent or Surgery
SPECT: Single photon emission computed tomography
STREAM: Strategic Reperfusion Early After Myocardial Infarction
SYNTAX: Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery
TACTICS: Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy
TIMI: Thrombolysis in Myocardial Infarction
VA Study: Veterans Administration Cooperative Study

or symptomatic indication for coronary revascularization exists and then to choose the most appropriate revascularization modality. This chapter presents criteria for both of these elements in clinical decision making and focuses primarily on the prognostic indication for coronary revascularization. Based on a review of the general criteria for revascularization, the efficacy and safety of PCI compared with CABG are discussed, and the role of PCI in symptomatic indications for coronary revascularization is also addressed, predominantly in comparison with medical therapy alone. The focus is on stable coronary disease. Acute coronary syndromes (ACSs) that include MI are touched on only briefly because these are discussed in depth in other chapters.

PROGNOSTIC INDICATIONS FOR CORONARY REVASCULARIZATION

Clinical Presentation

Several factors must be considered in regard to clinical presentation. Among these are ST-segment elevation, cardiac troponin release, and ischemic area, which can help the clinician discern the appropriate treatment.

Myocardial Infarction With ST-Segment Elevation

In acute MI, as shown by a meta-analysis of the randomized trials in this setting, fibrinolysis reduces mortality by 18% compared with conservative treatment.[5] On top of this benefit, coronary reperfusion by primary PCI reduces in-hospital mortality by an additional 37%.[6] In addition to its effect on survival, PCI compared with fibrinolysis reduces the risk of reinfarction and stroke, particularly that of hemorrhagic stroke, and the initial benefit is maintained during long-term follow-up.[7] The greatest survival benefit by PCI is obtained when the delay conferred by PCI, compared with fibrinolysis, is shorter than 35 minutes.[6] Nevertheless, even with delays in PCI, compared with fibrinolysis, that range between 35 and 120 minutes, a significant survival benefit is gained by PCI that is around 24% on average.[6] Prespecified subgroup analyses of the Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events (FINESSE) study suggest that even with delays as long as 2.55 to 4 hours, direct PCI is the preferred strategy in terms of safety and efficacy.[8] Because fibrinolysis is more effective within the first 1 to 3 hours after the onset of pain than after greater delays, the Strategic Reperfusion Early After Myocardial Infarction (STREAM) study compared prehospital fibrinolysis, coupled with timely coronary angiography, with primary PCI in patients with

ST-elevation myocardial infarction (STEMI) who presented within 3 hours after symptom onset and who were unable to undergo primary PCI within 1 hour.[9] STREAM did not find any benefit of fibrinolysis compared with primary PCI with respect to the 30-day composite incidence of death, shock, congestive heart failure (CHF), or reinfarction or of death alone but did confirm the increased risk of stroke associated with fibrinolysis.[9] Thus STREAM endorsed a meta-analysis of subgroups of earlier studies, indicating that the benefit from PCI, compared with fibrinolysis, was largely independent of the time from onset of pain to intervention.[6]

Although it can be performed, CABG in the setting of MI delays reperfusion, compared with PCI, and is associated with a high perioperative risk. Hence CABG has only a niche indication in this setting. In summary, acute MI is an accepted and well-documented prognostic indication for PCI.

Acute Coronary Syndromes Without ST-Segment Elevation

A long-standing debate has persisted about two competing treatment strategies for acute coronary syndromes without ST-segment elevation.[10] The conservative strategy reserves coronary angiography and revascularization to those patients who continue to have a spontaneous or inducible myocardial ischemia despite maximal medical therapy. On the other hand, the invasive strategy suggests coronary angiography and revascularization irrespective of the primary success of medical treatment. Various studies have addressed this issue. A meta-analysis published in 2005 concluded that the invasive strategy, although it increased the risk of in-hospital death and MI (early hazard), significantly reduced death and MI during the entire follow-up—ranging from 6 months to 2 years in various studies—by 18% (95% confidence interval [CI], 2% to 42%).[11] Supporting this analysis, the 5-year follow-up of the third Randomized Intervention Trial of Unstable Angina (RITA 3) revealed that compared with the conservative strategy, the benefit of the invasive strategy with respect to death and MI continued to increase with time.[12] At 5 years after intervention, the incidence of death and MI was 20.0% in the conservative arm but was 16.6% in the interventional arm ($P = .04$). Moreover, an increased survival benefit of the invasive strategy was reported compared with the conservative strategy during the 5-year follow-up (88% vs. 85%), which almost reached statistical significance ($P = .054$). The 5-year follow-up of the second Fragmin and Revascularization During Instability in Coronary Artery Disease (FRISC-II) also demonstrated a significant reduction in the long-term incidence of death and MI by the invasive strategy compared with the conservative strategy (5-year incidence 19.9% vs. 24.5%, $P = .009$).[13] Contrary to RITA 3 and FRISC-II, the Invasive Versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial compared a routine invasive strategy with a selective invasive strategy and did not show any significant differential effect of the two strategies on 5-year survival or survival free of MI.[14] In interpreting this finding, it must be kept in mind that the rate of coronary revascularization in the selective invasive arm of ICTUS was as high as that in the routine invasive arm of RITA 3. Moreover, inclusion of patients in ICTUS was based on a single troponin measurement, rather than dynamic troponin changes, as recommended by current guidelines.[15] Hence ICTUS may have included a number of patients without a coronary cause of troponin elevation. Despite equipoise in ICTUS, meta-analysis of individual patient data from FRISC-II, ICTUS, and RITA-3 found a significant reduction in the 5-year incidence of cardiovascular death and MI by the routine invasive strategy (hazard ratio [HR], 0.81; 95% CI, 0.71 to 0.93; $P = .02$), which comprised a significant reduction in the incidence of MI (HR, 0.77; 95% CI, 0.65 to 0.90; $P = .01$) and a trend toward a decrease in cardiovascular death (HR, 0.83; 95% CI, 0.68 to 0.01; $P = .068$).[16]

The benefit from the invasive strategy, compared with the conservative one, is not uniform across the spectrum of ACSs. The early studies—FRISC-II, RITA 3,[17-18] and the Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction (TACTICS-TIMI 18)[19]—have consistently shown that the benefit from the invasive strategy is linked to various markers of risk, whereas patients without these risk markers may be treated according to the same principles as patients with stable angina. The risk factors that could be established in previous studies include elevated myocardial marker proteins, dynamic ST-segment changes, ongoing myocardial ischemia, hemodynamic instability, and diabetes mellitus.[20] Corroborating these earlier findings, the meta-analysis of FRISC-II, ICTUS, and RITA 3 demonstrated that the benefit of routine invasive strategy versus conservative strategy increased substantially with increasing ischemic risk; although only a minor benefit was reported in low-risk patients, the routine invasive strategy afforded a significant, more than 10% absolute reduction in the 5-year incidence of death and MI in the tertile of patients with the highest risk.[16]

In summary, patients with high-risk ACSs benefit from coronary revascularization with respect to the possibility of imminent MI or death.

Stable Angina—Severe Angina or Large Ischemic Area

Among patients with chronic stable angina, those with severe angina, large or multiple perfusion defects on functional testing, or a low threshold for the induction of ischemia (Table 2-2) have a poor prognosis, with an annual mortality risk greater than 3%.[20a] If these high-risk features are associated with double- or triple-vessel disease, patients benefit from revascularization irrespective of left ventricular (LV) function. In an analysis of 5303 patients in the Coronary Artery Surgery Study (CASS) registry, surgical benefit was greatest in patients who exhibited at least 1 mm of ST-segment depression and could exercise only into stage 1 or less. In the surgical group with triple-vessel disease and severe exercise-induced ischemia, 7-year survival was 81%, whereas it was 58% in the corresponding medical group.[21] Likewise, in another registry that included 2023 patients with severe angina and two-vessel disease, 6-year survival was 76% in patients treated medically and 89% in patients treated surgically ($P < .001$).[22] Cox multivariate analyses showed that surgical treatment was a beneficial independent predictor of survival for patients with two-vessel coronary disease and Canadian Cardiovascular Society class 3 or 4 angina. The Asymptomatic Cardiac Ischemia Pilot (ACIP) is a more recent trial that was designed to compare the efficacy of medical therapy versus revascularization.[23] In ACIP, 558 patients with angiographically documented CAD, mostly multivessel disease, and stable CAD were randomly assigned to medical therapy, adjusted either to suppress angina or to suppress both angina and evidence of ischemia during ambulatory electrocardiogram (ECG) monitoring or revascularization with either PCI or CABG. Revascularization was significantly more effective in relieving ischemia than either of the medical strategies. During 1-year follow-up, the ACIP trial appeared to show better outcomes in patients treated with revascularization; mortality was 4.4% and 1.6% in the two conservative groups, whereas none of the patients in the revascularization group had died during the 1-year follow-up period. The apparent benefit of revascularization was largely confined to patients with double- or triple-vessel disease. Expanding the series done in 2003 and 2006,[24,25] a large observational study of patients who underwent exercise or adenosine myocardial perfusion single photon emission computed tomography (SPECT) analyzed the impact of the extent of

TABLE 2-2 Poor Prognosis in Stable Angina (Average Annual Mortality Risk >3%)

High-risk treadmill score
Stress-induced large or moderate-sized nuclear perfusion defect (particularly if in the anterior wall)
Stress-induced multiple perfusion defects with left ventricle dilation or increased lung parenchymal uptake of thallium-201 isotope
Echocardiographic wall-motion abnormality involving more than two segments, developing at a low dose of dobutamine (≤10 μg/kg/min) or at a low heart rate (120 beats/min)
Stress-induced echocardiographic evidence of extensive ischemia

inducible myocardial ischemia and of myocardial scar on the potential survival benefit of revascularization.[26] The study included 13,969 consecutive patients: 12,329 were treated medically, and 1226 underwent early revascularization (501 CABG, 725 PCI) in the first 90 days after scintigraphy. During a median follow-up of 8.9 years, 3893 patients (27.9%) died. Hazard ratios for all-cause death that compared early revascularization with medical treatment were derived from Cox models adjusted for logistic-based propensity scores for revascularization, extent of ischemia and scar, and baseline characteristics. In 11,880 patients without large myocardial scars (<10% fixed myocardial defect), a progressive decrease in the hazard ratios was found with increasing extent of inducible ischemia (Fig. 2-1). Thus the risk associated with conservative treatment increased as a function of percent myocardium ischemic, whereas the risk associated with revascularization decreased. Equipoise between revascularization and conservative treatment was reached at about 10% ischemic myocardium (Fig. 2-1). Only in patients with extensive scar (≥10% fixed myocardial defect), the ischemia-treatment interaction was not significant ($P = .469$), and an advantage of revascularization over conservative treatment could not be established. In summary, in the absence of extensive myocardial scars, myocardial revascularization compared with conservative treatment improved long-term survival in patients with significant (>10% myocardium) inducible ischemia. Early myocardial revascularization was, however, harmful in patients with minimal inducible ischemia.

Consistent results were obtained in a nuclear substudy on 314 patients in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE).[27] In this substudy, the extent of residual posttreatment ischemia—assessed as a percentage of the left ventricle by myocardial perfusion SPECT—was a predictor of outcome: rates of death or MI ranged from 0% to 39% for patients with no residual ischemia to 10% or more residual ischemia despite treatment, ($P = .001$ [risk-adjusted $P = .09$]; Fig. 2-2). With respect to treatment, a 5% or more reduction in ischemic myocardium lowered the risk of death or MI ($P = .037$ [risk-adjusted $P = .26$]), particularly if baseline ischemia was 10% or greater ($P = .001$ [risk-adjusted $P = .08$]). PCI on top of optimal medical therapy increased the likelihood of achieving this goal. The findings of this substudy suggest that revascularization is indicated if, in addition to optimal medical therapy, it affords at least a 5% reduction in myocardial ischemia.

Thus although adequately powered randomized trials to address the impact of severe angina or large perfusion defects on outcome in patients with chronic stable angina are lacking, the bulk of the currently available evidence suggests that these patients benefit from revascularization, particularly if more than one vessel is affected.

Coronary Anatomy

Until now our understanding of the anatomic conditions that constitute a survival benefit from coronary revascularization compared with medical therapy alone has been largely based on milestone studies performed during the 1970s. Soon after CABG was introduced in 1969, three randomized trials compared surgical revascularization with lone medical therapy: the VA Study, the European Coronary Surgery Study (ECSS), and CASS. Although these studies are outdated in many respects, including a low use of arterial conduits and limited means of pharmacologic risk-factor modification and platelet inhibition, it is unlikely that they will ever be replicated. In concert with analyses of large registry databases, these early studies established the conditions under which CABG improves survival compared with medical therapy (Table 2-3). A meta-analysis of the seven published randomized trials of CABG versus medical treatment alone for CAD identified left main CAD (diameter of stenosis ≥50%), multivessel disease, and involvement of the proximal left anterior descending coronary artery (LAD) as significant predictors of a survival benefit from CABG.[28] In the cumulative experience of the seven studies, the VA study being the first, surgical revascularization for left main CAD was associated with a 65% relative reduction in mortality compared with medical therapy alone.[28] Notably, in left main CAD, a survival benefit of surgery was

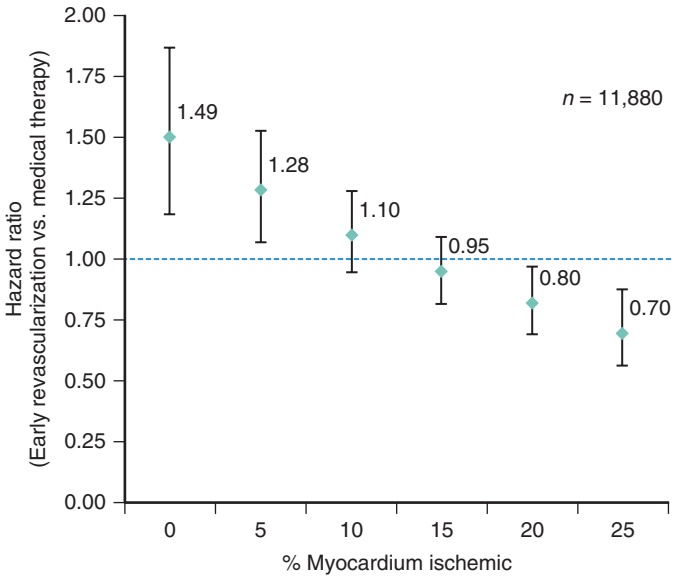


FIGURE 2-1 Hazard ratio associated with early revascularization compared with medical therapy at specific values of percent myocardium ischemic in patients with less than 10% myocardial scar. P values per Cox proportional hazards model. (From Hachamovitch R, Rozanski A, Shaw LJ, et al: Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J* 32[8]:1012-1024, 2011.)

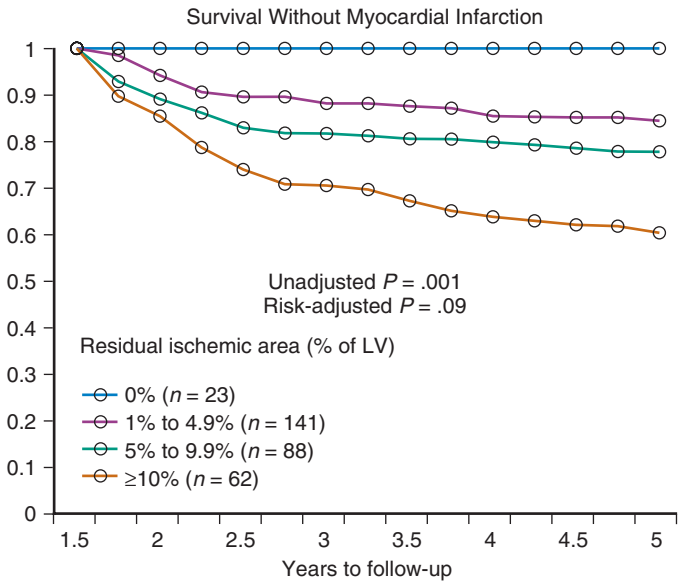


FIGURE 2-2 Survival without myocardial infarction depending on residual ischemic area. *LV,* Left ventricle. (From Shaw LJ, Berman DS, Maron DJ, et al: Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation [COURAGE] trial nuclear substudy. *Circulation* 117[10]:1283-1291, 2008.)

TABLE 2-3 Conditions in Which Coronary Artery Bypass Grafting Improves Survival Compared With Medical Therapy

Left main coronary artery disease
Triple- or double-vessel disease involving the proximal left anterior descending coronary artery
Triple- or double-vessel disease in the presence of severe angina or large areas of ischemia on functional testing
Triple-vessel disease associated with impaired left ventricle function

reported irrespective of the presence or absence of spontaneous or inducible symptoms or signs of ischemia or reduced LV function. The same is also true for triple- or double-vessel disease involving the proximal LAD.[29]

In all other conditions, the indication for surgical coronary revascularization depends on a combination of anatomic and clinical criteria. If triple-vessel disease is associated with impaired LV function (LV ejection fraction <50%), surgical revascularization improves survival irrespective of LAD involvement.[30,31] In the presence of severe angina or large areas of ischemia on functional testing, surgical revascularization of triple- or double-vessel disease is also indicated for both symptomatic and prognostic reasons even in the absence of LV dysfunction.[21,22] Coronary revascularization has never been shown to confer a survival benefit in patients with single-vessel disease. This is also true for isolated proximal LAD stenoses. Yusuf and colleagues' meta-analysis[28] that showed a survival benefit from surgery in patients with LAD involvement must be interpreted with the notion that this result was obtained in a cohort that had predominantly multivessel disease, and no dedicated subgroup analysis was undertaken for isolated LAD stenosis. More recently, the randomized Medicine, Angioplasty, or Surgery Study (MASS) trial compared medical treatment alone with plain balloon angioplasty or CABG in 214 patients with symptomatic, isolated, high-grade stenosis of the LAD.[32] During a 5-year follow-up, no appreciable difference was found among the three treatment arms with regard to either death or MI. Although the power to detect small differences in event rates was low in MASS, its results are consistent with the current judgment that no prognostic indication exists for coronary revascularization in stable single-vessel disease. No study ever demonstrated that in patients with stable angina, the risk of subsequent MI could be reduced by either bypass surgery or PCI. The degree of stenosis is a notoriously poor predictor of subsequent events. Although the risk of subsequent MI is higher with high-grade stenoses than with low-grade stenoses, the latter are far more frequent. Thus the majority of infarctions are triggered by low-grade stenoses. Despite recent advances,[33,34] our current means of identifying vulnerable plaques are limited.

Technical Feasibility

Apart from the extent and distribution of CAD, the probability of achieving complete revascularization is an important criterion for the choice of the most appropriate revascularization strategy. In CABG, a number of studies have demonstrated that patients who are completely revascularized have better long-term outcomes than those with incomplete revascularization.[35] The same is also true for PCI. Several studies from the prestent era have confirmed better long-term outcomes after complete revascularization than after an incomplete procedure.[36,37] The reasons for not treating all diseased vessels may include technical obstacles such as heavy calcification, tortuous vessels or chronic total occlusions, the presence of serious concomitant disease, or the intention to treat only the "culprit lesion" thought to be responsible for the patient's symptoms. An analysis of a total of 21,945 patients with bare-metal stents from New York State's Percutaneous Coronary Interventions Reporting System assessed the issue of incomplete revascularization with current practices of coronary revascularization. A follow-up period of 3 years was reported.[38] In this registry, 68.9% of the stent patients were incompletely revascularized. After adjustment for comorbidities and other baseline characteristics associated with increased risk, incompletely revascularized patients were significantly more likely to die at any time than completely revascularized patients (adjusted HR, 1.15; 95% CI, 1.01 to 1.30). The risk associated with incomplete revascularization increased with the number of vessels that were not revascularized and was higher with nonrevascularized chronic total occlusions than in nonrevascularized nonocclusive lesions. Incompletely revascularized patients with total occlusions and two or more nonrevascularized vessels were at the highest risk compared with completely revascularized patients (HR, 1.36; 95% CI, 1.12 to 1.66).

The first analysis of the role of completeness of revascularization with drug-eluting stents was a post-hoc analysis of the second Arterial Revascularization Therapies Study (ARTS-II), which failed to show a significant impact of incomplete revascularization on survival or survival without MI after placement of sirolimus-eluting stents.[39] However, this analysis was grossly underpowered. More recently, an analysis that included a substantially larger cohort of the SYNTAX study appeared.[40] This analysis comprised the 899 patients randomized to PCI with paclitaxel-eluting stents, 890 patients randomized to CABG, and the patients who were deemed ineligible for randomization and who were included in the nested registries for PCI ($n = 198$) or CABG ($n = 649$). Consistent with previous studies, complete revascularization substantially reduced the risk of cardiac death during 4-year follow-up compared with incomplete revascularization both in the PCI group (HR, 0.64; 95% CI, 0.41 to 1.00; $P = .049$) and in the surgical group (HR, 0.50; 95% CI, 0.30 to 0.86; $P = .01$). Although the presence of a chronic total occlusion was independently associated with a higher incidence of incomplete revascularization, it showed no significant interaction with impact of completeness of revascularization on survival.

In a subsequent analysis, the same group quantitated the degree of incompleteness of revascularization in the randomized PCI cohort of the SYNTAX trial.[41] This analysis was based on the SYNTAX score that was developed prospectively to gauge the extent and complexity of CAD. To assess the degree of incompleteness of revascularization, the investigators calculated the SYNTAX score after PCI and thus obtained the residual SYNTAX score. A progressively higher residual SYNTAX score was shown to be associated with increased 5-year mortality.[41] Although patients with complete revascularization numerically had the lowest 5-year mortality, no significant differences were reported in 5-year mortality between patients with complete and those with minor incomplete revascularization (residual SYNTAX score 0, 8.5%; >0 to 4, 8.7%; >4 to 8, 11.4%; $P = .60$). In patients with a residual SYNTAX score greater than 8, however, 5-year mortality rose to 35.3% ($P < .001$; Fig. 2-3). Multivariable analysis confirmed the residual SYNTAX score as an independent predictor of 5-year mortality (HR, 1.65; 95% CI, 1.41 to 1.92; $P < .001$). Residual SYNTAX score was also associated with the composite of death, MI, and stroke and with major adverse cardiovascular and cerebrovascular events (MACCEs): death, MI, stroke, and target-vessel revascularization (see Fig. 2-3).

The studies mentioned above have been based on anatomic criteria. In the intermediate range of stenoses, however, the anatomic degree—as judged by visual estimation or even quantitative computerized angiography—is poorly correlated with functional relevance, as assessed by noninvasive functional imaging or invasive functional testing, such as measurement of fractional flow reserve (FFR).[42] Recent studies with measurement of FFR have indicated that functional testing reliably discriminates between coronary stenoses that should be treated conservatively and those in need of revascularization.[43-45] Moreover, basing the PCI strategy on functional, rather than purely anatomic, criteria reduces the periinterventional risk[46] and improves the long-term outcome[47] of PCI as shown by the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study.

A recent meta-analysis of the potential survival benefit of complete versus incomplete revascularization addressed not only the impact of the revascularization modality but also that of anatomic versus

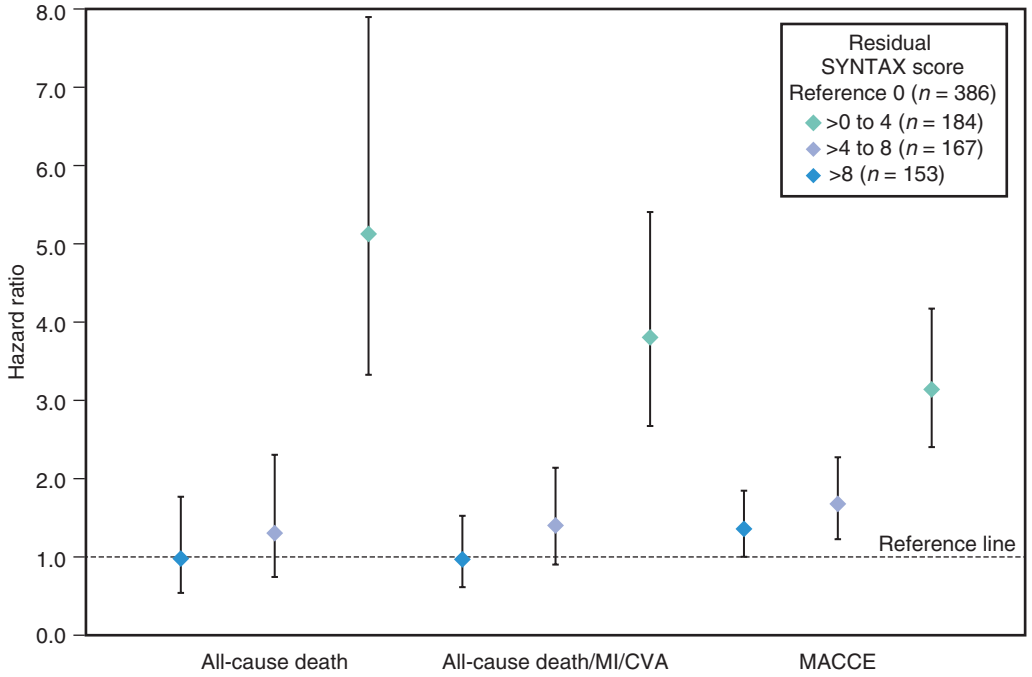


FIGURE 2-3 Five-year clinical outcomes stratified by tertiles of the residual SYNTAX score. Hazard ratios are relative to complete revascularization (reference line, residual SYNTAX score 0). Hazard ratios for tertiles of the residual SYNTAX score (>0) are shown. The error bars represent 95% confidence intervals. *CVA,* Cerebrovascular accident; *MACCE,* major adverse cardiac and cerebrovascular event; *MI,* myocardial infarction. (From Farooq V, Serruys PW, Bourantas CV, et al: Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery [SYNTAX] trial validation of the residual SYNTAX score. *Circulation* 128[2]:141-151, 2013.)

functional assessment.[48] This meta-analysis comprised 35 studies with 89,883 patients from subgroups of randomized trials or from observational studies. Irrespective of the revascularization modality, this meta-analysis confirmed a consistent survival benefit of complete versus incomplete revascularization with both anatomic and functional assessment (relative risk [RR] for mortality with complete revascularization, 0.73 [95% CI, 0.67 to 0.79; $P < .001$], with anatomic definition and RR, 0.57 [95% CI, 0.36 to 0.89; $P = .014$], with functional definition). Nevertheless, it is noteworthy that the point estimate of the relative risk of mortality, comparing complete with incomplete revascularization, was lower with functional complete revascularization than with anatomic complete revascularization.[48]

Given the major impact of the extent of revascularization on long-term survival, consideration must be given to the likelihood of achieving complete revascularization. When PCI is unlikely to achieve complete revascularization, surgery may offer better prospects, yet this may not always be the case; in some instances, poor target vessels for CABG may be treated by PCI with higher chances of success.

PROGNOSTIC INDICATION FOR REVASCULARIZATION: PERCUTANOUS CORONARY INTERVENTION VERSUS CORONARY ARTERY BYPASS GRAFTING

Multivessel Disease

From the late 1980s to the early 1990s, several studies compared plain balloon angioplasty with CABG. Among them were three larger trials—RITA (n = 1011), the Coronary Angioplasty Versus Bypass Revascularization Investigation (CABRI; n = 1154), and the Bypass Angioplasty Revascularization Investigation (BARI; n = 1829)—and three smaller trials—the German Angioplasty Bypass Surgery Investigation (GABI; n = 358), the Emory Angioplasty Versus Surgery Trial (EAST; n = 392), and the Toulouse monocentric study (n = 152). In each of these trials, survival after PCI versus CABG was similar, as was the incidence of Q-wave MI, but repeat revascularization was more frequently needed after PCI. However, in a meta-analysis based on data extracted from the literature, Hoffmann and colleagues[49] showed a significant survival benefit from surgery compared with PCI of 3% absolute at 5 years and of 4% absolute at 8 years. The results of the early studies antedating the stent era are, of course, not reflective of the current practice of coronary revascularization. Since the early studies, major advances have been achieved in PCI, CABG, and medical treatment; these include coronary stents, effective antiplatelet therapy, the use of arterial conduits up to complete arterial revascularization, and vigorous pharmacologic risk-factor modification. For these reasons, the results of randomized trials performed in the prestent era cannot be transferred to current practice.

Lessons From Studies With Bare-Metal Stents

Randomized Studies

Five randomized trials compared stenting with CABG for multivessel disease: ARTS,[50,51] Stent or Surgery (SoS),[52] the Argentine Randomized Trial of Percutaneous Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients with Multiple-Vessel Disease (ERACI-II),[53,54] the Medicine, Angioplasty, or Surgery Study (MASS-II),[55] and Angina With Extremely Serious Operative Mortality Evaluation (AWESOME).[56] Four major studies were incorporated in a meta-analysis based on individual patient data, which confirmed the results of the majority of the individual studies.[57] This meta-analysis comprised ARTS, SoS, ERACI-II, and MASS-II but excluded AWESOME because the high-risk characteristics of the patients in this last trial were clearly different from those of the patient population of the other four trials. This meta-analysis confirmed that PCI with stent placement was associated with a 1-year incidence of death, MI, or stroke similar to that of CABG. Nevertheless, the need for repeat

revascularization was considerably higher after PCI, although the observed gap with CABG surgery has narrowed from the approximately 30% reported in the present era to approximately 14%. Compared with PCI, CABG was associated with a slightly lower frequency of recurrent angina (77% vs. 82%; $P = .002$). Another meta-analysis based on aggregate data from ARTS,[50,51] SoS,[52] ERACI-II,[53,54] and Stenting Versus Internal Mammary Artery (SIMA)—a study on isolated proximal LAD stenosis—extended the analysis to a follow-up of 3 years.[49] The point estimates for both the 3-year incidence of death and nonfatal MI were lower after PCI than after CABG. However, a significant difference was found only for nonfatal MI. Moreover, this meta-analysis confirmed that the 1-year incidence of repeat intervention was 15% absolute higher after PCI than after CABG but did not demonstrate any significant further changes from 1 to 3 years. For ARTS, the largest trial to compare PCI with CABG for the treatment of multivessel disease,[50,51] 5-year results are available. ARTS included a total of 1205 patients with at least two de novo lesions located in different vessels and territories not including the LMCA. In this study, 600 patients were randomly assigned to stenting, and 605 were randomly assigned to bypass surgery; 67% of the patients had a double-vessel disease, and 32% had triple-vessel disease. At 5 years, the incidence of death was 8% in the stent group versus 7.6% in the CABG group (RR, 1.05; 95% CI, 0.71 to 1.55; $P = .83$). Likewise, no significant difference was found in cerebrovascular accident (3.8% vs. 3.5%; RR, 1.10; 95% CI, 0.62 to 1.97; $P = .76$), Q-wave MI (6.7% vs. 5.6%; RR, 1.19; 95% CI, 0.76 to 1.85; $P = .47$), non–Q-wave MI (1.8% vs. 0.8%; RR, 2.22; 95% CI, 0.78 to 6.35; $P = .14$), or the composite thereof (18.2% vs. 14.9%; RR, 1.22; 95% CI, 0.95 to 1.58; $P = .14$). However, a significant difference was reported in the incidence of repeat revascularization (30.3% vs. 8.8%; RR, 3.46; 95% CI, 2.61 to 4.60; $P < .001$). In the stent group, 10.5% of the revascularizations involved CABG, whereas in the CABG group 1.2% of the revascularizations involved CABG. In summary, the 5-year outcome with respect to the serious end points of death, MI, and cerebrovascular accident (CVA) with the surgical and nonsurgical approaches was similar. With the primarily catheter-based approach, the chance of avoiding CABG during the subsequent 5 years was 90%, with a similar outcome with respect to death, CVA, and MI as with the surgical approach but at the expense of a 20% higher incidence of repeat catheter interventions. Consistent with the long-term results of ARTS,[50,51] the 10-year results of MASS-II[58] showed no significant survival benefit of CABG over PCI (HR, 1.03; 95% CI, 0.69 to 1.53; $P = .88$), but a substantially increased need for repeat interventions was reported with PCI versus CABG (HR, 3.71; 95% CI, 1.82 to 7.52; $P < .0001$).

The studies described so far compared PCI with CABG in cohorts that were well suited for both procedures. The important question of whether patients at high risk for CABG surgery and refractory myocardial ischemia should undergo PCI as an alternative procedure was addressed in AWESOME.[56] This multicenter study included patients with myocardial ischemia refractory to medical management and the presence of one or more risk factors for adverse outcome with CABG, including prior open heart surgery, age greater than 70 years, LV ejection fraction less than 35%, MI within 7 days, or the need for intraaortic balloon pumping. Over a 5-year period, 2431 patients met the entry criteria. By physician consensus, 1650 patients formed a physician-directed registry assigned to CABG ($n = 692$), PCI ($n = 651$), or further medical therapy ($n = 307$), and 781 were angiographically eligible for random allocation. Of the patients who were angiographically acceptable, 454 consented to randomized assignment between CABG and PCI; the remaining 327 constituted a patient-choice registry. At all time points during the 5-year follow-up of the randomized study, an insignificant survival benefit of PCI over CABG was reported (97% vs. 95% at 30 days and 75% vs. 70% at 5 years).[59] Within the first 3 years after randomization, more patients randomized to PCI received a subsequent revascularization (37% vs. 18%, $P < .001$), whereas between 3 and 5 years of follow-up, repeat revascularization was similarly frequent in both the PCI group and the CABG group (6% vs. 4%). In the physician-directed subgroup, the 3-year survival rate was 76% for both CABG and PCI. In the patient-choice subgroup, the 3-year survival was 80% with CABG but 98% with PCI. The findings of the AWESOME registry[60] therefore support the findings of the main study. The AWESOME investigators specifically addressed the issue of whether PCI is the preferred option for repeat intervention in patients with previous CABG.[61] In the subgroup with previous CABG, 3-year survival rates were 73% and 76% with CABG or PCI, respectively, in the randomized patients; 71% versus 77% in the physician-directed registry; and 65% versus 86% ($P = .001$) in the patient-choice registry. The authors concluded that PCI is preferable to CABG for many post-CABG patients.

Registries

It has been argued that the randomized studies to compare PCI with CABG in multivessel disease comprised only a small proportion of the patients presenting at dedicated high-volume centers.[62] Therefore it is claimed that the results of these trials may not be applicable to the vast majority of patients in need of coronary revascularization. It is thus an important question whether the absence of a substantial difference in survival between PCI and CABG can also be verified in large registries. Contrary to the randomized studies that compared PCI bare-metal stents to CABG, several large registry analyses from the Cleveland, New York, and Rotterdam databases found a significant difference in risk-adjusted survival that favored CABG over PCI.[63-65] Despite these statistically clear-cut results, the implications of the findings in these registries must be interpreted cautiously because several limitations derive from the nonrandomized nature of these comparisons. Adjustment by proportional hazard models cannot fully substitute for randomization because comprehensive inclusion of all confounders is impossible. One important confounder that was not included in any of the risk adjustment was subsequently published by the New York group[38]—that is, incomplete revascularization. These investigators noted that in their registry, 69% of the patients who received a stent had incomplete revascularization. In the same registry, incomplete revascularization after PCI had a statistically significant and clinically relevant impact on outcome, as discussed above. Between patients completely revascularized and those incompletely revascularized, a 2.1% survival disadvantage was reported in 3 years in the absence of a total occlusion, and a 2.7% difference was reported in the presence of a nonrecanalized total occlusion.[38] The difference between complete and incomplete revascularization within the stent group of the New York registry was on the same order of magnitude as the difference between the stent group and the CABG group in the entire registry. The comprehensive analysis from the Duke registry gives additional insight.[66] This registry comprised 18,481 patients with significant CAD between 1986 and 2000 who were assigned by physician preference to medical therapy ($n = 6862$), PCI ($n = 6292$), or CABG ($n = 5327$). Each group was categorized into three subgroups according to the baseline severity of CAD: *low severity* (predominantly single vessel), *intermediate severity* (predominantly two vessel), and *high severity* (all three vessel). Mortality was evaluated by Cox models adjusted for cardiac risk, comorbidity, and propensity for selection of a specific treatment. In all three anatomic subgroups, revascularization conferred a significant survival benefit compared with medical therapy. The extent of this survival benefit varied with the degree of CAD and ranged from an additional 8 months gained during 15 years in the low-severity group to 24 months gained in the high-severity group. In the low- and intermediate-severity groups, the benefit from revascularization was independent of the treatment modality, with similar results by CABG and PCI. In the high-severity subgroup, however, CABG was associated with a small but significant survival benefit of 8 months during 15 years. It is noteworthy that the impact of revascularization versus medical treatment is substantially larger than the impact of the choice of revascularization modality. In summary, registry data that compared PCI that used bare-metal stents with CABG suggest a small survival benefit of surgery versus PCI in patients with multivessel disease. A large proportion of this survival benefit appears to be attributed to patients with the most complex anatomy and to those who do not achieve complete revascularization with PCI.

Lessons From Studies With Drug-Eluting Stents

Registries

ARTS II[67]—a 45-center, 607-patient registry—intended to compare 1-year outcomes of the sirolimus-eluting stent against the historical results of the two arms of ARTS I.[51,52] To achieve the number of treatable lesions per patient comparable to ARTS I, patients were stratified to ensure that at least one-third had three-vessel disease. Compared with ARTS I, ARTS II comprised a higher-risk cohort: 53.5% had three-vessel disease, and diabetes was present in 26.2%. Mean stented length was 72.5 mm, with 3.7 stents implanted per patient. The 5-year incidence[68] of death, stroke, or MI was 12.9% in ARTS II, versus 14% in the CABG arm of ARTS I ($P = .1$), and it was 18.1% in the bare-metal-stent arm of ARTS I ($P = .007$). The 5-year rate of MACCEs in ARTS II of 27.5% was significantly higher than that among patients in ARTS I who received CABG (21.1%, $P = .02$), and it was lower than that among ARTS I patients who received bare-metal stents (41.5%, $P < .001$). The authors concluded that at 5 years, the sirolimus-eluting stent had a safety record comparable to that of CABG and superior to that of bare-metal stents. Nevertheless, surgery still afforded a lower need for repeat revascularization, although overall event rates in ARTS II approached the surgical results in ARTS I.[51,52]

Two subsequent analyses based on larger registries subsequently challenged the promising results of ARTS II.[69,70] By linking several large databases, one study analyzed survival data of 185,793 patients 65 years of age or older who had two- or three-vessel CAD without acute MI.[69] Out of these patients, 86,244 had undergone CABG, and 103,549 had had PCI with a rate of drug-eluting stents of 86%. To reduce treatment-selection bias, inverse-probability-weighting adjustment was performed with the use of propensity scores. At 4-year follow-up, mortality was significantly lower in the CABG group than in the PCI group (16.4% vs. 20.8%; RR, 0.79; 95% CI, 0.76 to 0.82), a finding that was consistent across multiple subgroups.[69] Similar results were obtained in an observational study based on New York State's reporting system.[70] Confirming and extending their earlier studies based on the same registry,[71] the more recent analysis included patients undergoing the revascularization for two- or three-vessel disease without LMCA stenosis in the absence of acute MI.[70] To control for treatment-selection bias, patients were matched for several pertinent variables that included propensity of CABG. Thus 8121 pairs of matched patients were obtained. Compared with PCI patients, 5-year survival mortality was significantly lower in CABG patients (19.6% vs. 26.4 %; HR, 0.71; 95% CI, 0.67 to 0.77; $P < .001$).[70] There was a significant interaction (P interaction [P_{int}] = .01) with age that indicated a greater survival benefit of CABG at younger ages, thereby contradicting the results meta-analysis of randomized studies that compared CABG with PCI using bare-metal stents.[72] Despite this interaction, a significant survival benefit was found in both younger (<60 years) and older patients (>80 years), as well as in all other clinical and anatomic subsets investigated.

Although the registry data in the era of drug-eluting stents continue to find a survival benefit of CABG over PCI, the same limitations apply as for the registry-based analyses with bare-metal stents. Apart from unknown confounders, the issue of completeness of revascularization was not addressed, which obscures interpretation of the results. Moreover, none these registries stratified patients by state-of-the-art measures of anatomic complexity, such as the SYNTAX score.

Randomized Studies

The promising results of ARTS II had to be interpreted cautiously because this study does not account for advances in surgical technique that may have occurred since the days of ARTS I. Thus randomized studies were needed to clarify the role of drug-eluting stents compared with CABG for multivessel disease. This issue was the objective of the SYNTAX trial,[73] a randomized trial that compared PCI with paclitaxel-eluting stents and CABG for treating patients with previously untreated three-vessel or left main CAD or both. The study enrolled 1800 patients, in whom the local cardiac surgeon and interventional cardiologist determined that equivalent anatomic revascularization could be achieved with either treatment. At 1 year, the primary end point, MACCE, was significantly higher in the PCI group (17.8% vs. 12.4% for CABG; $P = .002$), in large part because of an increased rate of repeat revascularization (13.5% vs. 5.9%, $P < .001$). Apart from reintervention, no significant differences were found in any of the components of the primary end point or a combination thereof except for stroke, which was significantly more likely to occur with CABG (2.2% vs. 0.6% with PCI; $P = .003$). Five-year results of SYNTAX have been reported (Table 2-4).[74] By 5 years, the primary end point, MACCE, was reached in 37.3% of the PCI group and in 26.9% of the CABG group ($P < .001$). This difference was largely caused by a difference in the need for reintervention (25.9% vs. 13.7%, $P < .001$). The composite risk of all-cause death, MI, and stroke was also significantly higher in the PCI group than in the CABG group (20.8% vs. 16.7%, $P = .03$). This difference was driven by significant difference in cardiac death (9.0 % vs. 5.3%, $P = .003$) and MI (9.7% vs. 3.8%, $P < .001$) that favored CABG, whereas in the PCI group, a trend toward less frequent strokes prevailed (2.4% vs. 3.7%, $P = .09$). In SYNTAX, randomization was stratified according to LMCA involvement. In the 1095 patients who belonged to the subset defined by three-vessel disease without LMCA stenosis, PCI compared with CABG performed less well than in the entire SYNTAX study (see Table 2-4).[75] Five-year all-cause mortality after PCI in the three-vessel-disease stratum was significantly higher than that after CABG (14.6% vs. 9.2%, $P = .006$), as was the incidence of MI (10.6% vs. 3.3%, $P < .001$), but no significant difference was reported in stroke rate (3.0% vs. 3.4%, $P = .66$).[75] Thus both the 5-year composite of death, MI, and stroke—as well as 5-year MACCE after PCI—were significantly inferior to those after CABG (22.0% vs. 14.0%, $P < .001$; and 37.5% vs. 24.2%, $P < .001$, respectively).[75] The authors of the SYNTAX trial also stratified the study patients to tertiles of the SYNTAX score (see Table 2-4). In the lowest tertile of SYNTAX scores (those <23), 3-year mortality in the three-vessel-disease subset after PCI was similar to that after CABG (10.2% vs. 9.3%, $P = .81$).[75] Likewise, only a statistically insignificant numerical increase was found in MACCE with PCI compared with CABG (33.3% vs. 26.8%, $P = .45$).[75] These results in the lowest tertile of SYNTAX scores in the three-vessel-disease subset were consistent with the results in the corresponding subset of the entire study (10.1% vs. 8.9% [$P = .64$] for death; and 32.1% vs. 28.6% [$P = .43$] for MACCE).[74] In the highest tertile of SYNTAX scores (>32), PCI was associated with excess 5-year mortality compared with CABG both in the three-vessel-disease subset and in the entire study cohort (17.8% vs. 8.8% [$P = .015$] and 19.2% vs. 11.4% [$P = .005$], respectively).[74,75] Similar to the finding in the entire subset with three-vessel disease, mortality in the middle tertile was also higher at 5 years after PCI than after CABG (16.3% vs. 9.6%, $P = .047$).[74,75] In the two highest tertiles of SYNTAX scores of the three-vessel-disease subset, major differences were also found in 3-year MACCE rates that favored CABG over PCI (see Table 2-4).[75]

When interpreting the results of SYNTAX, two caveats deserve consideration: First, 50 patients of the CABG group, but only 11 of the PCI group, were lost to follow-up because of withdrawal of consent.[74] The authors report that a sensitivity analysis showed that the primary end point analysis was not significantly affected by this imbalance of follow-up.[74] Nevertheless, it cannot be excluded that the effect size was affected. Second, the paclitaxel-eluting stent used in SYNTAX carries a higher risk of late stent thrombosis compared with the contemporaneous first-generation sirolimus-eluting stent[4,76] and, particularly, compared with modern, new-generation drug-eluting stents.[4,77] Meta-analyses also suggest that the prevention of restenosis by paclitaxel-eluting stents is inferior to that of other drug-eluting stent types.[76,77]

Despite these caveats, the SYNTAX study demonstrates that CABG is the preferred revascularization strategy in the majority of patients suffering from three-vessel disease without LMCA involvement. In this setting, compared with PCI, CABG improves survival and reduces the risk of MI and the need for reintervention. In patients with SYNTAX

TABLE 2-4 5-Year Outcomes in SYNTAX Stratified to Coronary Involvement and SYNTAX Score

	ANY			<23			23 TO 32			>32		
SYNTAX Scores	**PCI**	**CABG**	***P***	**PCI**	**CABG**	***P***	**PCI**	**CABG**	***P***	**PCI**	**CABG**	***P***
Entire cohort (*N*)	903	897		299	275		310	300		290	315	
1° end point: MACCE	37.3%	26.9%	<.01	32.1%	28.6%	.43	36.0%	28.5%	.008	44.0%	26.8%	<.001
Death	13.9%	11.4%	.10	10.1%	8.9%	.64	13.8%	12.7%	.68	19.2%	11.4%	.005
Death, MI, stroke	20.8%	16.7%	.03	16.1%	14.9%	.81	20.7%	18.0%	.42	26.1%	17.1%	.007
Repeat revasc.	25.9%	13.7%	<.01	23.0%	16.9%	.56	24.1%	12.7%	<.001	30.0%	12.1%	<.001
Three-vessel subset (*N*)	546	549		181	171		207	208		155	166	
1° end point: MACCE	37.5%	24.2%	<.001	33.3%	26.8%	.21	37.9%	22.6%	<.001	41.9%	24.1%	<.001
Death	14.6%	9.2%	.006	10.2%	9.3%	.81	16.3%	9.6%	.047	17.8%	8.8%	.015
Death, MI, stroke	22.0%	14.0%	<.001	17.5%	14.8%	.56	23.2%	14.7%	.035	26.2%	12.5%	.002
Repeat revasc.	25.4%	12.6%	<.001	23.1%	14.9%	.038	25.1%	11.0%	<.001	28.2%	12.6%	<.001
LMCA subset (*N*)	357	348		118	104		103	92		135	149	
1° end point: MACCE	36.9%	31.0%	.12	30.4%	31.5%	.74	32.3%	32.7%	.88	46.5%	29.7%	.003
Death	12.8%	14.6%	.53	7.0%	11.3%	.28	8.9%	19.3%	.04	20.9%	14.1%	.11
Death, MI, stroke	19.0%	20.8%	.52	13.9%	15.2%	.71	15.7%	24.9%	.11	26.1%	22.1%	.40
Repeat revasc.	26.7%	15.5%	<.01	20.3%	23.0%	.65	22.2%	16.6%	.40	34.1%	11.6%	<.001

Data from Mohr FW, Morice MC, Kappetein AP, et al: Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 381(9867):629-638, 2013.
1°, Primary; *CABG,* coronary artery bypass grafting; *LMCA,* left main coronary artery; *MACCE,* major adverse cardiac and cardiovascular event; *MI,* myocardial infarction; *N,* number of patients; *P, P* value; PCI, percutaneous coronary intervention; *revasc.*, revascularization.

scores less than 23; however, PCI afforded similar outcomes with respect to survival and MACCEs, a finding that was independent of LMCA involvement. In this setting, PCI would be the treatment of choice because it is associated with less discomfort to the patient and less resource consumption.

Special Considerations in Diabetic Patients

Compared with nondiabetic patients, those with diabetes often have a more advanced type of coronary atherosclerosis, with diffuse disease in small-lumen vessels. With any treatment modality for coronary revascularization, diabetic patients have an inferior outcome compared with nondiabetics. This was first shown for CABG. In patients with diabetes mellitus compared with nondiabetics, CABG is associated with a more rapid progression of atherosclerosis in both grafted and nongrafted vessels and is also associated with an accelerated degeneration of venous bypass grafts. Nevertheless, the CASS researchers[78] demonstrated that in older diabetic patients, coronary revascularization confers a substantial benefit compared with medical therapy alone. Likewise, PCI in patients with diabetes is associated with a substantially increased risk of adverse short- and long-term outcome compared with PCI in nondiabetics. In particular, the risk of restenosis after any type of PCI is substantially increased in diabetics compared with nondiabetics.[79,80] Moreover, whereas restenosis has little impact on survival in patients without diabetes, van Belle and coworkers[81] demonstrated that restenosis after plain balloon angioplasty in diabetics has a major impact on 10-year mortality, with a 45% relative increase for nonocclusive stenosis and more than a twofold increase with occlusive stenosis. The risk of periinterventional death and MI is also increased by about twofold after plain balloon angioplasty in diabetics compared with nondiabetics.[82] Comparing coronary bypass surgery with plain balloon angioplasty for multivessel disease, BARI reported 5- and 7-year mortalities in diabetics of 34.5% and 44.3%, respectively, whereas after bypass surgery, the respective mortalities were 19.4% and 23.6% ($P = .03$ and .01, respectively).[83] The findings in BARI that were subsequently confirmed by the 8-year analysis of EAST[84] led to a clinical alert from the National Heart, Lung, and Blood Institute for the abandonment of plain balloon angioplasty as a treatment option for multivessel CAD. Studies done in the era of plain balloon angioplasty, however, are not transferable to current practice. As first demonstrated by the studies on abciximab, the increased risk of thrombotic complications during early and longer-term follow-up can be abrogated by intense antiplatelet therapy.[85,86] More recently, the Intracoronary Stenting and Antithrombotic Regimen: Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics (ISAR-SWEET) study suggested that a similar effect can be achieved by effective pretreatment with clopidogrel.[87] In addition, it has been shown by various studies that compared with plain balloon angioplasty, stents reduce the subsequent incidence of restenosis, although this incidence continues to be higher in diabetics than in nondiabetics.[80,88,89] Given the major impact of restenosis on survival, it is plausible that compared with plain balloon angioplasty, stents may improve the long-term outcome of PCI substantially. Finally, the recently improved means of achieving tight metabolic control can further improve outcome after catheter intervention.[90,91]

Because coronary revascularization in diabetics differs in many respects from that in nondiabetics, the indication for PCI in diabetics deserves special attention.

Studies With Bare-Metal Stents

Of the studies that compared bare-metal stents with CABG, the ARTS, AWESOME, and ERACI-II researchers reported subgroup analyses for diabetics. Of the 1205 patients included in ARTS, 112 diabetics were randomly assigned to stent implantation, and 69 were randomly assigned to bypass surgery.[92] Mortality during 1-year follow-up, however, was higher in the stent group (6.3%) than in the surgical group (3.1%), although statistical significance was missed ($P = .29$). Notably, in the PCI group, a significant difference was found in event-free survival between diabetics and nondiabetics (63.4% vs. 76.2%) that was not present in the surgical group. The number of diabetics included in ARTS was too low to allow for definite conclusions. Likewise, analysis of the 90 diabetics in ERACI (without stent) and ERACI-II (with stent) and of the 144 diabetics in MASS-II[93] randomized to CABG or PCI did not allow any firm conclusions because of a lack of power. The AWESOME study addressed patients with a high risk for CABG. The number of diabetics included in AWESOME was 144 in the

randomized study, 89 in the patient-choice registry, and 525 in the physician-choice registry.[94] In the randomized study, the 4-year mortality of diabetics after catheter intervention was not significantly different from that after bypass surgery, but the point estimates favored catheter intervention (19% vs. 28%, $P = .27$). Similar results were obtained in the patient-choice registry (11% vs. 15%, $P = .73$) and the physician-choice registry (29% vs. 27%, $P = .77$). The results of AWESOME therefore suggest that in patients with multivessel disease and refractory angina who have an increased risk with CABG, coronary implantation of bare-metal stents is a safe alternative to surgical revascularization. The Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH), the only large registry that addressed stent-supported PCI with bypass surgery in patients with diabetes, did not reveal any benefit of CABG compared with PCI.[95]

Studies With Drug-Eluting Stents

Drug-eluting stents (DESs) are particularly appealing in diabetics because they offer a solution to the most crucial problem of PCI in this patient subset—that is, restenosis. A meta-analysis of the diabetic patients in randomized studies that compared DESs with bare-metal stents (BMSs) confirmed that in diabetes mellitus, DESs significantly reduce the risk of restenosis compared with BMSs[96-98] by 37% to 69% depending on the stent type.[97] Nevertheless, the excess risk of restenosis in diabetics compared with nondiabetics prevailed even with DESs.[96] No safety issues were reported with respect to the 1-year incidence of death or of the composite of death and nonfatal MI when DESs were compared with BMSs in diabetics,[97] provided that dual antiplatelet therapy is pursued for at least 6 months.[98] Based on the older studies for PCI in diabetes, it may be anticipated that the reduction in restenosis by DESs compared with BMSs may confer a survival benefit during longer-term follow-up in diabetics.[81] Hence the role of PCI compared with CABG in the treatment of multivessel disease had to be reassessed in the era of DESs.

The Coronary Artery Revascularization in Diabetes (CARDia) trial was designed to compare PCI with CABG in patients with diabetes.[99] A total of 510 diabetic patients with multivessel or complex single-vessel coronary disease were randomized to CABG or PCI with BMSs in the first 30% of the patients and subsequently with sirolimus-eluting stents. CARDia included a low-risk cohort: three-vessel disease accounted for only 62% of the cohort, and only 1% of the lesions treated by PCI in CARDia were bifurcations. The primary end point—the 1-year composite incidence of all-cause mortality, MI, and stroke—was 10.5% in the CABG group and 13.0% in the PCI group ($P = .39$); all-cause mortality rates were 3.2% and 3.2%; and the rates of repeat intervention were 2.0% and 11.8% ($P < .001$), respectively. Thus the 1-year rate of MACCEs after CABG was significantly lower than that after PCI (11.3% vs. 19.3%; HR, 1.77; 95% CI, 1.11 to 2.82; $P = .02$). With respect to the primary end point, as well as MACCEs, interactions occurred with the stent type that favored DESs over BMSs ($P = .076$ and $P = .131$, respectively). Nevertheless, the observed 1-year rate of MACCEs in the subgroup with sirolimus-eluting stents was 18.0% after PCI compared with 12.9% after CABG. In the meantime, 5-year outcomes of CARDia were reported.[100] Still, no significant differences were reported between CABG and PCI in all-cause mortality (12.6% vs. 14%; HR, 0.85; 95% CI, 0.53 to 1.37; $P = .53$) or the composite of all-cause mortality, MI, or stroke (20.5% vs. 26.6%; HR, 0.75; 95% CI, 0.52 to 1.06; $P = .11$). The need for repeat intervention was, however, higher after PCI than after CABG (22.2% vs. 9.2%; HR, 0.41; 95% CI, 0.26 to 0.65; $P = .11$). It remains unclear to what extent the increased need for intervention after PCI had to be attributed to the use of BMSs in some of the patients. CARDia suggested that in diabetic patients with less complex CAD, PCI with DESs may be as safe as CABG but is associated with a higher need for intervention.

For diabetic patients with multivessel CAD, the Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial was the landmark trial to assess the optimal revascularization strategy with contemporary state-of-the art surgical, interventional, and medical

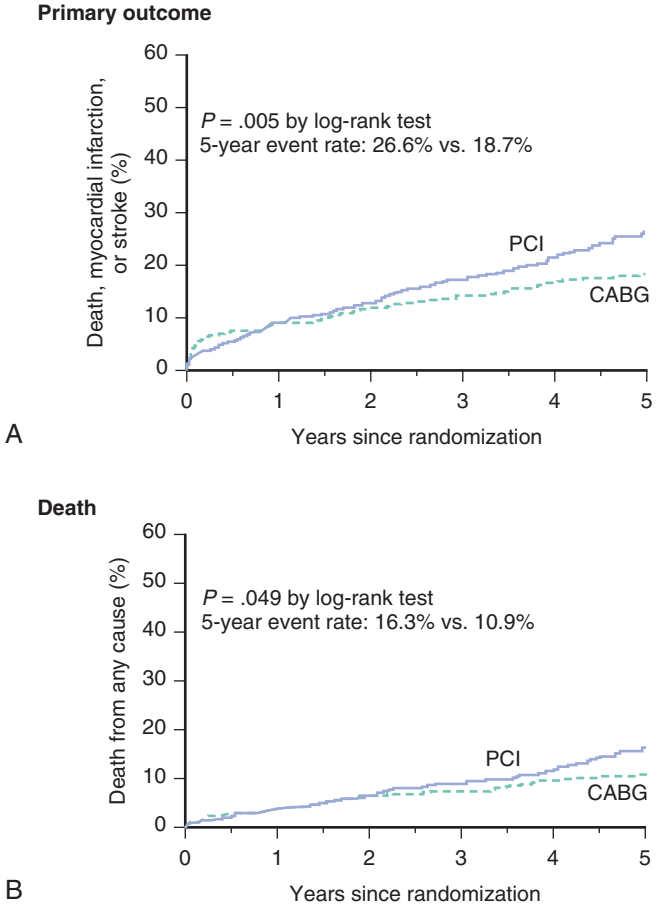


FIGURE 2-4 Kaplan-Meier estimates of the composite primary outcome and death in the FREEDOM trial comparing percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) in diabetic patients with coronary multivessel disease. Shown are rates of the composite primary outcome of death, myocardial infarction, or stroke (**A**) and death from any cause (**B**) truncated at 5 years after randomization. The *P* value was calculated by means of the log-rank test. (Reproduced with permission from Farkouh ME, Domanski M, Sleeper LA, et al: Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 367[25]:2375-2384, 2012.)

treatment.[101] With 1900 patients enrolled and a follow-up of 5 years, the study was adequately powered. The primary outcome, the 5-year composite incidence of death from any cause, nonfatal MI and nonfatal stroke occurred less frequently in the CABG group than in the PCI group (18.7% vs. 26.6%, absolute difference of 7.9%; 95% CI, 3.3 to 12.5, $P = .005$; Fig. 2-4, *A*).[101] This difference was driven by a significant 5-year survival benefit (10.9% vs. 16.3%, $P = .049$; see Fig. 2-4, *B*) and by a lower 5-year incidence of MI with CABG compared with PCI (6.0% vs. 13.9%, $P < .001$).[101] However, CABG was associated with a slight, but statistically significant, increase in the 5-year incidence of stroke (5.2% vs. 2.4%, $P = .03$). CABG also afforded a slightly better intermediate-term health status and quality of life than PCI.[102] The benefit of a CABG was similar in two-vessel and three-vessel disease (Fig. 2-5).[101] There also was a post-hoc assessment of SYNTAX score and a stratification to low (≤22), intermediate (23 to 32), and high (≥33) SYNTAX score. In the low range of SYNTAX score, the hazard ratio that compared CABG with PCI was close to unity and was statistically insignificant, whereas at SYNTAX scores above 22, a substantial and statistically significant benefit of CABG was found with respect to the primary end point (see Fig. 2-5). These findings are difficult to

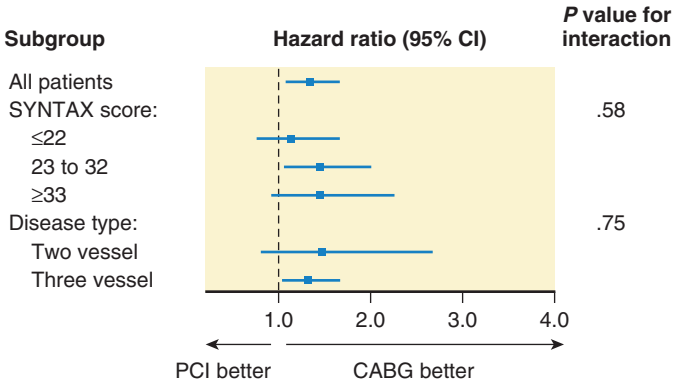


FIGURE 2-5 Primary composite outcome, according to a subgroup of the FREEDOM trial that compared percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) in diabetic patients with coronary multivessel disease. Subgroup analyses were performed with the use of Cox proportional hazards regression. *CI,* Confidence interval. (From Farkouh ME, Domanski M, Sleeper LA, et al: Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 367[25]:2375-2384, 2012.)

interpret, however, because the *P* value for interaction did not reach statistical significance (P_{int} = .485).[101] Thus the findings of FREEDOM demonstrate a substantial benefit of CABG over PCI in the majority of diabetic patients with multivessel disease, particularly those with more complex coronary anatomies, but they do not completely rule out the option of PCI in patients with simple coronary anatomies, such as those with SYNTAX scores below 23.

More recently, the 5-year results of the diabetic subset of SYNTAX were published.[103] In the PCI group, multivariate analysis identified diabetes as an independent predictor of MACCEs and of repeat revascularization but not of the composite of all-cause death, MI, or stroke. On the contrary, diabetes was not independently associated with any end point in the CABG group. In SYNTAX, randomization was stratified for diabetes. Among 452 patients with medically treated diabetes, 221 were assigned to CABG and 231 were assigned to PCI.[103] Concerning the 5-year incidence of MACCE, the primary end point of SYNTAX, CABG was superior to PCI (26.3% vs. 34.1%, *P* = .002).[103] To a large extent, this was due to a lower need for repeat revascularization (13.4% vs. 28.2%, *P* < .001). The differences in 5-year all-cause death (10.9% vs. 12.0%, *P* = .048) or the composite of all-cause death, MI, or stroke (15.9% vs. 19.8%, *P* = .069) were not significant between CABG and PCI. Nevertheless, significant differences that favored CABG were found for the 5-year incidence of cardiac death (4.9% vs. 7.7%, *P* = .035) and of MI (3.4% vs. 9.9%; *P* < .001). Stratifying the diabetic subgroup of SYNTAX to anatomic complexity as judged by tertiles of SYNTAX scores revealed diverse 5-year outcomes (Fig. 2-6): In the lowest tertile of SYNTAX scores (<23), the 5-year incidence of the composite of all-cause death, MI, or stroke was similar between CABG and PCI (20.1% vs. 19.4%, *P* = .79). Although there was a significantly lower need for reintervention after CABG versus PCI (18.5% vs. 38.5%, *P* = .014), it did not result in a significant difference in 5-year MACCE rates (33.7% vs. 42.5%, *P* = .38). The middle tertile of SYNTAX scores (23 to 32) exhibited a similar pattern of outcomes as the lowest tertile. In the highest tertile of SYNTAX scores (>32), however, 5-year MACCE rates were twice as high after PCI than after CABG (56.7% vs. 25.5%, *P* < .001). This comprised significant differences in the composite of all-cause death, MI, or stroke (*P* = .034) and in repeat revascularization (*P* < .001). In summary, the overall level of risk in the diabetic cohort of SYNTAX was higher than in the entire cohort, but on the whole, the findings are largely consistent with those in the entire study except for a higher risk of restenosis. Specifically, the subgroup analysis of diabetics suggests that the noninferiority of PCI compared with CABG in patients with SYNTAX scores less than 23, as found in the entire study, also applies to people with diabetes, at least as far as the hard end points are concerned.

The Collaborative Atorvastatin Diabetes Study (CARDS) was another dedicated trial that compared CABG with PCI using drug-eluting stents in diabetic patients. Although CARDS had a small size (*N* = 198) because of premature termination, 2-year follow-up revealed a survival benefit in diabetic patients with severe CAD treated with CAGB compared with those treated by PCI with drug-eluting stents.[104]

Taken together, the four randomized controlled trials that compared CABG with PCI using drug-eluting stents in diabetic patients—CARDia, FREEDOM, SYNTAX, and CARDS—show a survival benefit with CABG, as well as a reduction in the risk of MI and in the need for repeat revascularization.[105] In a meta-analysis of these trials, the relative risk of all-cause mortality comparing CABG with PCI was 0.65 (95% CI, 0.48 to 0.90; *P* = .008) at 5-year (or longest) follow-up.[105] However, some degree of heterogeneity was apparent (I^2 = 49%), with the numerically lowest and insignificant benefit of CABG in CARDia and the largest in CARDS. The overall findings of the meta-analysis are reproducible in large, unselected patient cohorts. In a registry that comprised 2885 multivessel diabetic patients, a propensity-matched comparison between patients treated by PCI and those treated by CABG revealed higher all-cause mortality with PCI (HR, 1.8; 95% CI, 1.4 to 2.2; *P* < .0001), as well as a higher risk of MI (HR, 3.3; 95% CI, 2.4 to 4.6; *P* < .0001) and of target-vessel revascularization (HR, 4.5; 95% CI, 3.4 to 6.1; *P* < .0001) during 5-year follow-up.[106]

In summary, based on currently available evidence, CABG is the preferred method of revascularization for most diabetic patients with coronary multivessel disease. Nevertheless, the risk associated with PCI, as well as the benefit of CABG, is not uniform across the spectrum of complex CAD. This is suggested by the analysis of outcomes stratified to levels of SYNTAX score and also by the more favorable results of PCI in the lower-risk cohort of CARDia. Accordingly, PCI remains an option to be considered in low-complexity subsets of multivessel disease, such as those with a SYNTAX score less than 23.

Left Main Coronary Artery Disease

Since the early days of Andreas Grüntzig, plain balloon angioplasty has been considered contraindicated in unprotected left main stem lesions because of the almost inevitable fatality when the procedure fails and because CABG had been established as a therapy that reduced mortality compared with medical treatment alone. With the advent of coronary stents, however, the verdict against catheter treatment of LMCA stenosis was challenged. Stents are particularly attractive for percutaneous treatment of left main CAD because they reduce acute complications and restenosis, especially in large-diameter vessels. Moreover, stents overcome the elastic recoil within the aortic wall, which represents a major problem with LMCA percutaneous transluminal coronary angioplasty (PTCA). It was thus not surprising that several groups reported favorable results of registries on bare-metal stenting of unprotected LMCA stenosis.[107-111]

Registries With Drug-Eluting Stents

Several registries have addressed the efficacy and safety of drug-eluting stents in the treatment of left main CAD. In 2005, three key studies were published that comprised cohorts of 85 to 102 patients treated with drug-eluting stents for unprotected left main CAD and historic control groups with bare-metal stents of 64 to 121 patients.[112-114] These studies suggested that drug-eluting stents, compared with bare-metal stents, may improve outcome—an assumption that was subsequently confirmed by nonrandomized comparisons and a small randomized study.[115-118] In the Intracoronary Stenting and Antithrombotic Regimen: Drug-Eluting Stents for Unprotected Left Main Stem Disease (ISAR-LEFT-MAIN) study, which comprised 607 patients treated with a drug-eluting stent, 2-year mortality was 9.7% and angiographic restenosis was 17.7%, with no significant difference between sirolimus- and

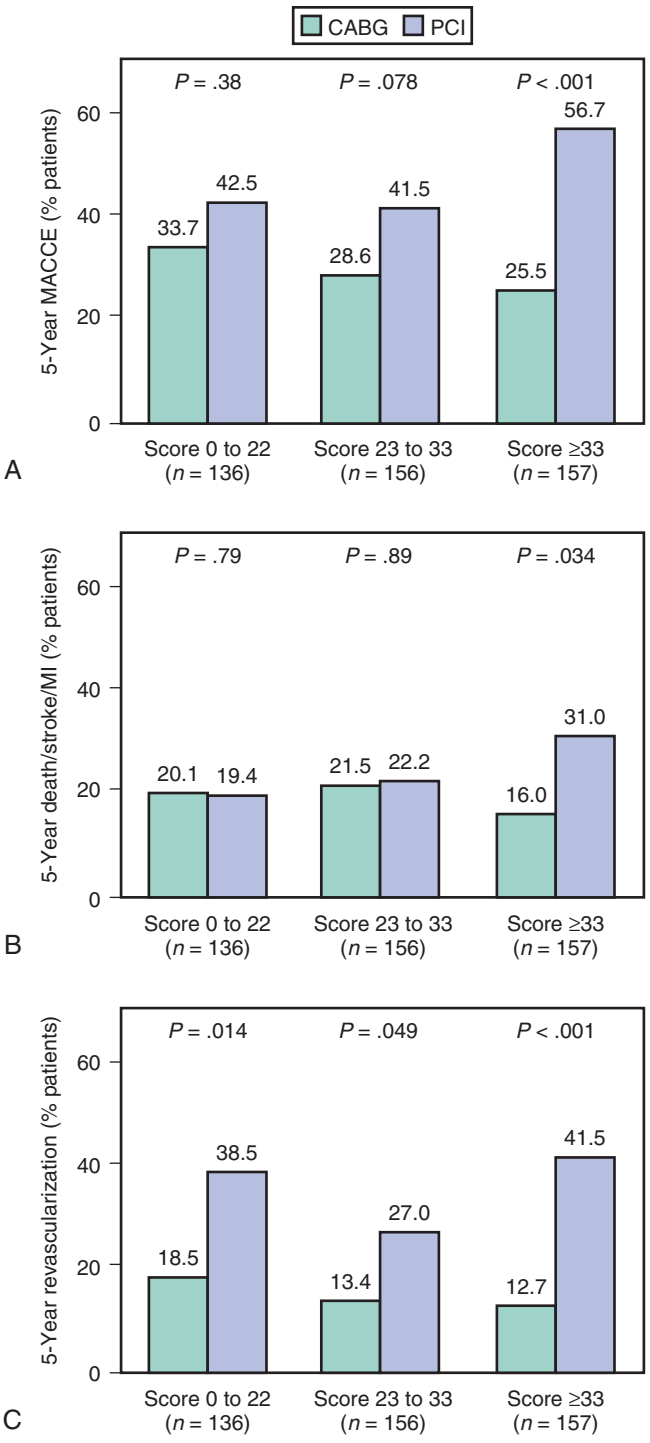


FIGURE 2-6 Five-year outcomes for diabetic patients and nondiabetic patients, according to anatomic lesion complexity as measured by the SYNTAX score. Results from the SYNTAX trial comparing percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) in patients with three-vessel disease or left main coronary artery disease with or without distal coronary artery stenosis. Binary event rates of (**A**) major adverse cardiac or cerebrovascular event (MACCE), (**B**) the composite end point of all-cause death/stroke/myocardial infarction (MI), and (**C**) repeat revascularization in diabetic patients. Rates are separated according to SYNTAX score tertiles, indicating low (0 to 22), intermediate (23 to 32), and high (≥33) anatomic lesion complexity. *CABG,* Coronary artery bypass grafting (*green bars*); *PCI,* percutaneous coronary intervention (*blue bars*). (From Kappetein AP, Head SJ, Morice MC, et al: Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *Eur J Cardiothorac Surg* 43[5]:1006-1013, 2013.)

paclitaxel-eluting stents.[119] Consistent results were reported from a multicenter registry.[120]

In 2006, the first two nonrandomized studies to compare implantation of drug-eluting stents for unprotected left main CAD with CABG were published.[121,122] With small sample sizes (N = 173 or 249) and short follow-up periods (6 or 12 months), these studies suggested similar outcomes of CABG or PCI with respect to survival and survival without MI and stroke, but somewhat higher rates of reintervention were reported after PCI than after CABG. Subsequently, several nonrandomized studies that compared PCI with drug-eluting stents versus CABG reported consistent results.[123-132] The largest of these studies was the Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization (MAIN-COMPARE) registry, for which 5-year results have been reported.[127] The MAIN-COMPARE registry evaluated 2240 patients with unprotected left main CAD who received coronary stents (n = 1102) or underwent CABG (n = 1138). Among the PCI-treated patients, 318 received bare-metal stents and 784 received drug-eluting stents. Median follow-up was 5.2 years. The 5-year incidences after PCI versus CABG were 11.8% and 13.6% (P = .06) for death; 12.2% and 14.7% (P = .03) for the composite of death, Q-wave MI, or stroke; and 16.0% versus 4.0% (P < .001) for target-vessel revascularization (TVR). After adjustment for differences in baseline risk factors, the corresponding hazard ratios were 1.13 (95% CI, 0.88 to 1.44; P = .35) for death; 1.07 (95% CI, 0.84 to 1.37; P = .59) for the composite of death, Q-wave MI, or stroke; and 5.11 (95% CI, 3.52 to 7.42; P < .001) for TVR. Comparisons of bare-metal stents with concurrent CABG and of drug-eluting stents with concurrent CABG yielded similar results. Hence with respect to clinically important end points, CABG for unprotected left main CAD did not afford a superior 5-year outcome compared with PCI. Yet a higher need for reintervention had to be faced when therapy was primarily based on PCI instead of CABG. After the results of the SYNTAX trial appeared, the investigators of MAIN-COMPARE performed a post-hoc analysis of 5-year outcomes stratified to SYNTAX scores.[133] After multivariate adjustment, the hazard ratios for death (adjusted HR, 0.52; 95% CI, 0.21 to 1.28; P = .15) and for death, MI, or stroke (adjusted HR, 0.54; 95% CI, 0.22 to 1.34; P = .18) favored PCI with SYNTAX scores less than 23, whereas with SYNTAX scores greater than 32, they favored CABG (adjusted HR for death, 1.46; 95% CI, 0.92 to 2.30; P = .11; adjusted HR for the composite outcome, 1.36; 95% CI, 0.87 to 2.12; P = .18; Fig. 2-7). The interaction P was .047 for death and .08 for the composite outcome.

The second largest registry in this field was the Multicenter Registry Evaluating Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting for Left Main Treatment (DELTA), which included 1874 patients with unprotected left main coronary artery stenosis treated with PCI and 901 treated with CABG.[130] At a median follow-up of 3.5 years, the adjusted analysis did not reveal any significant differences comparing PCI with CABG with respect to the primary composite end point of all-cause death, MI, and stroke (adjusted HR, 1.11; 95% CI, 0.85 to 1.42; P = .47) or with respect to all-cause mortality (adjusted HR, 1.16; 95% CI, 0.87 to 1.55; P = .32). Nevertheless, because of a higher incidence of TVR with PCI, the risk of the secondary end point, MACCE, was higher with PCI than with CABG (adjusted HR,

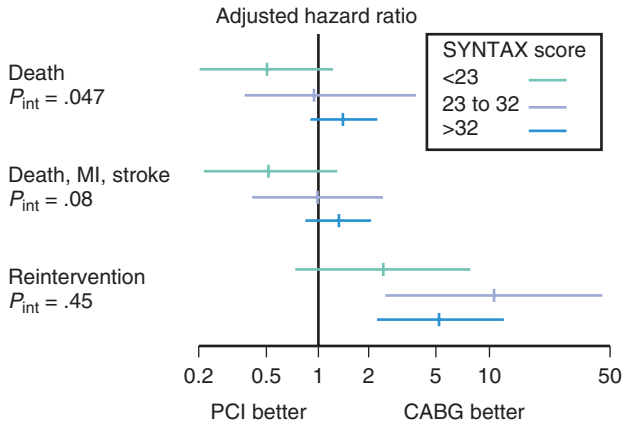


FIGURE 2-7 Adjusted hazard ratios of percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) in unprotected left main coronary artery stenoses stratified to levels of SYNTAX scores. Point estimates and 95% confidence intervals (CIs) for various outcomes are shown. *MI,* Myocardial infarction; P_{int}, interaction *P* value. (Data from Park DW, Kim YH, Yun SC, et al: Complexity of atherosclerotic coronary artery disease and long-term outcomes in patients with unprotected left main disease treated with drug-eluting stents or coronary artery bypass grafting. *J Am Coll Cardiol* 57[21]:2152-2159, 2011.)

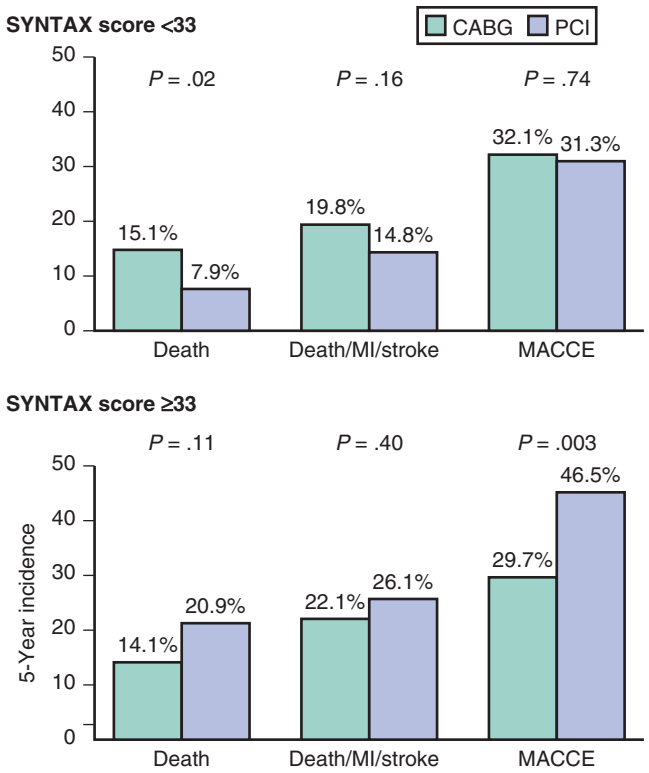


FIGURE 2-8 Five-year incidences of all-cause death; of the composite of death, myocardial infarction (MI), and stroke; and of major adverse cardiac or cerebrovascular events (MACCEs) after percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) in patients with unprotected left main coronary artery disease of SYNTAX trial stratified to levels of SYNTAX score. **A,** SYNTAX score less than 33. **B,** SYNTAX score 33 or greater. (Data from Morice MC, Serruys PW, Kappetein AP, et al: Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation* 129[23]:2388-2394, 2014.)

1.64; 95% CI, 1.33 to 2.03; $P < .0001$). Outcomes of the primary and the secondary end point were similar irrespective of sex.[134] The Appraise a Customized Strategy for Left Main Revascularization (CUSTOMIZE) registry, which comprised 894 patients, obtained similar results as the DELTA registry.[132] In addition, the CUSTOMIZE registry suggested that the excess need for reintervention with PCI was confined to patients younger than 75 years but was not present in older patients (adjusted $P_{int} = .034$).

In summary, the registry data do not support the concept that every left main coronary artery stenosis should be treated surgically.

Randomized Studies With Drug-Eluting Stents

In SYNTAX,[135-137] 705 patients belonged to the prespecified subset with left main CAD (see Table 2-4).[135-137] During 5-year follow-up,[135] the incidence of MACCEs did not differ significantly between PCI and CABG (36.9% vs. 31.0%, $P = .12$; see Table 2-4). The composite of death, MI, and stroke to 5 years was also similar between the two groups (19.0% vs. 20.8%, $P = .52$), as were mortality (12.6% vs. 14.6%, $P = .53$) and rate of MI (8.2% vs. 4.8%, $P = .10$). At 5 years, reintervention was significantly more frequent in the PCI group (26.7% vs. 15.0%, $P = .01$), whereas stroke was significantly more frequent in the CABG group (1.5% vs. 4.3%, $P = .03$). The extent of CAD outside the LMCA had a major impact on outcome after PCI versus CABG. As in the entire study, the 5-year MACCE rate was excessive after PCI compared with CABG in the tertile with SYNTAX scores above 32 (46.5% vs. 29.7%, $P = .003$), which included a trend for higher mortality with PCI (20.9% vs. 14.1%, $P = .11$; Fig. 2-8; see also Table 2-4). On the other hand, in the combined two lower tertiles of SYNTAX scores (5 through 32), all-cause mortality after PCI was significantly lower than that after CABG (7.9% vs. 15.1%, $P = .02$), and the 5-year MACCE incidence was almost identical between PCI and CABG (31.3% vs. 32.1%, $P = .74$; see Fig. 2-8). Moreover, only a clinically irrelevant and statistically insignificant numerical increase was found in the need for intervention after PCI compared with CABG (22.6% vs. 18.6%, $P = .36$). Thus the results of the SYNTAX study suggest that PCI is the treatment of choice for left main CAD unless extensive disease is present, as judged by SYNTAX scores above 32.

The key results of SYNTAX left main are corroborated by the Leipzig left main multicenter trial, which randomized 201 patients with an unprotected LMCA to undergo sirolimus-eluting stenting ($n = 100$) or CABG using predominantly arterial grafts ($n = 101$).[138] At 1 year, the primary clinical end point of major adverse cardiac events (MACEs)—comprising cardiac death, MI, and the need for TVR—was reached in 13.9% of patients after surgery as opposed to 19.0% after PCI ($P = .19$ for noninferiority). The combined rates for death and MI were comparable (surgery 7.9% vs. stenting 5.0%, noninferiority $P < .001$), but stenting was inferior to surgery for repeat revascularization (5.9% vs. 14.0%, noninferiority $P = .35$). Perioperative complications were higher after surgery (4% vs. 30%, $P < .001$). Like SYNTAX, the Leipzig trial suggests equipoise between PCI and CABG with respect to prognostically relevant end points.

To date, the largest published dedicated study to compare CABG with PCI for unprotected LMCA stenosis is the Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease (PRECOMBAT).[139] This trial randomly assigned 300 patients with unprotected LMCA stenosis to undergo CABG and 300 patients to undergo PCI with sirolimus-eluting stents. At 2-year follow-up, the primary composite end point of MACCE (death from any cause, MI, stroke, or ischemia-driven TVR) was reached in 12.2% of the PCI

group versus 8.1% of the CABG group (HR, 1.50; 95% CI, 0.90 to 2.52; $P = .12$). The composite rate of death, MI, or stroke at 2 years was similar between PCI and CABG (4.4% vs. 4.7%; HR, 0.92; 95% CI, 0.43 to 1.96; $P = .83$). However, ischemia-driven TVR occurred more frequently in the PCI group than in the CABG group (9.0% vs. 4.2%; HR, 2.18; 95% CI, 1.10 to 4.32; $P = .02$). In line with the Leipzig left main artery study and the left main artery cohort of SYNTAX, PRECOMBAT demonstrated that in terms of prognostically relevant end points, PCI is noninferior to CABG in the treatment of unprotected LMCA stenosis. Moreover, the need for repeat revascularization after PCI was low in PRECOMBAT with only a small, albeit statistically significant, surplus compared with CABG.

A meta-analysis[141] of randomized trials summarized 1-year outcomes of SYNTAX, the Leipzig study, PRECOMBAT, and the smaller ($N = 105$) Left Main Coronary Artery Stenting (LE MANS) study[140] with drug-eluting stents in only 35 of the PCI procedures. No significant differences in death (odds ratio [OR] of PCI vs. CABG, 0.74; 95% CI, 0.43 to 1.28) or MI were reported (OR, 0.98; 95% CI, 0.54 to 1.78), but a lower risk of stroke (OR, 0.15; 95% CI, 0.33 to 0.67) and a higher risk of reintervention with PCI (OR, 2.25; 95% CI, 1.53 to 3.28) were found. Thus the total rate of MACCEs tended to be higher with PCI compared with CABG (OR, 1.28; 95% CI, 0.95 to 1.72). However, the odds ratios for MACCEs varied substantially depending on the burden of coronary disease, and it favored PCI with isolated left main CAD and left main plus single-vessel disease and CABG with left main plus multivessel disease (Fig. 2-9). Yet a statistically significant benefit of CABG over PCI was only found for left main plus triple-vessel disease (10.4% vs. 17.9%, $P = .03$). A subsequent meta-analysis also included registry data and addressed longer follow-ups.[142] It showed equipoise between CABG and PCI in 5-year survival, an advantage of CABG with respect to reintervention, and an advantage of PCI with respect to stroke. Up to 4 years, the odds ratios for MACCEs did not show significant differences between PCI and CABG, whereas at 5 years, a marginally significant benefit of PCI over CABG appeared. The results of this meta-analysis must be interpreted cautiously because of the mix-up between randomized and nonrandomized studies. From 3 years onward, SYNTAX was the only randomized trial that contributed to this meta-analysis. A more recent meta-analysis integrated both direct and indirect evidence by performing a Bayesian cross design and network meta-analysis of four randomized trials and eight observational studies.[143] Confirming the result obtained by conventional meta-analysis designs, the odds ratios of 1-year mortality after PCI versus CABG did not reveal significant differences between the two revascularization modalities in randomized clinical trials (OR, 0.99; 95% Bayesian credible interval, 0.67 to 1.43), matched cohort studies (OR, 1.10; 95% Bayesian credible interval, 0.76 to 1.73), or other types of cohort studies (OR, 0.93; 95% Bayesian credible interval, 0.58 to 1.35). Moreover, the network meta-analysis demonstrated a lower 1-year mortality after PCI for unprotected left main CAD than with medical therapy alone (OR, 0.31; 95% Bayesian credible interval, 0.19 to 0.51).[143]

None of the randomized studies to compare CABG with PCI for unprotected left main CAD was adequately powered, and only SYNTAX had sufficient length of follow-up. Moreover, nonrandomized comparisons can yield only circumstantial evidence. Thus the need still exists for a large randomized trial in this field. The ongoing Evaluation of Xience Prime Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial has been designed to meet this need with the intent to recruit 2600 patients with unprotected left main CAD randomly assigned to CABG or PCI with everolimus-eluting stents with a follow-up of up to 5 years. As a primary end point, the composite measure of all-cause mortality, MI, or stroke will be assessed at 3 years.

Until the results of EXCEL become available, currently available evidence suggests that PCI with drug-eluting stents is a reasonable treatment option for many patients with unprotected left main CAD. In general, survival and survival without MI or stroke are at least as good as after surgery, and patients may thus decide whether they want

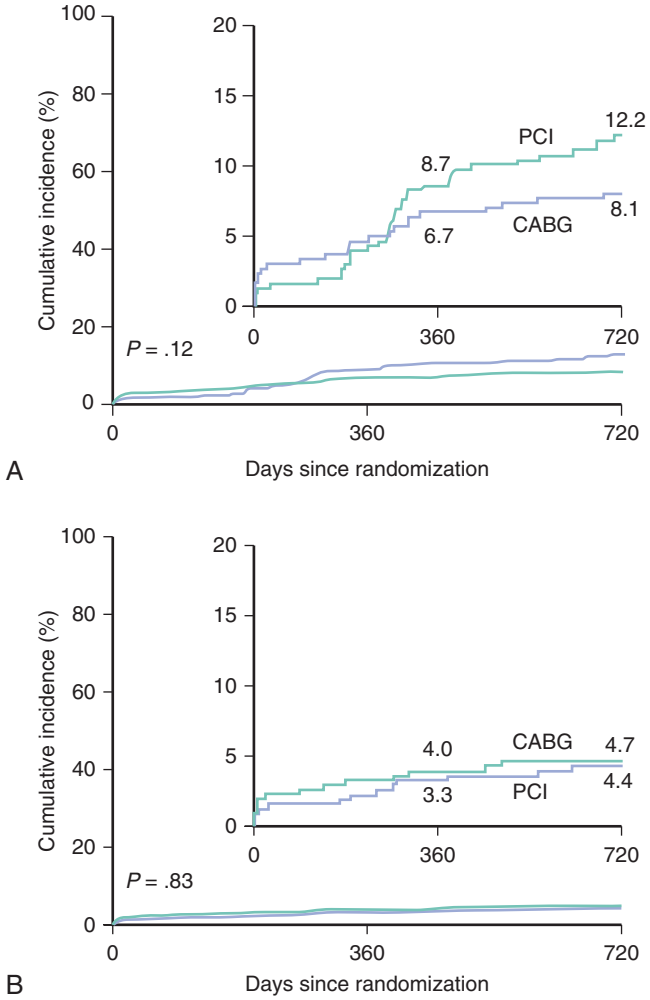


FIGURE 2-9 Kaplan-Meier estimates of major adverse cardiac or cerebrovascular events (MACCEs) in the PRECOMBAT trial. **A,** MACCEs. **B,** The composite of death, myocardial infarction, and stroke. The PRECOMBAT trial compared percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) in patients with unprotected left main coronary artery disease. The *P* value was calculated by means of the log-rank test. (From Park SJ, Kim YH, Park DW, et al: Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med* 364[18]:1718-1727, 2011.)

to exchange the discomfort of surgery for the potential inconvenience of repeat revascularization procedures. Concerning specific subsets, SYNTAX has taught us that the differential outcome of the two treatment strategies critically depends on the extent of concomitant CAD outside the left main artery. With moderate or no disease outside the LMCA, PCI leads to better outcomes than CABG, which includes a potential survival benefit; whereas with widespread diffuse disease outside the LMCA, CABG is more beneficial.

PERCUTANEOUS CORONARY INTERVENTION VERSUS MEDICAL THERAPY ALONE

Several studies of the prestent era compared PCI with medical therapy alone in single- or double-vessel disease without a prognostic indication for bypass surgery. Apart from the Angioplasty Compared to Medicine (ACME), RITA 2, and Atorvastatin Versus Revascularization Treatments (AVERT) studies, a meta-analysis that also included MASS and one smaller German trial demonstrated a significant (30%)

reduction in angina but found a significant increase in the need for CABG with PCI compared with medical treatment and trends toward increased risk of death, MI, and nonscheduled PCI.[144] This meta-analysis supports the concept that compared with medical therapy alone, PCI in patients with stable angina reduces symptoms but may be associated with a higher incidence of serious complications, such as death and MI. However, it must be considered that none of the studies included in this meta-analysis used contemporary interventional techniques, which includes the systematic use of stents with vigorous periinterventional and postinterventional antiplatelet treatment, or strict risk-factor modification, in particular the administration of statins. Modern periinterventional and postinterventional drug therapy would have reduced the risk of death and MI, and each of the three elements of modern interventional treatment—stents, statins, and antiplatelet drugs—would have reduced the need for subsequent unplanned revascularization procedures. Hence it may be anticipated that with modern interventional approaches, the complications of catheter intervention would have been substantially lower without corrupting the beneficial effect of this treatment of angina as compared with medical therapy alone. The role of PCI compared with medical therapy alone in patients without an established prognostic indication for coronary revascularization therefore needed reassessment in the light of contemporary interventional techniques and optimal periinterventional and postinterventional treatment.

This was the goal of the randomized COURAGE trial.[145] COURAGE involved 2287 patients who had objective evidence of myocardial ischemia and significant CAD; 1149 patients were assigned to undergo PCI with optimal medical therapy (PCI group), and 1138 were to receive optimal medical therapy alone (medical therapy group). Patients with persistent Canadian Cardiovascular Society (CCS) class IV angina, a markedly positive stress test, unprotected left main CAD, or hazardous PCI—as in ostial stenosis of the LAD—were not eligible for the study. COURAGE was highly successful in applying state-of-the-art preventive and antiischemic pharmacologic treatment. Drug-eluting stents, however, were not available except for the last 6 months of the study, thus only 2.7% of the COURAGE trial PCI patients received drug-eluting stents. Among patients randomized to PCI, 6.4% did not have the procedure. On the other hand, 32% of the patients assigned to the medical therapy group crossed over to PCI during follow-up. Repeat PCI was also performed in 21% of the patients in the PCI group. During a median follow-up of 4.6 years, the cumulative primary event rates, the composite of death from any cause and nonfatal MI, were 19.0% in the PCI group and 18.5% in the medical therapy group (HR for the PCI group was 1.05; 95% CI, 0.87 to 1.27; $P = .62$).[145] Considering components of the primary end point, 85 deaths occurred in the PCI group and 95 occurred in the medical therapy group; spontaneous MIs numbered 108 and 109, and those of peri-PCI MI were 35 and 9, respectively. At 1 year and 3 years, but not at 5 years, a significantly higher proportion of patients in the PCI group were free of angina compared with the medical therapy group (66% vs. 58%, $P < .001$; 72% vs. 67%, $P = .02$; and 74% vs. 72%, $P = .35$; respectively). The striking 72% angina-free status at 5 years in the medical therapy group may have been attributed to the fact that 43% of these patients began the trial with minimal (CCS class I) or no angina, and 32% went on to subsequent revascularization for relief of symptoms. Given the failure to reduce the risk of death and MI and the marginal symptomatic benefit of PCI plus optimal medical therapy (OMT) over OMT alone, it was concluded that an initial recommendation of PCI on top of OMT offers no important advantage over an initial recommendation of OMT alone.

More recently, results consistent with the COURAGE trial were reported from the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial,[146] which included 2368 patients with both type 2 diabetes and CAD. These patients were stratified as potential candidates for CABG ($n = 763$) or for PCI ($n = 1605$) and were then randomly assigned to prompt revascularization or intense medical therapy. Participants were also subrandomized to insulin-sensitization or insulin-provision therapy. At 5 years, rates of survival did not differ significantly between the revascularization group (88.3%) and the medical therapy group (87.8%, $P = .97$). The rates of freedom from major cardiovascular events also did not differ significantly among the groups: they were 77.2% in the revascularization group and 75.9% in the medical treatment group ($P = .70$). Taken together, COURAGE and BARI 2D suggest that with OMT, a conservative approach that reserves revascularization to patients with progression of angina, the development of an acute coronary syndrome, or severe ischemia is preferred over a strategy of prompt revascularization. Some caveats against an uncritical generalization of this concept must be considered. The first comes from the authors of the COURAGE trial. In their nuclear substudy of COURAGE, they demonstrated that the beneficial effect of therapy on prognosis is linked to a substantial reduction in stress-induced ischemia to a low residual level.[27] In their substudy, a reduction of the area of stress-induced ischemia of 5% or more and to 10% or less of the left ventricle was needed for a prognostic effect, especially if baseline ischemia was greater than 10%. Although this was achieved more frequently after PCI than after medical therapy alone, a substantial number of PCI patients fell short of this goal. This may not be considered an inherent limitation of PCI but rather a consequence of a PCI strategy that focused on the culprit lesion. Despite the fact that 69% of patients assigned to PCI had multivessel disease and 65% had multiple reversible perfusion defects on nuclear imaging, only 36% of the patients received more than one stent. Thus in a substantial proportion of patients, PCI resulted in incomplete revascularization. With respect to the overall outcome of the study, this will have diluted the beneficial effect of complete revascularization in some of the patients, as demonstrated in the nuclear substudy of COURAGE.[27] The findings of the BARI 2D trial also support the concept that revascularization will improve prognosis if a relevant area of the left ventricle can be relieved from ischemia. In this trial, the low-risk patients stratified as PCI candidates derived no benefit from revascularization compared with primarily medical treatment, whereas patients stratified as CABG candidates fared better with revascularization (major adverse events = 22.4% vs. 30.5%, $P = .01$; for interaction between stratum and study group, $P = .002$). Compared with PCI candidates, CABG candidates more often had three-vessel disease and a jeopardy score greater than 50% (ORs were 4.4 and 4.1, respectively). Thus in BARI 2D, the larger reduction in ischemia in the CABG group, compared with that in the PCI group, resulted in a prognostic benefit. The second caveat comes from the observation of a 13% relative reduction in mortality by PCI plus OMT compared with OMT alone in the COURAGE trial. However, the trial was not sufficiently powered to establish the statistical significance of this finding.

The most recent trial to assess potential benefits of revascularization by PCI in patients with stable CAD was FAME 2,[45] which included patients with stable angina in whom coronary angiography revealed at least one coronary artery stenosis of 50% or greater. All stenoses were interrogated by measurement of fractional flow reserve (FFR). Patients with at least one functionally relevant stenosis (FFR ≤ 0.80) were randomly assigned to PCI with drug-eluting stents plus the best available medical therapy (PCI group) or the best available medical therapy alone (medical-therapy group). Patients who did not have any functionally relevant stenoses were included in a registry. The study was designed to include 1632 randomized patients. The Data Safety Monitoring Committee, however, recommended a premature end to the study for a significant difference in event rates that favored PCI. Thus recruitment was halted prematurely after inclusion of 1220 patients. Out of these, 888 had undergone randomization, and 332 had entered the registry. With a mean duration of follow-up of 214 days, the primary end point—the composite of death, MI, or urgent revascularization—was reached in 4.3% of the PCI group and in 12.7% of the medical-therapy group (HR with PCI, 0.32; 95% CI, 0.19 to 0.53; $P < .001$).[45] This difference was driven by a lower need for urgent revascularization in the PCI group than in the medical therapy group (1.6% vs. 11.1%; HR, 0.13; 95% CI, 0.06 to 0.30; $P < .001$). However, no significant differences were reported in mortality (0.2% vs. 0.7%,

$P = .31$) or in the incidence of MI (3.4% vs. 3.2%, $P = .89$). Yet PCI reduced the risk of death or MI beyond 7 days (HR with PCI, 0.42; 95% CI, 0.17 to 1.04; $P = .053$; $P_{int} = .003$ with 7-day landmark). Moreover, in the PCI group, fewer patients suffered from CCS class II to IV angina than patients in the medical therapy group (HR, 0.39; 95% CI, 0.28 to 0.53; $P < .001$ [at 30 days]; HR, 0.46; 95% CI, 0.28 to 0.74; $P = .002$ [at 6 months]). Confirming the validity of functional testing, the event rate was lowest in the registry (3% for the primary end point). Thus FAME 2 suggested some advantages of PCI with OMT over OMT alone, but it did not demonstrate better survival with PCI or better survival without MI.

One of the limitations of COURAGE, BARI 2D, and FAME 2 is the limited sample size. This problem may be overcome by meta-analyses. A meta-analysis of 17 randomized trials to compare a PCI-based invasive treatment strategy with medical treatment suggested that the PCI-based invasive strategy improves long-term survival compared with a strategy of medical treatment only (OR for all-cause death was 0.80 [95% CI, 0.64 to 0.99; $P = .263$] for heterogeneity across trials).[147] Another group performed a meta-analysis of COURAGE and BARI 2D and six smaller trials (together, 7229 patients) and did not find any significant benefit of PCI over conservative treatment for prevention of death, MI, unplanned revascularization, and angina.[148] These researchers subsequently restricted their analysis to studies with objectively documented myocardial ischemia and with greater than 50% use of stents and statins. They also included FAME 2,[149] yet they reached essentially the same results. The most comprehensive recent conventional meta-analysis comprised 12 studies, including COURAGE and BARI 2D but not FAME 2, with 37,548 patient-years in 7182 patients.[150,151] PCI compared with conservative treatment was associated with a significantly lower incident rate ratio (IRR) for spontaneous nonprocedural MI (IRR, 0.76; 95% CI, 0.58 to 0.99) at the expense of a higher rate of procedural MI (IRR, 4.11; 95% CI, 2.53 to 6.88).[151] Finally, no significant difference was found in the total risk of MI (IRR, 0.96; 95% CI, 0.74 to 1.21). Consistent with the beneficial effect of PCI on spontaneous MI, all-cause mortality (IRR, 0.88; 95% CI, 0.75 to 1.03) and cardiovascular mortality (IRR, 0.70; 95% CI, 0.44 to 1.09) were lower after PCI than with medical treatment alone, and statistical significance was only just missed.[151] The point estimate for PCI versus conservative treatment for mortality paralleled that for spontaneous MI but not for procedural MI, indicating that procedural MIs are less relevant for survival than spontaneous MIs. In addition to the reduction in spontaneous MI, the meta-analysis revealed a significantly higher freedom from angina after PCI than with medical therapy alone (RR, 0.83; 95% CI, 0.72 to 0.94).[150]

A common conundrum of studies that assess the benefits of PCI versus stable angina is the problem that within the spectrum of patients with stable angina, the higher-risk patients were underrepresented or not included at all. Specifically, this is true for patients with an accepted indication for CABG, in whom randomization would have been unethical. This means that patients who potentially derive the most benefit from revascularization by PCI hardly entered any of the studies that compared PCI with medical treatment alone. This problem in the assessment of the true benefit of PCI in stable angina may be overcome by network meta-analysis, as published recently. This network meta-analysis was based on 95 studies with 93,553 patients with stable coronary disease and assessed outcome data closest to 5 years (Fig. 2-10).[152] PCI with new-generation stents significantly reduced the risk of mortality with rate ratios of 0.75 (95% CI, 0.55 to 0.96) for everolimus-eluting stents and 0.65 (95% CI, 0.42 to 1.00) for zotarolimus-eluting stents.[152] With everolimus-eluting stents, a significant reduction of MI was also found compared with initial medical treatment (RR, 0.78; 95% CI, 0.63 to 0.96). Moreover, stent-supported PCI significantly reduced the need for subsequent revascularization compared with initial medical therapy but to a variable degree. The largest reduction was found with new-generation drug-eluting stents (RR, 0.27 [95% CI, 0.21 to 0.35] for everolimus-eluting stents and 0.26 [95% CI, 0.17 to 0.35] for zotarolimus-eluting stents). The findings of the network meta-analysis are consistent with a nonrandomized comparison

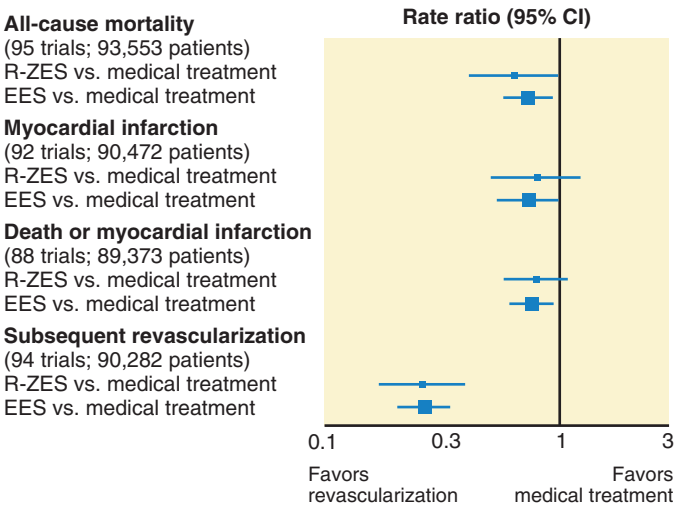


FIGURE 2-10 Summary of a network meta-analysis based on 95 studies with 93,553 patients with stable coronary disease, assessing outcome after initial revascularization with new-generation drug-eluting stents or initial medical treatment without revascularization. Rate ratios of percutaneous coronary intervention (PCI) with 95% confidence intervals (CIs) are shown for the everolimus-eluting stent (EES) and resolute zotarolimus-eluting stent (R-ZES) based on data closest to 5 years. (Adapted from Windecker S, Stortecky S, Stefanini GG, et al: Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. *BMJ* 348:g3859, 2014.)

between PCI and conservative therapy for stable angina using the New York State Cardiac Database.[153] Of 9586 patients, 8486 underwent PCI (71% with drug-eluting stents) and 1100 were initially treated conservatively. By propensity matching through the use of 20 pertinent factors, 933 matched pairs were obtained. During 4-year follow-up, patients treated with PCI had an improved outcome compared with patients initially treated medically, with a significant reduction in mortality (10.2% vs. 14.5%; $P = .02$), MI (8.0% vs. 11.3%; $P = .007$), and subsequent revascularization (24.1% vs. 29.1%; $P = .005$). Adjusted hazard ratios of PCI compared with medical treatment were 0.67 (95% CI, 0.52 to 0.86) for death and MI and 0.68 (95% CI, 0.51 to 0.93) for death.

In summary, compared with OMT alone, OMT plus PCI with modern devices and interventional techniques more effectively relieves symptoms of angina, reduces the risk of unplanned revascularization procedures and of spontaneous MIs, and may even improve survival of patients with stable angina. The survival benefit appears to be linked to effective revascularization of large areas that demonstrate inducible ischemia. Hence currently available evidence suggests that patients who have an area of stress-induced ischemia involving more than 10% of the left ventricle[26] or who are not free of symptoms or do not tolerate medical therapy should undergo PCI if they are anatomically suited. Stable patients who are free of symptoms following antianginal medication and are free of relevant residual inducible ischemia should be managed conservatively.

SUMMARY

When coronary revascularization is considered, prognostic and symptomatic indications must be distinguished. With prognostic indications, PCI offers an alternative to CABG; with symptomatic indications, PCI competes with medical treatment. In the absence of an acute coronary syndrome, PCI for single-vessel disease is justified only if an improvement in symptoms can be anticipated or if there is a large area (>10% of the LV) of inducible ischemia.

In patients with multivessel disease, with or without left main coronary artery stenosis, the choice of revascularization therapy will depend on the complexity of coronary artery involvement. With low complexity, such as with a SYNTAX score below 23, no current evidence suggests that CABG offers a relevant benefit over PCI with drug-eluting stents. However, in patients with a high complexity (e.g., SYNTAX score >32), current evidence demonstrates a survival benefit of CABG over PCI; therefore PCI in such patients should be discouraged. With three-vessel disease of intermediate complexity, surgery is preferred because of the lower risk of death and MI after CABG. Patients must also be informed about the higher need for repeat procedures after PCI, which should be weighed against the discomfort of surgery.

Left main coronary artery stenosis is not a contraindication to PCI. In fact, at low- to medium-range SYNTAX scores, the outcome after PCI with LMCA involvement may be superior to that with CABG. In patients with diabetes mellitus, however, multivessel PCI does not achieve a prognostic benefit similar to that of CABG. Despite drug-eluting stents, vigorous antiplatelet treatment, and tight metabolic control, diabetic patients continue to be at increased risk of death, MI, and reintervention if treated by PCI. Thus PCI in patients with diabetes may be considered only in low-complexity subsets of multivessel disease, such as with SYNTAX scores less than 23. Individualized decisions must consider the likelihood of complete revascularization, the risk associated with either approach, the patient's life expectancy based on age and comorbidities, and the patient's preference after thorough counseling. In many instances, decisions must be reached jointly by the cardiac surgeon and the interventional cardiologist at institutionalized meetings of the heart team.

REFERENCES

1. Mauri L, Hsieh WH, Massaro JM, et al: Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 356(10):1020–1029, 2007.
2. Roukoz H, Bavry AA, Sarkees ML, et al: Comprehensive meta-analysis on drug-eluting stents versus bare-metal stents during extended follow-up. *Am J Med* 122(6):581 e1–e10, 2009.
3. Bangalore S, Kumar S, Fusaro M, et al: Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117762 patient-years of follow-up from randomized trials. *Circulation* 125(23):2873–2891, 2012.
4. Palmerini T, Biondi-Zoccai G, Della Riva D, et al: Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 379(9824):1393–1402, 2012.
5. Fibrinolytic Therapy Trialists: Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 343(8893): 311–322, 1994.
6. Boersma E, Primary Coronary Angioplasty vs. Thrombolysis Group: Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J* 27:779–788, 2006.
7. Keeley EC, Boura JA, Grines CL: Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 361:13–20, 2003.
8. Ellis SG, Tendera M, de Belder MA, et al: Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med* 358(21):2205–2217, 2008.
9. Armstrong PW, Gershlick AH, Goldstein P, et al: Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 368(15):1379–1387, 2013.
10. Hillis LD, Lange RA: Optimal management of acute coronary syndromes. *N Engl J Med* 360(21):2237–2240, 2009.
11. Mehta SR, Cannon CP, Fox KA, et al: Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA* 293: 2908–2917, 2005.
12. Fox KA, Poole-Wilson P, Clayton TC, et al: 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *Lancet* 366(9489):914–920, 2005.
13. Lagerqvist B, Husted S, Kontny F, et al: 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. *Lancet* 368(9540):998–1004, 2006.
14. Damman P, Hirsch A, Windhausen F, et al: 5-year clinical outcomes in the ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) trial: a randomized comparison of an early invasive versus selective invasive management in patients with non-ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol* 55(9):858–864, 2010.
15. Hamm CW, Bassand JP, Agewall S, et al: ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the Management of Acute Coronary Syndromes (ACS) in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 32(23): 2999–3054, 2011.
16. Fox KA, Clayton TC, Damman P, et al: Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome: a meta-analysis of individual patient data. *J Am Coll Cardiol* 55(22):2435–2445, 2010.
17. FRISC-II Investigators: Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 354:708–715, 1999.
18. Fox KA, Poole-Wilson PA, Henderson RA, et al: Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. *Lancet* 360(9335):743–751, 2002.
19. Cannon CP, Weintraub WS, Demopoulos LA, et al: Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 344(25):1879–1887, 2001.
20. Bertrand ME, Simoons ML, Fox KA, et al: Task Force on the Management of Acute Coronary Syndromes of the European Society of Cardiology. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 23:1809–1840, 2002.

20a. Gibbons RJ, Chatterjee K, Daley J, et al: ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). *J Am Coll Cardiol* 33(7):2092–2197, 1999.

21. Weiner DA, Ryan TJ, McCabe CH, et al: The role of exercise testing in identifying patients with improved survival after coronary artery bypass surgery. *J Am Coll Cardiol* 8(4):741–748, 1986.
22. Mock MB, Fisher LD, Holmes DR, Jr, et al: Comparison of effects of medical and surgical therapy on survival in severe angina pectoris and two-vessel coronary artery disease with and without left ventricular dysfunction: a Coronary Artery Surgery Study Registry Study. *Am J Cardiol* 61(15):1198–1203, 1988.
23. Rogers WJ, Bourassa MG, Andrews TC, et al: Asymptomatic Cardiac Ischemia Pilot (ACIP) study: outcome at 1 year for patients with asymptomatic cardiac ischemia randomized to medical therapy or revascularization. The ACIP Investigators. *J Am Coll Cardiol* 26(3):594–605, 1995.
24. Hachamovitch R, Hayes SW, Friedman JD, et al: Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 107(23):2900–2907, 2003.
25. Hachamovitch R, Rozanski A, Hayes SW, et al: Predicting therapeutic benefit from myocardial revascularization procedures: are measurements of both resting left ventricular ejection fraction and stress-induced myocardial ischemia necessary? *J Nucl Cardiol* 13(6):768–778, 2006.
26. Hachamovitch R, Rozanski A, Shaw LJ, et al: Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J* 32(8):1012–1024, 2011.
27. Shaw LJ, Berman DS, Maron DJ, et al: Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 117(10):1283–1291, 2008.
28. Yusuf S, Zucker D, Peduzzi P, et al: Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 344(8922):563–570, 1994.
29. European Coronary Surgery Study Group: Long-term results of prospective randomised study of coronary artery bypass surgery in stable angina pectoris. *Lancet* 2(8309):1173–1180, 1982.
30. Passamani E, Davis KB, Gillespie MJ, et al: A randomized trial of coronary artery bypass surgery. Survival of patients with a low ejection fraction. *N Engl J Med* 312(26):1665–1671, 1985.
31. Peduzzi P, Hultgren HN: Effect of medical vs surgical treatment on symptoms in stable angina pectoris. The Veterans Administration Cooperative Study of surgery for coronary arterial occlusive disease. *Circulation* 60(4):888–900, 1979.
32. Hueb WA, Bellotti G, de Oliveira SA, et al: The Medicine, Angioplasty or Surgery Study (MASS): a prospective, randomized trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending artery stenoses. *J Am Coll Cardiol* 26(7):1600–1605, 1995.
33. Kubo T, Maehara A, Mintz GS, et al: The dynamic nature of coronary artery lesion morphology assessed by serial virtual histology intravascular ultrasound tissue characterization. *J Am Coll Cardiol* 55(15):1590–1597, 2010.
34. Barlis P, Serruys PW, Gonzalo N, et al: Assessment of culprit and remote coronary narrowings using optical coherence tomography with long-term outcomes. *Am J Cardiol* 102(4):391–395, 2008.
35. Bell MR, Gersh BJ, Schaff HV, et al: Effect of completeness of revascularization on long-term outcome of patients with three-vessel disease undergoing coronary artery bypass surgery. A report from the Coronary Artery Surgery Study (CASS) Registry. *Circulation* 86(2):446–457, 1992.
36. Bourassa MG, Kip KE, Jacobs AK, et al: Is a strategy of intended incomplete percutaneous transluminal coronary angioplasty revascularization acceptable in nondiabetic patients who are candidates for coronary artery bypass graft surgery? The Bypass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol* 33(6):1627–1636, 1999.
37. Cowley MJ, Vandermael M, Topol EJ, et al: Is traditionally defined complete revascularization needed for patients with multivessel disease treated by elective coronary angioplasty? Multivessel Angioplasty Prognosis Study (MAPS) Group. *J Am Coll Cardiol* 22(5):1289–1297, 1993.
38. Hannan EL, Racz M, Holmes DR, et al: Impact of completeness of percutaneous coronary intervention revascularization on long-term outcomes in the stent era. *Circulation* 113(20):2406–2412, 2006.
39. Sarno G, Garg S, Onuma Y, et al: Impact of completeness of revascularization on the five-year outcome in percutaneous coronary intervention and coronary artery bypass graft patients (from the ARTS-II study). *Am J Cardiol* 106(10):1369–1375, 2010.
40. Farooq V, Serruys PW, Garcia-Garcia HM, et al: The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol* 61(3):282–294, 2013.
41. Farooq V, Serruys PW, Bourantas CV, et al: Quantification of incomplete revascularization and its association with five-year mortality in the Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation* 128(2):141–151, 2013.
42. Tonino PA, Fearon WF, De Bruyne B, et al: Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol* 55(25):2816–2821, 2010.
43. Bech GJ, De Bruyne B, Pijls NH, et al: Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation* 103(24):2928–2934, 2001.
44. Legalery P, Schiele F, Seronde MF, et al: One-year outcome of patients submitted to routine fractional flow reserve assessment to determine the need for angioplasty. *Eur Heart J* 26(24):2623–2629, 2005.
45. De Bruyne B, Pijls NH, Kalesan B, et al: Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 367(11):991–1001, 2012.
46. Tonino PA, De Bruyne B, Pijls NH, et al: Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 360(3):213–224, 2009.
47. Pijls NH, Fearon WF, Tonino PA, et al: Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol* 56(3):177–184, 2010.

48. Garcia S, Sandoval Y, Roukoz H, et al: Outcomes after complete versus incomplete revascularization of patients with multivessel coronary artery disease: a meta-analysis of 89,883 patients enrolled in randomized clinical trials and observational studies. *J Am Coll Cardiol* 62(16):1421–1431, 2013.
49. Hoffman SN, TenBrook JA, Wolf MP, et al: A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one-to eight-year outcomes. *J Am Coll Cardiol* 41(8):1293–1304, 2003.
50. Serruys PW, Ong AT, van Herwerden LA, et al: Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol* 46(4):575–581, 2005.
51. Serruys PW, Unger F, Sousa JE, et al: Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 344(15):1117–1124, 2001.
52. SoS Investigators: Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial. *Lancet* 360(9338): 965–970, 2002.
53. Rodriguez A, Bernardi V, Navia J, et al: Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in patients with Multiple-Vessel Disease (ERACI II): 30-day and one-year follow-up results. ERACI II Investigators. *J Am Coll Cardiol* 37(1):51–58, 2001.
54. Rodriguez AE, Baldi J, Fernandez Pereira C, et al: Five-year follow-up of the Argentine randomized trial of coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple vessel disease (ERACI II). *J Am Coll Cardiol* 46(4):582–588, 2005.
55. Hueb W, Soares PR, Gersh BJ, et al: The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. *J Am Coll Cardiol* 43(10):1743–1751, 2004.
56. Morrison DA, Sethi G, Sacks J, et al: Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. The Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). *J Am Coll Cardiol* 38(1): 143–149, 2001.
57. Mercado N, Wijns W, Serruys PW, et al: One-year outcomes of coronary artery bypass graft surgery versus percutaneous coronary intervention with multiple stenting for multisystem disease: a meta-analysis of individual patient data from randomized clinical trials. *J Thorac Cardiovasc Surg* 130(2):512–519, 2005.
58. Hueb W, Lopes N, Gersh BJ, et al: Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 122(10):949–957, 2010.
59. Stroupe KT, Morrison DA, Hlatky MA, et al: Cost-effectiveness of coronary artery bypass grafts versus percutaneous coronary intervention for revascularization of high-risk patients. *Circulation* 114(12):1251–1257, 2006.
60. Morrison DA, Sethi G, Sacks J, et al: Percutaneous coronary intervention versus coronary bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: The VA AWESOME multicenter registry: comparison with the randomized clinical trial. *J Am Coll Cardiol* 39(2):266–273, 2002.
61. Morrison DA, Sethi G, Sacks J, et al: Percutaneous coronary intervention versus repeat bypass surgery for patients with medically refractory myocardial ischemia: AWESOME randomized trial and registry experience with post-CABG patients. *J Am Coll Cardiol* 40(11):1951–1954, 2002.
62. Grapow MT, von Wattenwyl R, Guller U, et al: Randomized controlled trials do not reflect reality: real-world analyses are critical for treatment guidelines! *J Thorac Cardiovasc Surg* 132(1):5–7, 2006.
63. Brener SJ, Lytle BW, Casserly IP, et al: Propensity analysis of long-term survival after surgical or percutaneous revascularization in patients with multivessel coronary artery disease and high-risk features. *Circulation* 109(19):2290–2295, 2004.
64. Hannan EL, Racz MJ, Walford G, et al: Long-term outcomes of coronary-artery bypass grafting versus stent implantation. *N Engl J Med* 352(21):2174–2183, 2005.
65. van Domburg RT, Takkenberg JJ, Noordzij LJ, et al: Late outcome after stenting or coronary artery bypass surgery for the treatment of multivessel disease: a single-center matched-propensity controlled cohort study. *Ann Thorac Surg* 79(5):1563–1569, 2005.
66. Smith PK, Califf RM, Tuttle RH, et al: Selection of surgical or percutaneous coronary intervention provides differential longevity benefit. *Ann Thorac Surg* 82(4):1420–1428, discussion 1428–1429, 2006.
67. Serruys PW, Ong ATL, Morice MC, et al: Arterial Revascularisation Therapies Study Part II—Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. *EuroIntervention* 1:147–156, 2005.
68. Serruys PW, Onuma Y, Garg S, et al: 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. *J Am Coll Cardiol* 55(11):1093–1101, 2010.
69. Weintraub WS, Grau-Sepulveda MV, Weiss JM, et al: Comparative effectiveness of revascularization strategies. *N Engl J Med* 366(16):1467–1476, 2012.
70. Wu C, Camacho FT, Zhao S, et al: Long-term mortality of coronary artery bypass graft surgery and stenting with drug-eluting stents. *Ann Thorac Surg* 95(4):1297–1305, 2013.
71. Hannan EL, Wu C, Walford G, et al: Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. *N Engl J Med* 358(4):331–341, 2008.
72. Hlatky MA, Boothroyd DB, Bravata DM, et al: Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 373(9670):1190–1197, 2009.
73. Serruys PW, Morice MC, Kappetein AP, et al: Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 360(10):961–972, 2009.
74. Mohr FW, Morice MC, Kappetein AP, et al: Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 381(9867):629–638, 2013.
75. Head SJ, Davierwala PM, Serruys PW, et al: Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial. *Eur Heart J* 35(40):2821–2830, 2014.
76. Zhang X, Xie J, Li G, et al: Head-to-head comparison of sirolimus-eluting stents versus paclitaxel-eluting stents in patients undergoing percutaneous coronary intervention: a meta-analysis of 76 studies. *PLoS ONE* 9(5):e97934, 2014.
77. Cassese S, Piccolo R, Galasso G, et al: Twelve-month clinical outcomes of everolimus-eluting stent as compared to paclitaxel- and sirolimus-eluting stent in patients undergoing percutaneous coronary interventions. A meta-analysis of randomized clinical trials. *Int J Cardiol* 150(1):84–89, 2011.
78. Barzilay JI, Kronmal RA, Bittner V, et al: Coronary artery disease and coronary artery bypass grafting in diabetic patients aged > or = 65 years (report from the Coronary Artery Surgery Study [CASS] Registry). *Am J Cardiol* 74:334–339, 1994.
79. Van Belle E, Abolmaali K, Bauters C, et al: Restenosis, late vessel occlusion and left ventricular function six months after balloon angioplasty in diabetic patients. *J Am Coll Cardiol* 34(2):476–485, 1999.
80. Elezi S, Kastrati A, Pache J, et al: Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. *J Am Coll Cardiol* 32(7):1866–1873, 1998.
81. Van Belle E, Ketelers R, Bauters C, et al: Patency of percutaneous transluminal coronary angioplasty sites at 6-month angiographic follow-up: A key determinant of survival in diabetics after coronary balloon angioplasty. *Circulation* 103(9):1218–1224, 2001.
82. Kip KE, Faxon DP, Detre KM, et al: Coronary angioplasty in diabetic patients. The National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *Circulation* 94(8):1818–1825, 1996.
83. BARI investigators: Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. *J Am Coll Cardiol* 35(5):1122–1129, 2000.
84. King SB, 3rd, Kosinski AS, Guyton RA, et al: Eight-year mortality in the Emory Angioplasty versus Surgery Trial (EAST). *J Am Coll Cardiol* 35(5):1116–1121, 2000.
85. Marso SP, Lincoff AM, Ellis SG, et al: Optimizing the percutaneous interventional outcomes for patients with diabetes mellitus: results of the EPISTENT diabetic substudy. *Circulation* 100(25):2477–2484, 1999.
86. Bhatt DL, Marso SP, Lincoff AM, et al: Abciximab reduces mortality in diabetics following percutaneous coronary intervention. *J Am Coll Cardiol* 35:922–928, 2000.
87. Mehilli J, Kastrati A, Schühlen H, et al: Randomized clinical trial of abciximab in diabetic patients undergoing elective percutaneous coronary interventions after treatment with a high loading dose of clopidogrel. *Circulation* 110:3627–3635, 2004.
88. Van Belle E, Bauters C, Hubert E, et al: Restenosis rates in diabetic patients: a comparison of coronary stenting and balloon angioplasty in native coronary vessels. *Circulation* 96(5):1454–1460, 1997.
89. Van Belle E, Perie M, Braune D, et al: Effects of coronary stenting on vessel patency and long-term clinical outcome after percutaneous coronary revascularization in diabetic patients. *J Am Coll Cardiol* 40(3):410–417, 2002.
90. Otsuka Y, Myazaki S, Okumara H: Abnormal glucose tolerance, not small vessel diameter, is a determinant of long-term prognosis in patients treated with balloon coronary angioplasty. *Eur Heart J* 21:1790–1796, 2000.
91. Takagi T, Akasaka T, Yamamuro A, et al: Troglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with non-insulin dependent diabetes mellitus: a serial intravascular ultrasound study. *J Am Coll Cardiol* 36(5):1529–1535, 2000.
92. Abizaid A, Costa MA, Centemero M, et al: Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary disease patients: insights from the Arterial Revascularization Therapy Study (ARTS) trial. *Circulation* 104(5):533–538, 2001.
93. Lima EG, Hueb W, Garcia RM, et al: Impact of diabetes on 10-year outcomes of patients with multivessel coronary artery disease in the Medicine, Angioplasty, or Surgery Study II (MASS II) trial. *Am Heart J* 166(2):250–257, 2013.
94. Sedlis SP, Morrison DA, Lorin JD, et al: Percutaneous coronary intervention versus coronary bypass graft surgery for diabetic patients with unstable angina and risk factors for adverse outcomes with bypass: outcome of diabetic patients in the AWESOME randomized trial and registry. *J Am Coll Cardiol* 40(9):1555–1566, 2002.
95. Dzavik V, Ghali WA, Norris C: Long-term survival in 11,661 patients with multivessel coronary artery disease in the era of stenting: a report from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. *Am Heart J* 142:119–126, 2001.
96. Scheen AJ, Warzee F, Legrand VM: Drug-eluting stents: meta-analysis in diabetic patients. *Eur Heart J* 25(23):2167–2168, author reply 2168–2169, 2004.
97. Bangalore S, Kumar S, Fusaro M, et al: Outcomes with various drug eluting or bare metal stents in patients with diabetes mellitus: mixed treatment comparison analysis of 22,844 patient years of follow-up from randomised trials. *BMJ* 345:e5170, 2012.
98. Stettler C, Allemann S, Wandel S, et al: Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. *BMJ* 337:a1331, 2008.
99. Kapur A, Hall RJ, Malik IS, et al: Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. *J Am Coll Cardiol* 55(5):432–440, 2010.
100. Kapur A, Baumbach A, Beatt KJ, et al: *CARDia: coronary artery revascularisation in diabetes trial (5-year follow-up data)*, Munich, Germany, 2012, European Society of Cardiology Congress.
101. Farkouh ME, Domanski M, Sleeper LA, et al: Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 367(25):2375–2384, 2012.
102. Abdallah MS, Wang K, Magnuson EA, et al: Quality of life after PCI vs CABG among patients with diabetes and multivessel coronary artery disease: a randomized clinical trial. *JAMA* 310(15):1581–1590, 2013.
103. Kappetein AP, Head SJ, Morice MC, et al: Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *Eur J Cardiothorac Surg* 43(5):1006–1013, 2013.
104. Kamalesh M, Sharp TG, Tang XC, et al: Percutaneous coronary intervention versus coronary bypass surgery in United States veterans with diabetes. *J Am Coll Cardiol* 61(8):808–816, 2013.
105. Verma S, Farkouh ME, Yanagawa B, et al: Comparison of coronary artery bypass surgery and percutaneous coronary intervention in patients with diabetes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol* 1(4):317–328, 2013.
106. Contini GA, Nicolini F, Fortuna D, et al: Five-year outcomes of surgical or percutaneous myocardial revascularization in diabetic patients. *Int J Cardiol* 168(2):1028–1033, 2013.
107. Marso SP, Steg G, Plokker T, et al: Catheter-based reperfusion of unprotected left main stenosis during an acute myocardial infarction (the ULTIMA experience). Unprotected Left Main Trunk Intervention Multi-center Assessment. *Am J Cardiol* 83(11):1513–1517, 1999.
108. Silvestri M, Barragan P, Sainsous J, et al: Unprotected left main coronary artery stenting: immediate and medium-term outcomes of 140 elective procedures. *J Am Coll Cardiol* 35(6):1543–1550, 2000.
109. Park SJ, Park SW, Hong MK, et al: Stenting of unprotected left main coronary artery stenoses: immediate and late outcomes. *J Am Coll Cardiol* 31(1):37–42, 1998.
110. Lee BK, Hong MK, Lee CW, et al: Five-year outcomes after stenting of unprotected left main coronary artery stenosis in patients with normal left ventricular function. *Int J Cardiol* 115(2):208–213, 2007.
111. Park SJ, Park SW, Hong MK, et al: Long-term (three-year) outcomes after stenting of unprotected left main coronary artery stenosis in patients with normal left ventricular function. *Am J Cardiol* 91(1):12–16, 2003.
112. Park SJ, Kim YH, Lee BK, et al: Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis: comparison with bare metal stent implantation. *J Am Coll Cardiol* 45(3):351–356, 2005.
113. Chieffo A, Stankovic G, Bonizzoni E, et al: Early and mid-term results of drug-eluting stent implantation in unprotected left main. *Circulation* 111(6):791–795, 2005.
114. Valgimigli M, van Mieghem CA, Ong AT, et al: Short- and long-term clinical outcome after drug-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: insights from the Rapamycin-Eluting and Taxus Stent Evaluated At Rotterdam Cardiology Hospital registries (RESEARCH and T-SEARCH). *Circulation* 111(11):1383–1389, 2005.
115. Buszman PE, Buszman PP, Kiesz RS, et al: Early and long-term results of unprotected left main coronary artery stenting: the LE MANS (Left Main Coronary Artery Stenting) registry. *J Am Coll Cardiol* 54(16):1500–1511, 2009.
116. Palmerini T, Marzocchi A, Tamburino C, et al: Two-year clinical outcome with drug-eluting stents versus bare-metal stents in a real-world registry of unprotected left main coronary artery stenosis from the Italian Society of Invasive Cardiology. *Am J Cardiol* 102(11):1463–1468, 2008.

117. Biondi-Zoccai GG, Lotrionte M, Moretti C, et al: A collaborative systematic review and meta-analysis on 1278 patients undergoing percutaneous drug-eluting stenting for unprotected left main coronary artery disease. *Am Heart J* 155(2):274–283, 2008.
118. Erglis A, Narbute I, Kumsars I, et al: A randomized comparison of paclitaxel-eluting stents versus bare-metal stents for treatment of unprotected left main coronary artery stenosis. *J Am Coll Cardiol* 50(6):491–497, 2007.
119. Mehilli J, Kastrati A, Byrne RA, et al: Paclitaxel- versus sirolimus-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol* 53(19):768–2009, 1760.
120. Khattab AA, Hamm CW, Senges J, et al: Sirolimus-eluting stent treatment for unprotected versus protected left main coronary artery disease in widespread clinical routine: 6-month and 3-year clinical follow-up results from the prospective multicentre German Cypher Registry. *Heart* 93(10):1251–1255, 2007.
121. Lee MS, Kapoor N, Jamal F, et al: Comparison of coronary artery bypass surgery with percutaneous coronary intervention with drug-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol* 47(4):864–870, 2006.
122. Chieffo A, Morici N, Maisano F, et al: Percutaneous treatment with drug-eluting stent implantation versus bypass surgery for unprotected left main stenosis: a single-center experience. *Circulation* 113(21):2542–2547, 2006.
123. Palmerini T, Marzocchi A, Marrozzini C, et al: Comparison between coronary angioplasty and coronary artery bypass surgery for the treatment of unprotected left main coronary artery stenosis (the Bologna Registry). *Am J Cardiol* 98(1):54–59, 2006.
124. Chieffo A, Park SJ, Valgimigli M, et al: Favorable long-term outcome after drug-eluting stent implantation in nonbifurcation lesions that involve unprotected left main coronary artery: a multicenter registry. *Circulation* 116(2):158–162, 2007.
125. Kang SJ, Park DW, Mintz GS, et al: Long-term vascular changes after drug-eluting stent implantation assessed by serial volumetric intravascular ultrasound analysis. *Am J Cardiol* 105(10):1402–1408, 2010.
126. Park DW, Kim YH, Yun SC, et al: Long-term outcomes after stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 10-year results of bare-metal stents and 5-year results of drug-eluting stents from the ASAN-MAIN (ASAN Medical Center-Left MAIN Revascularization) Registry. *J Am Coll Cardiol* 56(17):1366–1375, 2010.
127. Park DW, Seung KB, Kim YH, et al: Long-term safety and efficacy of stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 5-year results from the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry. *J Am Coll Cardiol* 56(2):117–124, 2010.
128. Cheng CI, Lee FY, Chang JP, et al: Long-term outcomes of intervention for unprotected left main coronary artery stenosis: coronary stenting vs coronary artery bypass grafting. *Circ J* 73(4):705–712, 2009.
129. Sanmartin M, Baz JA, Claro R, et al: Comparison of drug-eluting stents versus surgery for unprotected left main coronary artery disease. *Am J Cardiol* 100(6):970–973, 2007.
130. Chieffo A, Meliga E, Latib A, et al: Drug-eluting stent for left main coronary artery disease. The DELTA registry: a multicenter registry evaluating percutaneous coronary intervention versus coronary artery bypass grafting for left main treatment. *JACC Cardiovasc Interv* 5(7):718–727, 2012.
131. Roh JH, Kim YH, Ahn JM, et al: Readmission rate after coronary artery bypass grafting versus percutaneous coronary intervention for unprotected left main coronary artery narrowing. *Am J Cardiol* 113(10):1639–1646, 2014.
132. Capodanno D, Caggegi A, Capranzano P, et al: Comparative one-year effectiveness of percutaneous coronary intervention versus coronary artery bypass grafting in patients <75 versus >/=75 years with unprotected left main disease (from the CUSTOMIZE Registry). *Am J Cardiol* 110(10):1452–1458, 2012.
133. Park DW, Kim YH, Yun SC, et al: Complexity of atherosclerotic coronary artery disease and long-term outcomes in patients with unprotected left main disease treated with drug-eluting stents or coronary artery bypass grafting. *J Am Coll Cardiol* 57(21):2152–2159, 2011.
134. Buchanan GL, Chieffo A, Meliga E, et al: Comparison of percutaneous coronary intervention (with drug-eluting stents) versus coronary artery bypass grafting in women with severe narrowing of the left main coronary artery (from the Women-Drug-Eluting stent for LefT main coronary Artery disease Registry). *Am J Cardiol* 113(8):1348–1355, 2014.
135. Morice MC, Serruys PW, Kappetein AP, et al: Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation* 129(23):2388–2394, 2014.
136. Morice MC, Serruys PW, Kappetein AP, et al: Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation* 121(24):2645–2653, 2010.
137. Kappetein AP: *Long-term Safety and Efficacy of Percutaneous Coronary Intervention With Stenting and Coronary Artery Bypass Surgery for Left Main Disease: Final Five-year Follow-up of the SYNTAX Trial*, San Francisco. CA, 2013, Transcatheter Therapeutics Conference.
138. Boudriot E, Thiele H, Walther T, et al: Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. *J Am Coll Cardiol* 57(5):538–545, 2011.
139. Park SJ, Kim YH, Park DW, et al: Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med* 364(18):1718–1727, 2011.
140. Buszman PE, Kiesz SR, Bochenek A, et al: Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol* 51(5):538–545, 2008.
141. Capodanno D, Stone GW, Morice MC, et al: Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. *J Am Coll Cardiol* 58(14):1426–1432, 2011.
142. Athappan G, Patvardhan E, Tuzcu ME, et al: Left main coronary artery stenosis: a meta-analysis of drug-eluting stents versus coronary artery bypass grafting. *JACC Cardiovasc Interv* 6(12):1219–1230, 2013.
143. Bittl JA, He Y, Jacobs AK, et al: Bayesian methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. *Circulation* 127(22):2177–2185, 2013.
144. Bucher HC, Hengstler P, Schindler C, et al: Percutaneous transluminal coronary angioplasty versus medical treatment for nonacute coronary heart disease: meta-analysis of randomised controlled trials. *BMJ* 321(7253):73–77, 2000.
145. Boden WE, O'Rourke RA, Teo KK, et al: Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 356(15):1503–1516, 2007.
146. Frye RL, August P, Brooks MM, et al: A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 360(24):2503–2515, 2009.
147. Schömig A, Mehilli J, de Waha A, et al: A meta-analysis of 17 randomized trials of a percutaneous coronary intervention-based strategy in patients with stable coronary artery disease. *J Am Coll Cardiol* 52(11):894–904, 2008.
148. Stergiopoulos K, Brown DL: Initial coronary stent implantation with medical therapy vs medical therapy alone for stable coronary artery disease: meta-analysis of randomized controlled trials. *Arch Intern Med* 172(4):312–319, 2012.
149. Stergiopoulos K, Boden WE, Hartigan P, et al: Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: a collaborative meta-analysis of contemporary randomized clinical trials. *JAMA Intern Med* 174(2):232–240, 2014.
150. Pursnani S, Korley F, Gopaul R, et al: Percutaneous coronary intervention versus optimal medical therapy in stable coronary artery disease: a systematic review and meta-analysis of randomized clinical trials. *Circ Cardiovasc Interv* 5(4):476–490, 2012.
151. Bangalore S, Pursnani S, Kumar S, et al: Percutaneous coronary intervention versus optimal medical therapy for prevention of spontaneous myocardial infarction in subjects with stable ischemic heart disease. *Circulation* 127(7):769–781, 2013.
152. Windecker S, Stortecky S, Stefanini GG, et al: Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. *BMJ* 348:g3859, 2014.
153. Hannan EL, Samadashvili Z, Cozzens K, et al: Comparative outcomes for patients who do and do not undergo percutaneous coronary intervention for stable coronary artery disease in New York. *Circulation* 125(15):1870–1879, 2012.

Diabetes

3

MARCO ROFFI | BARIS GENCER

KEY POINTS

- In individual older than 40 years of age, diabetes mellitus confers a cardiovascular (CV) risk equivalent to aging 15 years.
- Although mortality rates from coronary artery disease (CAD) have declined in the Western world during the past 30 years and diabetic individuals have also benefited from the decline, the more than twofold higher risk of dying from CAD in diabetic patients compared with nondiabetic individuals has persisted over time.
- Whereas the beneficial effect of optimal glycemic control on microvascular complications of diabetes has been established, the effect on macrovascular complications remains controversial.
- Glucose control in diabetic patients with CAD should be individualized: the longer the diabetes disease duration, the older the patient, the more advanced the CAD, the more important the comorbidities, the less stringent the glucose control should be.
- CAD is more prevalent, more severe, and occurs at younger age in patients with diabetes compared with their nondiabetic counterparts. Chronic hyperglycemia, dyslipidemia, oxidative stress, and insulin resistance have been associated with an accelerated form of atherogenesis observed in diabetes, characterized by a prothrombotic state, enhanced inflammation, and endothelial dysfunction.
- Although stress testing should be performed in all symptomatic patients and in those with additional high-risk features, a routine screening for CAD in asymptomatic patients is not justified.
- In diabetic patients with stable angina and documented coronary artery disease not requiring immediate revascularization, medical management is a valuable alternative.
- In the individual diabetic patient, the choice of revascularization modality—percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)—should be based on clinical presentation, comorbidities, pattern and severity of coronary involvement, left ventricular (LV) function, and estimated surgical mortality. However, the threshold for CABG should be lower in diabetic patients than in their nondiabetic counterparts.
- Diabetic patients with acute coronary syndrome (ACS) have higher short- and long-term morbidity and mortality rates than their nondiabetic counterparts and benefit from aggressive management that includes early invasive strategy, potent platelet inhibition, and primary angioplasty.

The prevalence of diabetes mellitus is increasing over time and parallels the growth of the elderly population and the rise in rates of obesity.[1] According to the 2013 World Health Organization statistics, 347 million people worldwide have diabetes.[2] In 2012, 29.1 million Americans were diagnosed with diabetes, representing 9.3% of the adult population in the United States. The number of people with undiagnosed diabetes in the United States is also rapidly growing and represents an estimated 8.1 million individuals in 2012 compared with 7 million in 2010.[3] Finally, in 2012, 86 million Americans had prediabetes, and the percentage slightly increased from 35% of the adult population in 2010 to 37% in 2012. The costs related to diabetes were estimated at $245 billion dollars in the United States in 2012, and after adjusting for population age and sex differences, average medical expenditures among people with diabetes were 2.3 times higher than in the nondiabetic population.[3] Diabetes was the seventh leading cause of death in the United States in 2010,[3] and 50% of people with diabetes died of cardiovascular disease (CVD), primarily heart disease and stroke.[4,5]

Type 2 diabetes is by far the most frequent type of diabetes in Western countries and is the focus of the present chapter. The screening for diabetes is important both in CVD prevention and in patients with established CVD because diabetes represents one of the most important CV risk factors, and adequate glucose control decreases microvascular and possibly macrovascular complications of the disease.[6] The diagnostic criteria of diabetes according to the American Diabetes Association (ADA) are reported in Table 3-1.[7] Based on a combination of hemoglobin A1C (Hb_{A1c}) and fasting plasma glucose, the diagnosis of diabetes can be made after two consecutive values are found to be above the diagnostic criteria. An oral glucose tolerance test is recommended in addition if the diagnosis of diabetes is inconclusive or for the diagnosis of impaired glucose tolerance.[8]

PATHOPHYSIOLOGY OF ATHEROSCLEROSIS IN DIABETES

In patients with diabetes, CAD is more prevalent, more advanced, and occurs at a younger age than with nondiabetic counterparts. Several metabolic abnormalities—including chronic hyperglycemia, dyslipidemia, oxidative stress, and insulin resistance—have been associated with the accelerated atherogenesis observed in people with diabetes (Fig. 3-1).[9] In addition to metabolic disturbances, diabetes alters the function of multiple cell lines, including endothelial cells, smooth muscle cells, and platelets. Despite the description of several peculiarities that characterize diabetes-associated atherosclerosis, the exact mechanisms underlying the initiation and progression of the atherosclerotic process remain elusive.[10]

Long-standing insulin resistance, characterized by elevated plasma glucose and compensatory hyperinsulinemia, has been associated with diabetic microvascular and macrovascular complications. The supposed link is via the development of (1) endothelial dysfunction and oxidative stress, (2) an inflammatory state, (3) a prothrombotic state, and (4) atherosclerotic plaque instability with subsequent risk of plaque rupture and occlusive thrombus formation. These proatherogenic mechanisms observed in diabetic patients may be responsible for the higher rate of mortality and reinfarction in patients with CAD, as well as for the higher stent thrombosis and stent restenosis after PCI observed in the diabetic population.[11]

CARDIOVASCULAR DISEASE IN DIABETES

A population-based study estimated that in patients older than 40 years, diabetes confers an equivalent CV risk to aging 15 years.[12] The 2013 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines on cholesterol treatment considered the diabetic population as a group of patients at higher risk who would benefit from intensive statin therapy in primary prevention, although the overall CV risk was considered to be lower than that of nondiabetic patients with established CVD.[13] Although in Western countries, the age-adjusted mortality rates of CAD and stroke have declined over the last 20 years, the diabetes "epidemic" led to a 30% increase in the

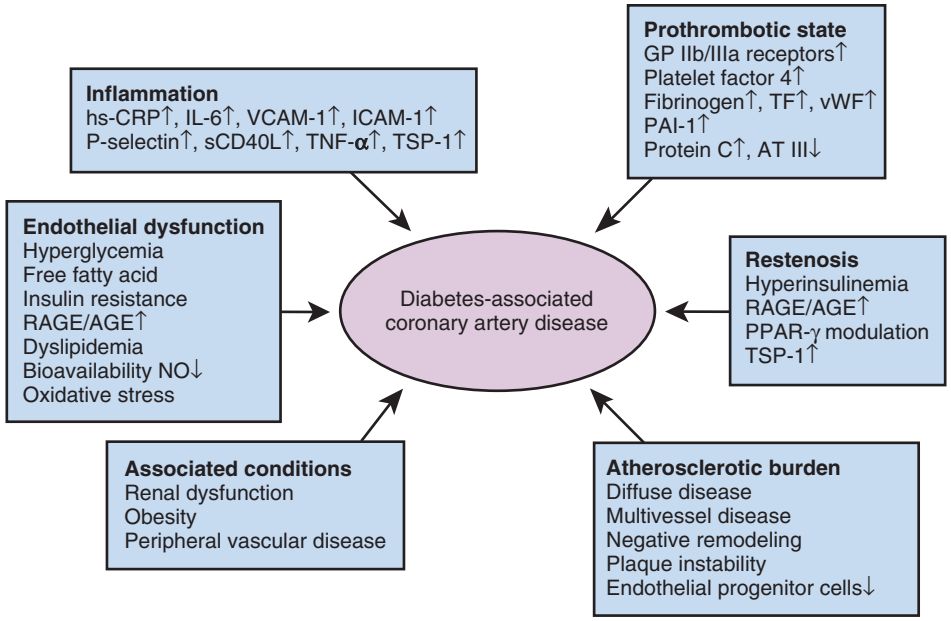


FIGURE 3-1 Pathophysiology of diabetes mellitus–associated coronary artery disease. *AT,* Antithrombin; *GP,* glycoprotein; *hs-CRP,* high-sensitivity C-reactive protein; *ICAM-1,* intracellular adhesion molecule 1; *IL-6,* interleukin 6; *NO,* nitric oxide; *PAI-1,* plasminogen activator inhibitor 1; *PPAR-γ,* peroxisome proliferator-activated receptor gamma; *RAGE,* receptor for advanced glycation end products (AGE); *sCD40L,* soluble CD40 ligand; *TF,* tissue factor; *TNF-α,* tumor necrosis factor alpha; *TSP-1,* thrombospondin 1; *VCAM-1,* vascular cell adhesion molecule 1; *vWF,* von Willebrand factor. (Adapted from Roffi M, Topol EJ: Percutaneous coronary intervention in diabetic patients with non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 25:190-198, 2004.)

TABLE 3-1 Diagnosis of Diabetes Mellitus According to the American Diabetes Association

Hb_{A1c} (glycated hemoglobin) greater than 6.5%*
or
fasting plasma glucose ≥126 mg/dL (7.0 mmol/L) with *fasting* defined as no caloric intake for at least 8 hours
or
two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test performed as described by the World Health Organization using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water
or
in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L)

From the American Diabetes Association: Standards of medical care in diabetes—2014. *Diabetes Care* 37(Suppl 1):S14-S80, 2014.
*The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.

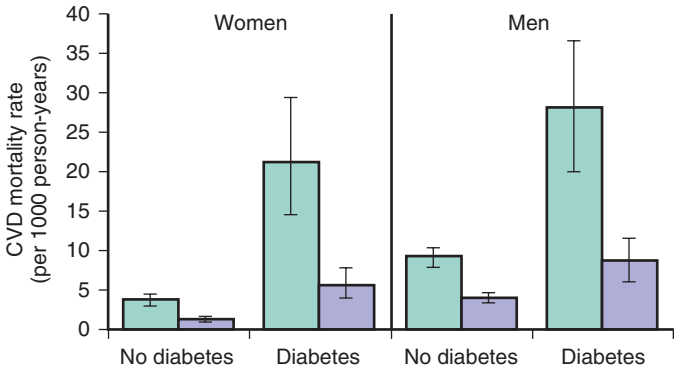


FIGURE 3-2 Age-adjusted cardiovascular disease (CVD) mortality rates among participants in the Framingham Heart Study with and without diabetes mellitus by sex and time period. *Teal bars* represent the years 1950 to 1975; *purple bars* represent 1976 to 2001. (From Preis SR, Hwang SJ, Coady S, et al: Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. *Circulation* 119:1728-1735, 2009.)

diabetes-related death rate in the same time span.[14] The Framingham Heart Study documented a major reduction in CV mortality both in diabetic (hazard ratio [HR] 0.31) and nondiabetic (HR 0.38) individuals enrolled in the years 1975 through 2001 compared with those enrolled in the years 1950 through 1975 (Fig. 3-2).[15] The absolute reduction was dramatic in the diabetic population: mortality rates dropped from 24.1 to 6.8 to per 1000 person-years, whereas among nondiabetic individuals, it went from 6.3 to 2.4 per 1000 person-years.

Nevertheless, the more than twofold higher risk of dying from CAD in men and women with diabetes has persisted over time.[16] Autopsy and angiographic studies have shown that patients with diabetes more frequently have left main coronary artery lesions, multivessel disease, and diffuse CAD than their nondiabetic counterparts. A recent angiographic study on patients with angina demonstrated that the greater the impairment of glucose metabolism (i.e., normal vs. impaired glucose tolerance vs. newly diagnosed diabetes vs. known diabetes), the smaller the average coronary artery diameter and the longer the lesions detected. In addition, a retrospective study of 3805 patients with diabetes showed a significant association between the Hb_{A1c} levels and the severity of the CAD according to the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score.[17]

TABLE 3-2 Summary of Studies Using Stress Testing in the Diagnosis of Suspected Coronary Artery Disease in Patients With Symptomatic Diabetes Mellitus

Type of Test	Study	Subjects (*n*)	Reference Standard	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ECG	Lee et al. (2001)	190	Angiography	47	81	85	41
ECG	Gheydari et al. (2013)	130	Angiography	NA	NA	77	NA
DSE	Hennessy et al. (1997)	52	Angiography	82	54	84	50
Nuclear	Kang et al. (1999)	138	Angiography	86	56	NA	NA

Modified from Albers AR, Krichavsky MZ, Balady GJ: Stress testing in patients with diabetes mellitus: diagnostic and prognostic value. *Circulation* 2006;113:583-592, 2006.
DSE, Dobutamine stress echocardiography; *ECG,* exercise electrocardiogram stress test; *NA,* not available; *NPV,* negative predictive value; *PPV,* positive predictive value.

TABLE 3-3 Summary of Studies Using Stress Testing in the Diagnosis of Coronary Artery Disease in Patients With Asymptomatic Diabetes Mellitus

Type of Test	Study	Subjects (*n*)	Reference Standard	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ECG	Blandine et al. (1999)	98	Angiography	NA	NA	90	NA
ECG	Koistinen et al. (1990)	136	Angiography	NA	NA	94	NA
ECG	Bacci et al. (2002)	206	Angiography	NA	NA	79	NA
ECG	Penfornis et al. (2001)	56	Angiography	NA	NA	60	NA
DSE	Penfornis et al. (2001)	56	Angiography	NA	NA	69	NA
Nuclear	Blandine et al. (1999)	103	Angiography	NA	NA	63	NA
Nuclear	Wackers et al. (2004)	1123	None	NA	NA	NA	NA
Nuclear	Rajagopalan et al. (2005)	1427	Angiography	92	68	89	60
Nuclear	Penfornis et al. (2001)	56	Angiography	NA	NA	75	NA

Modified from Albers AR, Krichavsky MZ, Balady GJ: Stress testing in patients with diabetes mellitus: diagnostic and prognostic value. *Circulation* 2006;113:583-592, 2006.
DSE, Dobutamine stress echocardiography; *ECG,* exercise electrocardiogram stress test; *NA,* not available; *NPV,* negative predictive value; *PPV,* positive predictive value.

MYOCARDIAL ISCHEMIA DETECTION IN DIABETIC PATIENTS

Diabetic patients have significantly higher rates of silent ischemia and silent myocardial infarction (MI) than the general population. It has been estimated that as many as 12.5 million diabetic patients in United States may have asymptomatic CAD.[18-20]

Exercise electrocardiography (ECG) testing is a well-established and inexpensive test to guide the clinician in the diagnosis and risk stratification of diabetic patients with suspected CAD. Sensitivity and specificity for the diagnosis of CAD in diabetic and nondiabetic patients who present with angina appear comparable.[20] In asymptomatic patients, an abnormal exercise ECG test may be helpful to identify a subgroup of patients with advanced CAD.[20] Patients with a negative stress test in the presence of normal exercise capacity are at low risk for CV events, at least in the short run. Stress nuclear imaging has the most extensive literature among the noninvasive modalities for both diagnostic and prognostic purposes in diabetes. With respect to stress echocardiography, several studies have addressed its prognostic accuracy in diabetes, although the data on its diagnostic value are scarce (Tables 3-2 and 3-3).[20]

The assessment of coronary artery calcium is a well-established index of atherosclerosis. Electron beam computed tomography (CT) and multidetector CT (MDCT) enable measurement of the calcium content of coronary arteries, and a scoring system has been developed for that purpose. Several studies have identified coronary artery calcium score as a strong predictor for CV events and all-cause mortality in diabetic individuals. The Prospective Evaluation of Diabetic Ischaemic Disease by Computed Tomography (PREDICT) study[21] evaluated calcium score as a predictor of CV events in 589 asymptomatic individuals with type 2 diabetes prospectively. The risk of a CV event increased with increasing category of calcium score. In addition, calcium score had greater predictive value for end points than a broad range of conventional and novel risk factors. Finally, a prospective cohort study in West London found that calcium score was superior to established risk factors in predicting the presence of silent myocardial ischemia on perfusion scans.[22]

The value of screening for CAD in asymptomatic diabetic patients is a source of controversy. Cardiac testing should be considered in the presence of additional features of increased CV risk, such as peripheral or cerebrovascular disease, renal disease, albuminuria, abnormal resting ECG, microvascular diabetic complications, or additional CV risk factors.[23] In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, 1123 diabetic participants with no symptoms of CAD were randomly assigned to adenosine stress radionuclide myocardial perfusion imaging (MPI) or no screening in addition to optimal medical treatment.[24] At a mean follow-up of 4.8 years, the cumulative cardiac death or MI rate was 2.9% (0.6% per year), with no difference between the two groups. In the screened group, participants with normal results ($n = 409$) or small defects ($n = 50$) had lower event rates than the 33 patients with moderate or large defects on perfusion imaging (0.4% per year vs. 2.4% per year; HR, 6.3; 95% CI, 1.9 to 20.1; $P = .001$; Fig. 3-3). Nevertheless, the positive predictive value (PPV) of having moderate or large defects on perfusion scans was only 12%. The overall rate of coronary revascularization was low in both groups (5.5% in the screened group and 7.8% in the unscreened group). The authors concluded that more aggressive screening for CAD did not improve the outcome of asymptomatic diabetic patients over optimal medical therapy and lifestyle modification. However, because the event rates were lower than estimated, the study was underpowered. In addition, among the 33 patients with moderate to large perfusion defects detected by screening, the rate of coronary angiography was only 15%.

In summary, although stress testing should be performed at a lower suspicion of CAD in patients with diabetes, compared with their nondiabetic counterparts, and in those with associated high-risk conditions, a routine screening for CAD in asymptomatic patients is not justified.[25,26]

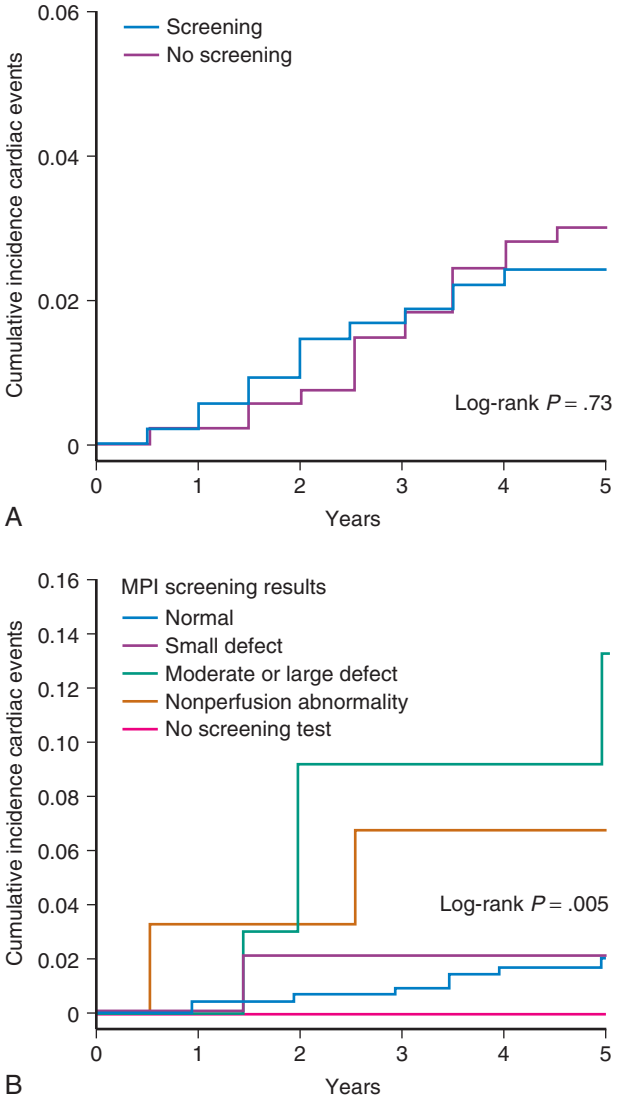


FIGURE 3-3 **A,** Cumulative incidence of cardiac events in 561 participants randomized to systematic baseline screening with stress myocardial perfusion imaging (MPI) and 562 participants randomized to receive no screening in the DIAD study. **B,** Cumulative incidence of cardiac events according to results of systematic screening with stress MPI: normal, small defect, moderate or large defect, and nonperfusion abnormality. (From Young LH, Wackers FJ, Chyun DA, et al: Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA* 301:1547-1555, 2009.)

REVASCULARIZATION IN DIABETIC PATIENTS WITH STABLE CORONARY ARTERY DISEASE

It is estimated that the diabetic population represents 30% to 35% of patients undergoing coronary revascularization in the United States.[27] Despite improvements in the management of diabetic patients undergoing coronary revascularization—from a pharmacologic, device, and surgical standpoint—diabetes remains an independent predictor of CV events following both percutaneous and surgical revascularization.

Quality comparative data are available on medical management versus revascularization and on drug-eluting stent (DES)–based PCI versus CABG in diabetic patients. Similar to the increase of several randomized clinical trials, new meta-analysis designs ("individual participant data analysis collaborations") have been developed, such as both direct (head-to-head) randomized controlled trial (RCT) comparisons, as well as indirect RCT combinations. This leads to an increase of statistical power regarding the diabetic population.[28]

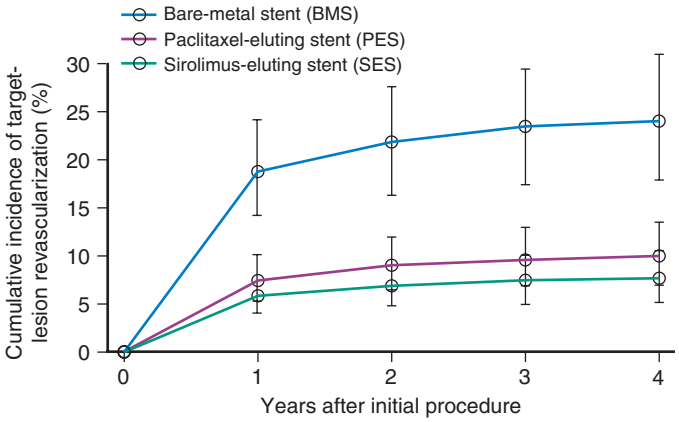


FIGURE 3-4 Cumulative incidence of target-lesion revascularization and corresponding hazard ratios (95% confidence intervals) for three stent types estimated from a network meta-analysis for pairwise comparisons in patients with diabetes. *BMS,* Bare-metal stent; *PES,* paclitaxel-eluting stent (Taxus, Boston Scientific); *SES,* sirolimus-eluting stent (Cypher, Cordis). (From Stettler C, Allemann S, Wandel S, et al: Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. *BMJ* 337:a1331, 2008.)

PERCUTANEOUS CORONARY INTERVENTION

Whereas in-hospital and 30-day outcomes after PCI in diabetic patients were frequently found to be comparable with those of their nondiabetic counterparts, longer-term outcomes found diabetes to be associated with increased target-vessel revascularization (TVR), major adverse cardiac and cerebrovascular events (MACCEs), and late mortality even in the era of drug-eluting stents.[28] A network meta-analysis of 35 RCTs compared drug-eluting stents (DESs) with bare-metal stents (BMSs) in 3852 diabetic patients and showed that DESs, although they do not affect overall mortality or MI rates in diabetic patients, were associated with sizable reductions in target-lesion revascularization (TLR), with a relative risk ratio (RRR) of 60% to 70%, depending on the type of stent used, and an absolute risk reduction of about 16% (Fig. 3-4).[29] Whereas first-generation DES use in diabetes was found to be an independent predictor of late stent thrombosis in several studies (Fig. 3-5),[28] this does not seem to be the case with newer-generation DESs.[30] A recent individual participant data analysis from 18 prospective RCTs that included 18,441 patients who underwent DES-based PCI, of whom 3467 were diabetic, reported significantly higher TLR in diabetic patients only in cases of complex lesions (type B2/C) and not in simple lesions (type A/B1; type B2/C according to ACC/AHA lesion classification and type A/B1 according to ACC/AHA lesions classification).[31]

Sufficient comparative data among DESs for diabetic patients are available for the first-generation devices, namely the Cypher (Cordis) sirolimus-eluting stent (SES) and the paclitaxel-eluting stent (PES) Taxus (Boston Scientific). A meta-analysis of 13 RCTs that included 2422 diabetic patients and compared PES with SES reported similar event rates in terms of TVR (PES 8.6%: 95% confidence interval [CI], 6.5 to 11.3; SES 7.6%: 95% CI, 5.8 to 9.9) and MACCEs (PES 15.4%: 95% CI, 12.4 to 19.1; SES 12.9%: 95% CI, 8.5 to 19.2). The same authors pooled 16 registries with 10,156 diabetic patients and again reported similar TVR (PES 5.8%: 95% CI, 3.9% to 8.5%; SES 7.2%: 95% CI, 4.6% to 11.2%) and MACCE rates (PES 10.1%: 95% CI, 7.3% to 13.8%; SES 11.9%: 95% CI, 8.6% to 16.4%).[32] With respect to newer-generation

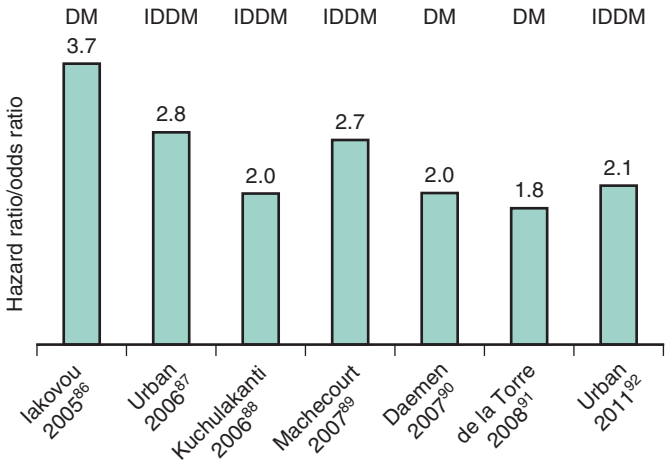


FIGURE 3-5 Studies that have detected diabetes mellitus or insulin-dependent diabetes mellitus as an independent predictor of drug-eluting stent thrombosis. Reported is the hazard ratio or odds ratio of multivariate analyses. *DM,* Diabetes mellitus; *IDDM,* insulin-dependent diabetes mellitus. (From Roffi M, Angiolillo D, Kappetein AP: Current concepts on coronary revascularization in diabetic patients. *Euro Heart J* 32: 2748-2757, 2011.)

DESs, a subgroup analysis of the diabetic population ($n = 414$) of the head-to-head trial to compare the biolimus-eluting stent (Biomatrix, Biosensor) and the Cypher stent showed no difference in death, MI, or TVR at 9 months.[33] Similarly, a subgroup analysis for the diabetic population ($n = 1140$) of the head-to-head trial that allocated patients to the everolimus-eluting stent (Xience, Abbott) and the Taxus stent showed no difference in the target lesion failure at 1 year (6.4% vs. 6.9%).[34]

In summary, current evidence supports the contention that in diabetic patients, the use of DESs compared with BMSs dramatically reduces the risk of restenosis and repeat revascularization and has no harmful effect in terms of MI. Whereas with first-generation DESs, diabetic patients had an increase in stent thrombosis rates compared with nondiabetic individuals, this does not seem to be the case with newer-generation devices. Current European Society of Cardiology (ESC) guidelines on myocardial revascularization recommend the DES as the device of choice for diabetic patients (class I, level of recommendation A).[35] Recent U.S. guidelines for PCI recommended the DES as the device of choice (class I, level of recommendation A) for patients at high risk of restenosis.[36]

CORONARY ARTERY BYPASS SURGERY

Paralleling PCI, diabetes still negatively affects outcomes following CABG. The impact of diabetes on morbidity and mortality in patients undergoing surgical coronary revascularization was addressed in a retrospective analysis of the Society of Thoracic Surgery database and included 41,663 diabetic patients among a total population of 146,786 patients.[37] At 30 days, the mortality was significantly higher in the diabetes group (3.7% vs. 2.7%). Looking into long-term mortality following CABG, a prospective cohort study that included 11,186 consecutive diabetic patients and 25,455 nondiabetic patients who underwent CABG from 1992 to 2001 detected a significantly higher annual mortality rate among diabetic patients (5.5%) compared with that of nondiabetic individuals (3.1%).[38] In addition to increased periprocedural morbidity and mortality, as well as long-term mortality, diabetic patients need to undergo repeat revascularization following CABG more frequently than their nondiabetic counterparts.[39]

The use of multiple arterial conduits, including bilateral internal mammary artery (BIMA) grafting, has been shown to improve the long-term results of CABG and to reduce the need for repeat revascularization in the diabetic population. The Leipzig experience on 1515 consecutive patients who underwent BIMA grafting included 519 diabetic patients. Multiple regression analysis showed that, in addition to repeat operation (odds ratio [OR] 12.7), both non–insulin-dependent (OR 4.6) and insulin-dependent diabetes (OR 6.9) were associated with a significantly increased risk of sternal infection.[40] An analysis of a population of 1107 consecutive patients with diabetes showed no difference in operative mortality (2.4% vs. 3.1%, $P = .28$), sternal wound infection (1.7% vs. 3.1%, $P = .18$), or total complications (17.1% vs. 17.1%, $P = 1.00$) using propensity score-matching in the groups of single internal mammary artery (SIMA) or BIMA. Late survival was significantly improved with the use of BIMA grafting after 13.1 years compared with SIMA grafting after 9.8 years.[41] A recent meta-analysis of nine observational studies with up to 10-years follow-up that included 15,583 patients reported a reduction of mortality (HR, 0.79; 95% CI, 0.75 to 0.84) with BIMA compared with SIMA (Fig. 3-6).[42]

The Arterial Revascularisation Trial (ART) randomized 3102 diabetic and nondiabetic patients to SIMA or BIMA with a primary outcome of survival at 10 years.[43] A mean of three grafts were applied in both groups, and 41% of the procedures were performed off pump. Mortality at 30 days was 1.2% in both groups, whereas at 1 year, it was 2.3% in the SIMA group and 2.5% in the BIMA group (Fig. 3-7). The rates of stroke, MI, and repeat revascularization were all 2% or less at 1 year and were similar between the two groups. Sternal wound reconstruction for infection was required in 0.6% and 1.9% of the SIMA and BIMA groups, respectively (RR, 3.2; 95% CI, 1.5 to 6.8). The results of the ART trial suggest that the use of BIMA grafts is feasible on a routine basis. The 10-year outcome analysis of the study will show whether BIMA grafting results in lower mortality and the need for repeat intervention. Despite the overall encouraging results of BIMA grafting, a cross-sectional observational study on over 1.5 million CABG surgeries performed in the United States between 2002 and 2008 showed that this revascularization technique was performed in only 3.9% of the patient population.[44]

With respect to the impact of off-pump surgery, an RCT of 4752 patients (2253 with diabetes) treated with CABG compared the use of off-pump with the use of on-pump surgery; the primary outcome was a composite of death, nonfatal stroke, nonfatal MI, or new renal failure that required dialysis at 30 days.[45] No significant difference was reported in primary end point (9.8% vs. 10.3%; HR, 0.95; 95% CI, 0.79 to 1.14); however, the use of off-pump CABG significantly reduced the rates of blood-product transfusion (50.7% vs. 63.3%; RR, 0.80; 95% CI, 0.75 to 0.85; $P < .001$), reoperation for perioperative bleeding (1.4% vs. 2.4%; RR, 0.61; 95% CI, 0.40 to 0.93; $P = .02$), acute kidney injury (28.0% vs. 32.1%; RR, 0.87; 95% CI, 0.80 to 0.l96; $P = .01$), and respiratory complications (5.9% vs. 7.5%; RR, 0.79; 95% CI, 0.63 to 0.98; $P = .03$), but it increased the rate of early revascularization (0.7% vs. 0.2%; HR, 4.01; 95% CI, 1.34 to 12.0; $P = .01$). The presence of diabetes did not significantly change the observations.

REVASCULARIZATION VERSUS MEDICAL MANAGEMENT

The Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial randomly assigned 2368 diabetic patients with stable CAD in a two-by-two design to either prompt revascularization with intensive medical therapy or intensive medical therapy alone and to either insulin-sensitization or insulin-provision therapy.[46] Primary end points were the 5-year rates of death and of MACCE defined as a composite of death, MI, or stroke. Randomization was stratified according to the choice of PCI or CABG as the more appropriate intervention. Survival did not differ between the revascularization group (88.3%) and the medical-therapy group (87.8%). The rates of freedom from MACCE also did not differ significantly between the groups: it was 77.2% in the revascularization group and 75.9% in the medical-treatment group (Fig. 3-8). Whereas in the PCI stratum, no significant difference was reported in primary end points between the

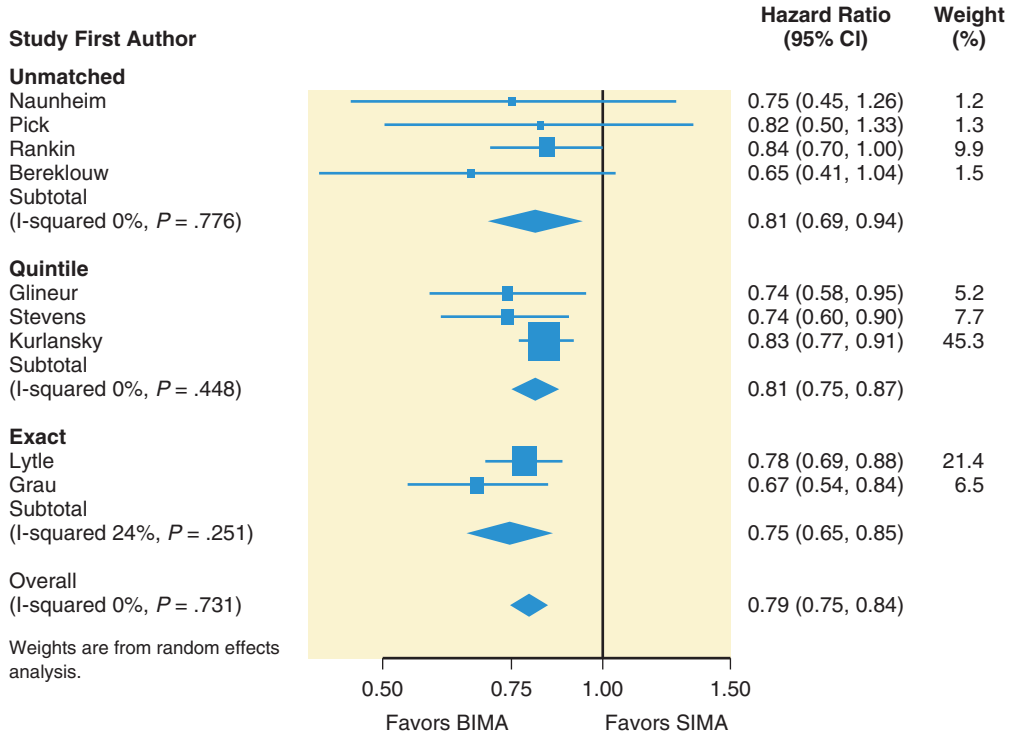


FIGURE 3-6 Effects of bilateral internal mammary artery grafting on long-term survival. This random-effects meta-analysis is from nine studies. Horizontal lines indicate a 95% confidence interval (CI). The "unmatched" group included studies with no statistical matching method. The "quintile" group included studies that used a quintile-based stratification method with propensity score. The "exact" group included studies with a propensity score–based exact (1 : 1) matching method. *BIMA,* Bilateral internal mammary artery; *SIMA,* single internal mammary artery. (From Yi G, Shine B, Rehman SM, et al: Effect of bilateral internal mammary artery on long-term survival: a meta-analysis approach. *Circulation* 130:539-545, 2014.)

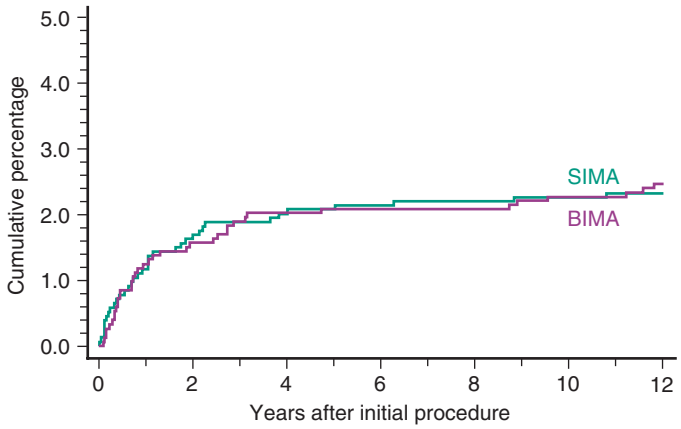


FIGURE 3-7 All-cause mortality at 1 year in the Arterial Revascularisation Trial (ART). *BIMA,* Bilateral internal mammary artery; *SIMA,* single internal mammary artery. (From Taggart DP, Altman DG, Gray AM, et al: Randomized trial to compare bilateral versus single internal mammary coronary artery bypass grafting: 1-year results of the Arterial Revascularisation Trial [ART]. *Euro Heart J* 31:2470-2481, 2010.)

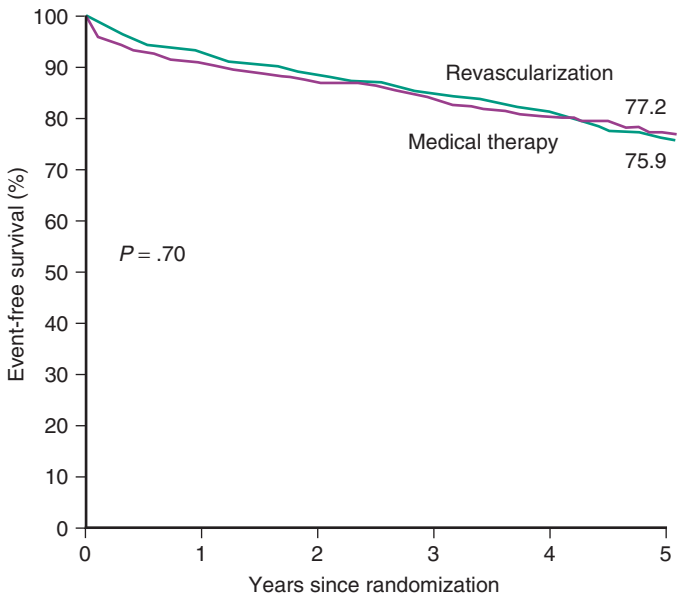


FIGURE 3-8 Freedom from major cardiovascular events, revascularization versus medical therapy at 5 years in the BARI 2D trial. (From Frye RL, August P, Brooks MM, et al: A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 360:2503-2515, 2009.)

revascularization group and the medical-therapy group, in the CABG stratum, the rate of MACCE was significantly lower in the revascularization group (22.4%) than in the medical-therapy group (30.5%, $P = .01$; $P = .002$ for interaction between stratum and study groups).[46]

Because BARI 2D did not compare PCI and CABG, no conclusion can be drawn from that trial on the efficacy of these strategies in diabetic patients. Patients randomized in the CABG stratum were at higher risk than those randomized in the PCI stratum. With respect to the factors that influenced the choice of revascularization in BARI 2D, multivariate analysis showed that selection of CABG over PCI was significantly driven by age greater than 65 years (OR, 1.4) and angiographic factors that included triple-vessel disease (OR, 4.4), left anterior descending coronary artery (LAD) stenosis of 70% or more (OR, 2.9), proximal LAD stenosis of 50% or more (OR, 1.8), total occlusion (OR, 2.4), and multiple type C lesions (OR, 2.1).[47]

PERCUTANEOUS CORONARY INTERVENTION VERSUS CORONARY ARTERY BYPASS GRAFTING IN DIABETIC PATIENTS WITH MULTIVESSEL DISEASE

The New York cardiac registries identified 37,212 patients with multivessel CAD who underwent CABG and 22,102 patients with multivessel CAD who underwent BMS-based PCI. Over 12,300 patients in the CABG group and over 5500 patients in the PCI group had diabetes. Among the diabetic patients, multivariate analyses showed a significant mortality benefit at 3 years for CABG versus PCI in patients with three-vessel disease with proximal and nonproximal LAD involvement and in those with two-vessel disease with proximal and nonproximal LAD involvement (adjusted HR ranged from 0.59 to 0.71). Only among diabetic patients with two-vessel disease and no LAD involvement did the mortality benefit not reach statistical significance (HR, 0.69; 95% CI, 0.46 to 1.03).[48] Another epidemiologic study assessed the clinical outcomes of patients with multivessel disease who underwent revascularization with CABG ($n = 7437$) or with a DES ($n = 9963$) between the years 2003 and 2004 in New York state.[49] Patients who underwent CABG were older, more likely to be male and white, and had a lower ejection fraction, prior MI, other coexisting conditions, and three-vessel CAD. The outcomes of diabetic patients treated with CABG ($n = 2844$) did not differ from those who underwent PCI ($n = 3256$) with respect to the adjusted rate of death (HR, 0.97; $P = .75$) and death or MI (HR, 0.84; $P = .07$).

The Coronary Artery Revascularization in Diabetes (CARDia) trial compared PCI and CABG in 510 diabetic patients with symptomatic multivessel CAD. At 1 year of follow-up, the primary end point of death, MI, and stroke was 10.5% in the CABG group and 13.0% in the PCI group (HR, 1.25; $P = .39$). The need for repeat revascularization was 2.0% in the CABG group and 11.8% in the PCI group (HR, 6.2; $P < .001$). All-cause mortality rates were the same, 3.2%, and the rates of death, MI, stroke, or repeat revascularization were 11.3% and 19.3%, respectively (HR, 1.77; $P = .16$; Fig. 3-9).[50] In the first phase of the study, patients were randomized to either CABG or BMS implantation, and thereafter patients were randomized to CABG or DES implantation ($n = 350$). In the patient population randomized after the introduction of the DES, the death, MI, stroke, or repeat revascularization rates in the CABG and PCI groups were 12.9% and 18.0%, respectively (HR, 1.41; P = nonsignificant [NS]).

The SYNTAX study randomly assigned 1800 patients (452 with diabetes) to receive paclitaxel DES-based PCI (Taxus) or CABG. The 1-year major adverse cardiac and cerebrovascular event rate (MACCE; death, stroke, MI, or repeat revascularization) was higher among diabetic patients treated with a DES (26.0%) than with CABG (14.2%; $P = .003$).[51] Conversely, no difference was observed in diabetic patients in the death, stroke, or MI rate (10.3% for CABG vs. 10.1% for PCI).[52] The presence of diabetes was associated with significantly increased mortality after either revascularization treatment. Mortality was higher after PCI than after CABG (4.1% vs. 13.5%, $P = .04$) for diabetic patients with highly complex lesions (i.e., SYNTAX score ≥33). Treatment with PCI, rather than CABG, resulted in higher repeat revascularization rates for diabetic patients (6.4% vs. 20.3%, $P < .001$). The more complex the lesions according to the SYNTAX score, the greater the disadvantage of PCI in terms of MACCE, driven by an increased TVR rate. The 5-year follow-up of the SYNTAX trial in diabetic patients showed the persistence of the benefit of CABG over PCI: the rates of MACCE were 29.0% in the CABG group versus 46% in the PCI group ($P < .0001$), mainly driven by repeat revascularization (35.3% for PCI vs. 14.6% for CABG, $P < .001$). However, no benefit of CABG was observed for the composite end point of death, MI, or stroke (23.9% vs. 19.1%, $P = .26$; Fig. 3-10). The final 5-year follow-up of the SYNTAX trial in the total population showed the persistence of the benefit of CABG over PCI: the rates of MACCE were 24.2% in the CABG group versus 37.5% in the PCI group ($P < .0001$). The benefit of CABG was observed for the composite end point of death, MI, and stroke (22.0% vs. 14.0%, $P < .001$), all-cause death (14.6% vs. 9.2%, $P = .006$), nonfatal MI (39.2% vs. 4.0%, $P = .001$), and the need for repeat revascularization (25.4% vs.12.6%, $P < .0001$). In the subgroup of patients with a low SYNTAX score (0 to 22 points), no differences in MACCE (26.8% vs. 33.3%, $P = .21$) were observed, but significantly more repeat revascularization was required (25.4% vs. 12.6%, $P = .038$).

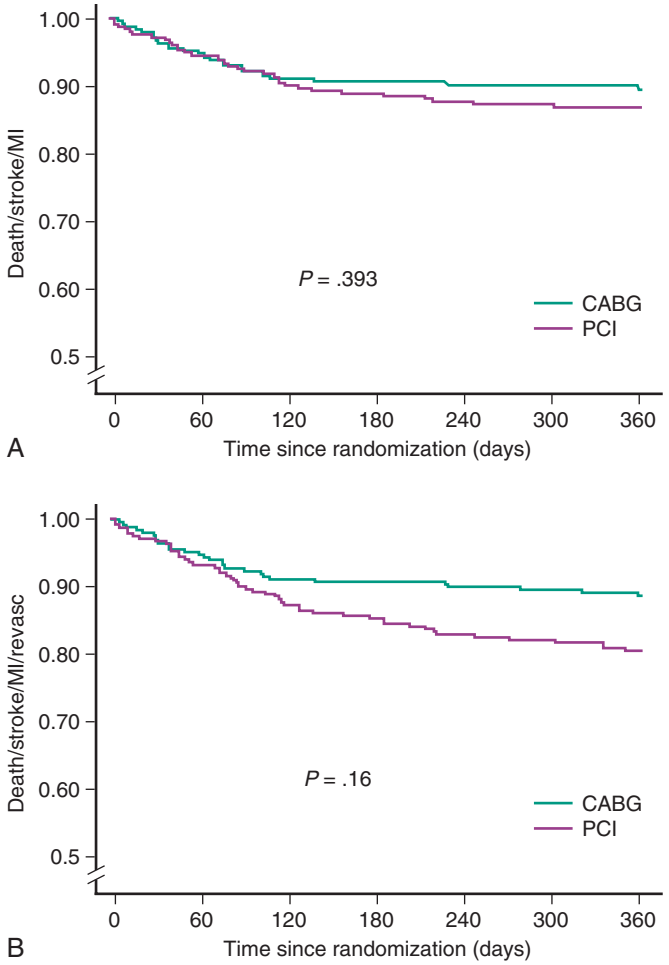
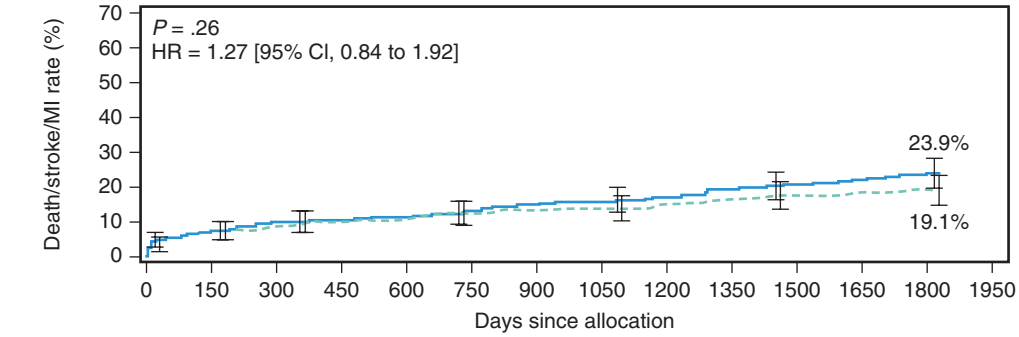
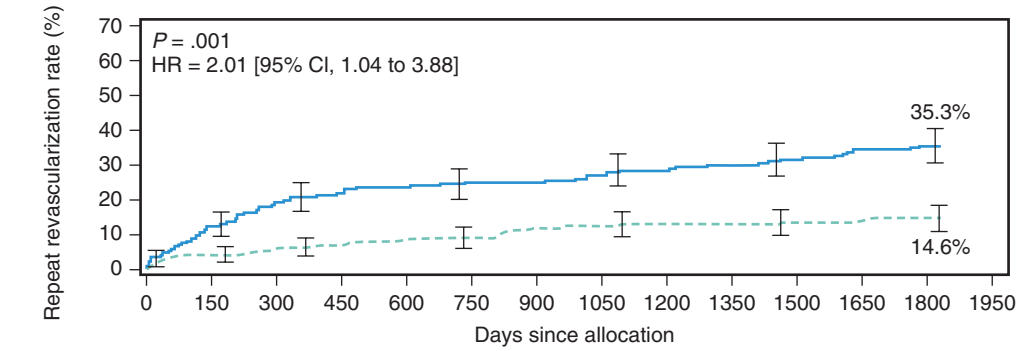


FIGURE 3-9 One-year Kaplan-Meier event-free survival curves for coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). The primary outcomes were death, myocardial infarction (MI), or stroke (**A**) and death, MI, stroke, or repeat revascularization (revasc) in the CARDia trial (**B**). (From Kapur A, Hall RJ, Malik IS, et al: Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia trial. *J Am Coll Cardiol* 55:432-440, 2010.)



Numbers at risk:

A	*t* = 0	180	365	730	1095	1460	1825
PCI	231	217	206	205	197	188	178
CABG	221	198	187	183	175	169	160



Numbers at risk:

B	*t* = 0	180	365	730	1095	1460	1825
PCI	231	212	179	172	158	142	131
CABG	221	198	183	180	168	156	150

FIGURE 3-10 Five-year outcomes of percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) in diabetic and nondiabetic patients. The composite end point of all-cause death, stroke, and myocardial infarction (MI; **A**) and repeat revascularization (**B**) in diabetic patients. *CI,* Confidence interval; *HR,* hazard ratio; *t,* time. (From Kappetein AP, Head SJ, Morice MC, et al: Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *Euro J Cardiothorac Surg* 43:1006-1013, 2013.)

Differences were greater in diabetics (HR, 2.30; 95% CI, 1.50 to 3.55) compared with nondiabetic patients (HR, 1.51; 95% CI, 1.15 to 1.96).[53]

The Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial compared PCI (first-generation DES) with CABG in 1900 diabetic patients with multivessel CAD and showed an increased risk of MACCE in the PCI group (26.6% vs. 18.7%, $P = .005$) compared with the CABG group after 5 years of follow-up.[54] CABG was superior to PCI in terms of a reduced overall death rate (16.3% vs. 10.9%, $P = .049$) and a reduced rate of nonfatal MI (13.9% vs. 6.0%, $P < .001$), but CABG was inferior to PCI in terms of a higher rate of stroke at 5 years (2.4% in the PCI group and 5.2% in the CABG group, $P = .03$; Fig. 3-11).

A recent mixed treatment comparison analysis of 68 RCTs in 24,015 patients with diabetes showed that PCI using cobalt-chromium everolimus-eluting stents showed similar mortality with CABG (RR, 1.11; 95% CI, 0.67 to 1.84), whereas paclitaxel-eluting stents (RR, 1.57; 95% CI, 1.15 to 2.19) and sirolimus-eluting stents (RR, 1.43; 95% CI, 1.07 to 1.97) were associated with increased mortality. In addition, the excess repeat revascularization for PCI with cobalt-chromium everolimus-eluting stents was not statistically significant (RR, 1.31; 95% CI, 0.74 to 2.29), although the point estimate favored CABG.[55]

Although PCI is commonly favored over CABG in patients with ongoing myocardial ischemia because of the increased risk when surgery is performed in the early phase of infarction, in stable diabetic patients, the choice of revascularization modality should take into account multiple parameters that include coronary anatomy, LV function, coexisting conditions, and estimated surgical risk (Fig. 3-12). Surgery should be favored in patients with multivessel coronary disease and acceptable surgical risk. Overall, the threshold for surgery compared with PCI should be lower in diabetic patients compared with their nondiabetic counterparts. According to the 2011 ACC Foundation/AHA/Society for Cardiovascular Angiography and Interventions (SCAI) guidelines,[36] CABG is recommended for the revascularization of diabetic patients with complex (SYNTAX score >22) multivessel disease (class I, level B) and patients with unprotected left main coronary artery disease (class I, level B). PCI is an acceptable alternative for patients with an unprotected left main coronary artery or multivessel disease with a low SYNTAX score (≤22 points) or for patients with a higher risk of adverse surgical long-term outcome (Society of Thoracic Surgeons [STS] predicted score of operative mortality ≥5%; class IIa, level B) and also for patients with multivessel disease and a low SYNTAX score (≤22 points; class IIa, level B). Those recommendations were published before the publication of the FREEDOM trial. Accordingly, the ESC guidelines on stable CAD recommend CABG in patients with diabetes and multivessel or complex disease (SYNTAX score >22) to improve survival free from MACCE (class I, level A).[26] PCI may be considered for symptom control as an alternative to CABG in patients with diabetes and less complex multivessel disease (SYNTAX score ≤22; class IIb, level B).

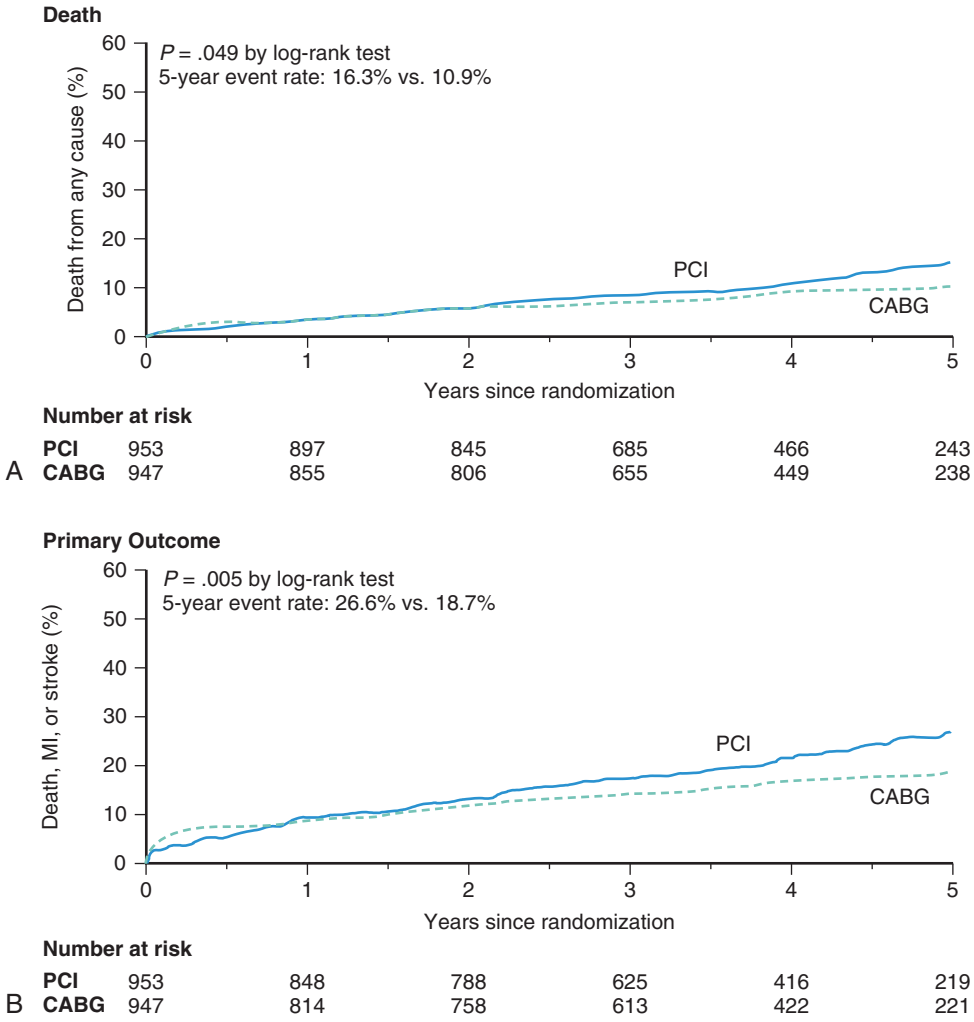


FIGURE 3-11 Rates of outcomes among the study patients according to treatment group. **A,** Kaplan-Meier curves for the percutaneous coronary intervention (PCI) group and the coronary artery bypass grafting (CABG) group for death from any cause. **B,** Death, stroke, or myocardial infarction (MI). The two groups had similar rates of death from any cause (relative risk with PCI vs. CABG, 1.24; 95% confidence interval [CI], 0.78 to 1.98) and rates of death from any cause, stroke, or MI (relative risk with PCI vs. CABG, 1.00; 95% CI, 0.72 to 1.38). In contrast, the rate of repeat revascularization was significantly increased with PCI (relative risk, 2.29; 95% CI, 1.67 to 3.14), as was the overall rate of major adverse cardiac or cerebrovascular events (relative risk, 1.44; 95% CI, 1.15 to 1.81). (From Farkouh ME, Domanski M, Sleeper LA, et al: Strategies for multivessel revascularization in patients with diabetes. *New Engl J Med* 367:2375-2384, 2012.)

DIABETES AND NON–ST-ELEVATION ACUTE CORONARY SYNDROMES

The high prevalence of abnormal glucose metabolism in patients with CAD, and in particular among those with acute manifestations of the disease, has been detected in large-scale surveys on both sides of the Atlantic. In the American registry, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE), the prevalence of diabetes was 33% among 46,410 patients who presented with non–ST-elevation acute coronary syndromes (non-ST ACS).[56] The prevalence of known diabetes in the Euro Heart Survey of patients with ACS was 32%, whereas using an oral glucose tolerance test, impaired glucose tolerance or undiagnosed diabetes were detected in 36% and 22% of patients, respectively.[57] Diabetic patients, more frequently than their nondiabetic counterparts, have characteristics and comorbidities that may negatively impact outcomes in the setting of acute ACS. Nevertheless, even after accounting for imbalances in baseline characteristics, several studies have shown that diabetes remains an independent predictor of short-term morbidity and mortality in the setting of ACS.[58] As an example, in the CRUSADE registry, the in-hospital mortality rates were 6.8% for diabetic patients on insulin, 5.4% for diabetic patients not treated with insulin, and 4.4% in nondiabetic patients.[58] A pooled study of ACS patients enrolled in several randomized clinical trials comprised 46,577 ST-elevation myocardial infarction (STEMI) patients and 15,459 non-ST ACS patients. The diabetic population (17% of the total) had a higher rate of mortality at 30 days compared with those who did not have diabetes, both in the setting of non-ST ACS (2.1% vs. 1.1%, $P < .001$) and STEMI (8.5% vs. 5.4%, $P < .001$).[59] Adjusted odds ratios for 30-day mortality in patients with diabetes after non-ST ACS was 1.78 (95% CI, 1.24 to 2.56), and it was 1.40 (95% CI, 1.24 to 1.57) for STEMI. At 1 year, diabetes at presentation with ACS was associated with significantly higher mortality after unstable angina (UA)/non–ST-elevation myocardial infarction (NSTEMI; HR, 1.65; 95% CI, 1.30 to 2.10) or after STEMI (HR, 1.22; 95% CI, 1.08 to 1.38; Fig. 3-13).[59]

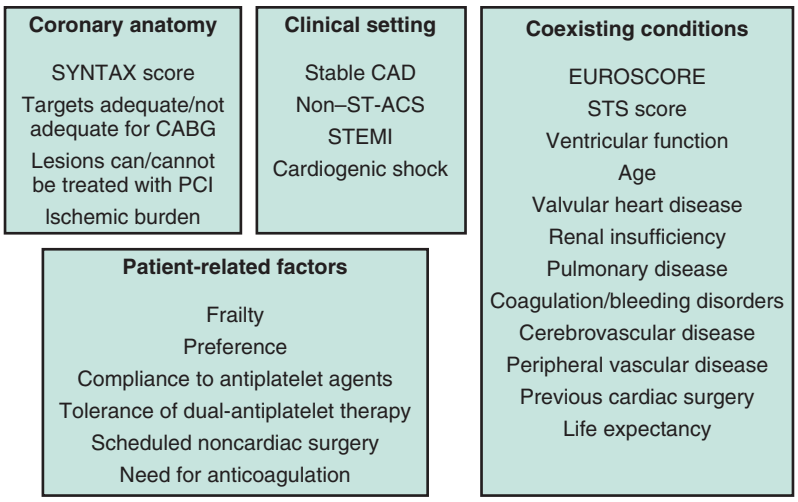


FIGURE 3-12 Parameters guiding the choice of revascularization strategy in diabetic patients. *ACS,* Acute coronary syndrome; *CABG,* coronary artery bypass grafting; *CAD,* coronary artery disease; *EuroSCORE,* European System for Cardiac Operative Risk Evaluation; *PCI,* percutaneous coronary intervention; *STEMI,* ST-elevation myocardial infarction; *STS,* Society of Thoracic Surgery. (From Roffi M, Angiolillo D, Kappetein AP: Current concepts on coronary revascularization in diabetic patients, *Euro Heart J* 32:2748-2757, 2011.)

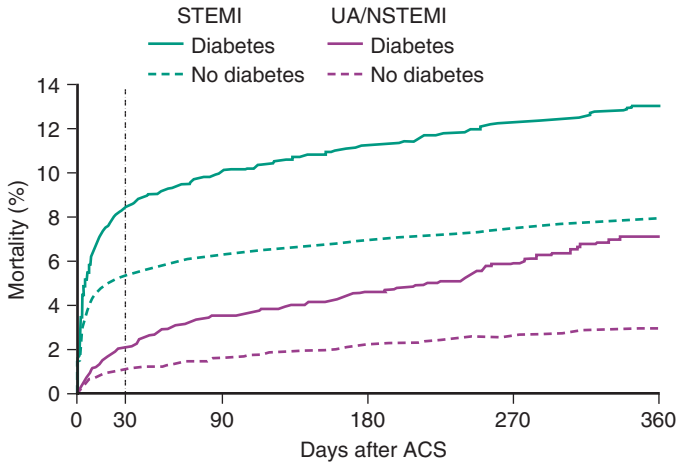


FIGURE 3-13 Patients with acute coronary syndrome (ACS) in 11 independent Thrombolysis in Myocardial Infarction (TIMI) Study Group clinical trials from 1997 to 2006 were pooled. This included 62,036 patients (46,577 with ST-segment–elevation myocardial infarction [STEMI] and 15,459 with unstable angina/non–STEMI [UA/NSTEMI]), of whom 10,613 (17.1%) had diabetes. STEMI, ST-segment–elevation myocardial infarction; UA, unstable angina; NSTEMI, non–ST-segment elevation myocardial infarction. (From Donahoe SM, Stewart GC, McCabe CH, et al: Diabetes and mortality following acute coronary syndromes. *JAMA* 298:765-775, 2007.)

EARLY INVASIVE VERSUS CONSERVATIVE STRATEGY

In diabetic patients with non–ST-elevation ACS, the positive impact of an early invasive strategy can be derived from a collaborative meta-analysis of nine RCTs that included 9904 subjects, 1789 of whom had diabetes. An early, routine invasive strategy compared with a selective invasive strategy was associated with a reduction of MI in diabetic patients (RR, 0.71; 95% CI, 0.55 to 0.92) but not in their nondiabetic counterparts (RR, 0.98; 95% CI, 0.74 to 1.29). The absolute risk reduction in MI was also significantly higher (3.7% vs. 0.1%, $P = .02$) in patients with diabetes compared with patients without diabetes.[60] However, the relative risk for death, nonfatal MI, or rehospitalization with an ACS with routine invasive versus selective invasive strategies was similar between diabetic patients (RR, 0.87; 95% CI, 0.73 to 1.03) and nondiabetic patients (RR, 0.86; 95% CI, 0.70 to 1.06). The 2011 ESC guidelines on the management of non-ST ACS recommend an early invasive strategy for all diabetic patients who present with ACS.[61] The 2012 ACCF/AHA update for the management of patients with UA/NSTEMI considered diabetes as a criteria to favor an invasive strategy over a conservative one.[62]

DIABETES AND ST-ELEVATION MYOCARDIAL INFARCTION

Paralleling the observations for non-ST ACS, also in the setting of STEMI, diabetes is an independent predictor of morbidity and mortality. A retrospective study that evaluated admission glucose for 141,680 patients who presented with acute MI demonstrated an association between admission glucose levels and 30-day mortality in both diabetic and nondiabetic individuals.[63] A recent retrospective analysis of a Swiss registry of 3565 diabetic and 15,531 nondiabetic patients hospitalized for STEMI showed that in-hospital mortality dramatically decreased from 19.9% in 1997 to 9.0% in 2010 among diabetic patients (P for trend < .001; Fig. 3-14). However, mortality remained twice as high in diabetic patients compared with nondiabetic patients (12.1% vs. 6.1%, $P < .001$), and diabetes was identified as an independent predictor of mortality.[64] In terms of medical and revascularization strategies, the guidelines recommend that diabetic patients be managed the same as nondiabetic patients.[65]

GLUCOSE-LOWERING THERAPY IN THE ACUTE PHASE

In the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction 2 (DIGAMI 2) study, three glucose-lowering strategies were compared among 1253 diabetic patients with suspected acute MI: in group 1, acute insulin-glucose infusion was titrated to glucose levels for 24 hours, followed by insulin-based long-term glucose control; in group 2, insulin-glucose infusion was given for 24 hours, followed by standard glucose control; and in group 3, routine metabolic management was undertaken according to local practice.[66] At 2 years, the mortality rates among the three groups were comparable, and no significant differences in nonfatal MI or stroke were detected. Very recently, the 20-year follow-up of the DIGAMI 1 trial, which enrolled MI patients who presented with blood glucose concentrations higher than 11 mmol/L at hospital admission, showed that the median

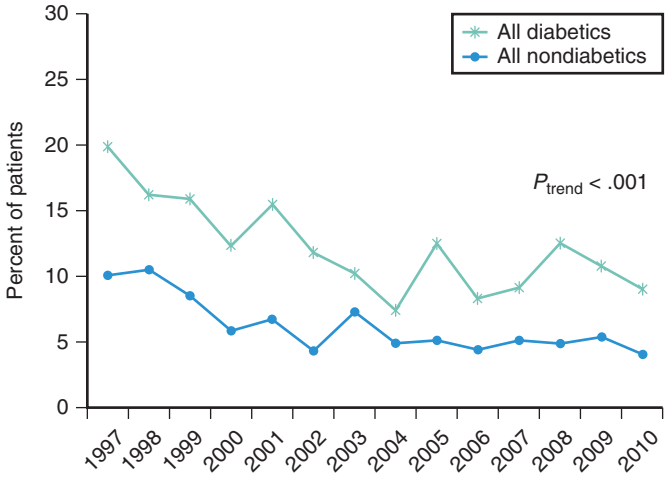


FIGURE 3-14 Trends in in-hospital mortality stratified by diabetes status. (From Roffi M, Radovanovic D, Erne P, et al: Gender-related mortality trends among diabetic patients with ST-segment elevation myocardial infarction: insights from a nationwide registry 1997-2010. *Eur Heart J Acute Cardiovasc Care* 2:342-349, 2013.)

survival time was 7.0 years (interquartile range [IQR] 1.8 to 12.4) in the insulin-based intensified glycemic control group ($n = 306$) and 4.7 years (IQR 1.0 to 11.4) in the standard group ($n = 314$; HR, 0.83; 95% CI, 0.70 to 0.98).[67] The ESC guidelines recommend that in the setting of ACS, treatment of elevated blood glucose should avoid both hyperglycemia (>180 mg/dL) and hypoglycemia (<90 mg/dL).[7,61]

ANTITHROMBOTIC THERAPY IN DIABETES

Diabetes patients are characterized by enhanced platelet reactivity and a procoagulant state, which exposes them to an increased risk of atherothrombotic events. Diabetic patients treated with antiplatelet agents such as aspirin and clopidogrel remain at higher risk of recurrent ischemic events in the setting of ACS and PCI. In part, this may be related to a reduced responsiveness or *resistance,* defined as the failure of an antiplatelet agent to adequately block its specific target on the platelet (i.e., the cyclooxygenase 1 [COX-1] receptor for aspirin and the $P2Y_{12}$ receptor for clopidogrel).

Whereas data on the prevalence of aspirin resistance and its impact on CV outcomes in diabetic patients are sparse, most of the evidence supports the notion that inadequate response to clopidogrel in this patient population is more prevalent, both after a loading dose and at a maintenance dose, than in nondiabetic individuals.[68] Platelet reactivity on dual-antiplatelet therapy was found to be particularly elevated in diabetic individuals treated with insulin.[69] This may also explain why studies with first-generation DESs have repeatedly identified diabetes, and especially its insulin-requiring form, as an independent predictor of stent thrombosis (see Fig. 3-5).

ASPIRIN AND CLOPIDOGREL

Although among diabetic patients, the value of aspirin in a dose ranging from 75 to 325 mg/day as secondary prevention has been well established, the benefit of aspirin in primary prevention is less well documented. The optimal antiplatelet therapy in the primary prevention of CVD in patients with diabetes has still not been established. Based on available data, aspirin had a modest reduction of ischemic events in the diabetic population, and accordingly, the 2013 ESC guidelines on diabetes do not recommend antiplatelet therapy with aspirin in patients with diabetes who are at low risk by primary prevention of CVD (class III, level of evidence A).[7] According to the 2014 updated guidelines of the American Diabetes Association (ADA), aspirin therapy (75 to 162 mg/day) is recommended as a primary prevention strategy in diabetic patients at increased CV risk (i.e., estimated 10-year risk >10%), such as most men older than 50 years of age or women older than 60 years of age who have at least one additional major CV risk factor, which includes family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria (class of recommendation I, level of evidence C).[8]

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial investigated the safety and efficacy of long-term administration of aspirin (75 to 162 mg/day) and clopidogrel (75 mg/day) in comparison with aspirin alone in patients with established atherosclerotic disease or with multiple CV risk factors.[70] In the large diabetic population enrolled ($n = 6556$), mainly a primary prevention cohort, no benefit of the combination therapy was observed after a median follow-up of 28 months, and the bleeding rated increased. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial randomized patients with ACS who were primarily medically managed to aspirin or aspirin and clopidogrel for 9 to 12 months. Diabetic patients ($n = 2840$) did not derive a significant benefit from the combined treatment.[71]

PRASUGREL AND TICAGRELOR

Prasugrel is a third-generation thienopyridine that inhibits the $P2Y_{12}$ receptor more rapidly and more consistently (i.e., with smaller individual variation) than standard and higher doses of clopidogrel, which is also true in diabetic individuals.[72] These properties may be particularly important for diabetic patients based on frequently encountered resistance to clopidogrel. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38)[73] randomized 13,608 subjects with ACS (both STEMI and non-ST ACS) to clopidogrel or prasugrel for 6 to 15 months. Among them, 3146 subjects had diabetes, and 776 were treated with insulin on admission. The primary end point—a composite of CV death, MI, or stroke—was significantly reduced with prasugrel among subjects without diabetes and those with diabetes (9.2% vs. 10.6%, HR 0.86, $P = .02$ for nondiabetic patients and 12.2% vs. 17.0%, HR 0.70, $P < .001$ for their diabetic counterparts; Fig. 3-15). The beneficial effect of prasugrel was observed among diabetic subjects treated with insulin (14.3% vs. 22.2%, HR 0.63, $P = .009$) and among those on oral hypoglycemic drugs (11.5% vs. 15.3%, HR 0.74, $P = .009$). Nonfatal MI was reduced by 18% with prasugrel among subjects without diabetes (7.2% vs. 8.7%, $P = .006$) and by 40% among subjects with diabetes (8.2% vs. 13.2%, $P < .001$). In the interaction analyses for treatment benefit, diabetic status showed a trend ($P = .09$) for the primary end point and was significant ($P = .02$) for MI, suggesting a preferential benefit of prasugrel in the diabetic population. Although TIMI major bleeds were increased among subjects without diabetes on prasugrel (1.6% vs. 2.4%, HR 1.43, $P = .02$), the rates were similar among subjects with diabetes for clopidogrel and prasugrel (2.6% vs. 2.5%). Net clinical benefit with prasugrel was greater for diabetic patients (14.6% vs. 19.2%, HR 0.74, $P = .001$) than for nondiabetic individuals (11.5% vs. 12.3%, HR 0.92, $P = .16$; P interaction [P_{int}] = .05). Finally, the rate of stent thrombosis, both in the overall population and in the diabetic population, was significantly reduced by the allocation to prasugrel (0.9% vs. 2.0% and 2.0% vs. 3.5%, respectively).

Ticagrelor is an oral, reversibly binding $P2Y_{12}$ inhibitor with a plasma half-life of 6 to 12 hours. Like prasugrel, ticagrelor has a more rapid and consistent onset of action compared with clopidogrel, but it also has a faster offset of action with more rapid recovery of platelet function.[74] In the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor reduced the primary composite end point of CV death, MI, or stroke but with similar rates of major bleeding compared with clopidogrel in 18,624 patients with ACS (both STEMI and non-ST ACS).[75,76] In diabetic patients ($n = 4662$), including 1036 patients on insulin, the reduction in the primary composite end point (HR, 0.88; 95% CI, 0.76 to 1.03; Fig. 3-16), all-cause mortality (HR, 0.82; 95% CI,

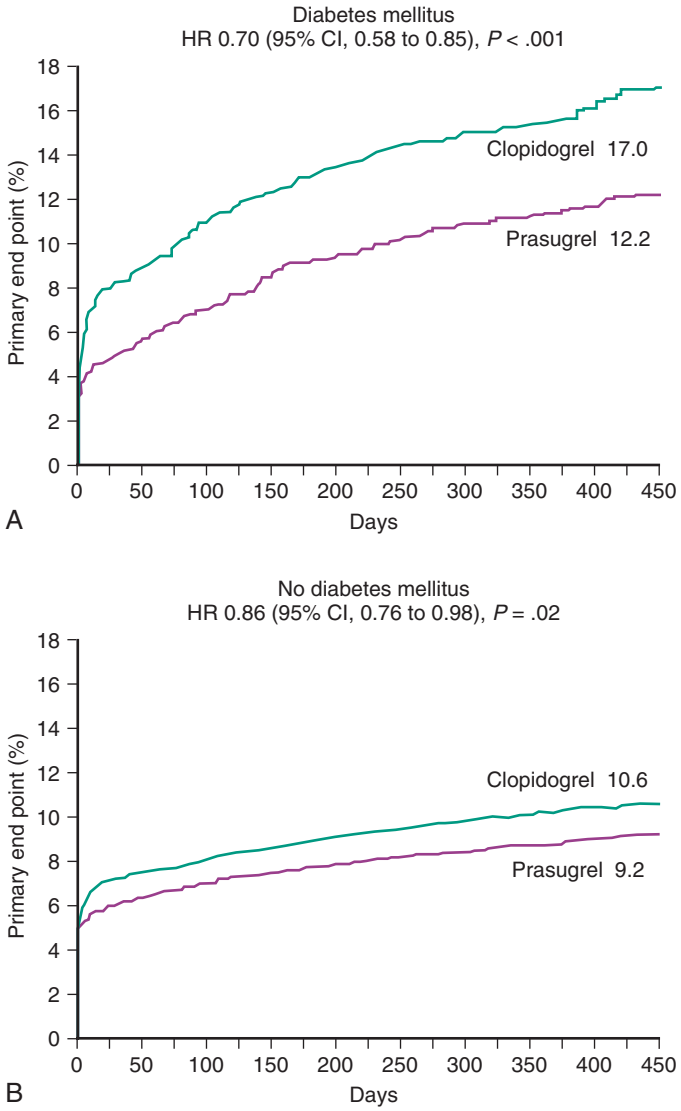


FIGURE 3-15 Kaplan-Meier event-free survival curves primary efficacy end point (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) stratified by diabetic status in the TRITON-TIMI 38 study. *CI,* Confidence interval. (From Wiviott SD, Braunwald E, Angiolillo DJ, et al: Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. *Circulation* 118:1626-1636, 2008.)

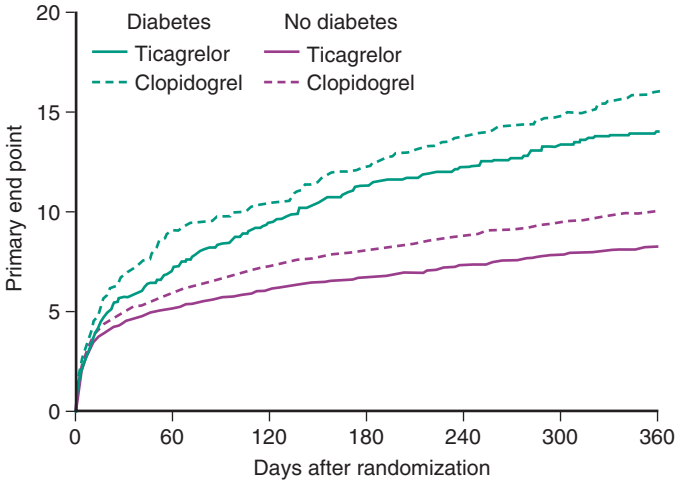


FIGURE 3-16 Cumulative incidence of the primary composite of cardiovascular death, myocardial infarction, and stroke in the PLATO trial. Randomization was to ticagrelor (*solid lines*) or clopidogrel (*dotted lines*) and the presence (*green lines*) or absence (*purple lines*) of diabetes. (From James S, Angiolillo DJ, Cornel JH, et al: Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes [PLATO] trial. *Eur Heart J* 31:3006-3016, 2010.)

0.66 to 1.01), and stent thrombosis (HR, 0.65; 95% CI, 0.36 to 1.17) with no increase in major bleeding (HR, 0.95; 95% CI, 0.81 to 1.12) with ticagrelor was consistent with the overall cohort and without significant diabetes status-by-treatment interactions.[76] No heterogeneity in treatment efficacy was found among patients with or without ongoing insulin treatment. Because of the differences in protocols and populations enrolled in the TRITON-TIMI 38 and the PLATO studies, no comparisons with respect to safety or efficacy of the two molecules in diabetic patients can be made at this time. Although the 2011 ACC/AHA guidelines on UA/NSTEMI did not address prasugrel or ticagrelor—because at that time, these drugs were not available in the United States—the ESC non-ST ACS guidelines for the same year recommended the newer $P2Y_{12}$ inhibitors, especially prasugrel, in diabetic patients for 1 year.[61]

GLYCOPROTEIN IIB/IIIA RECEPTOR ANTAGONISTS AND ANTICOAGULANTS

In the pre–clopidogrel-loading era, the use of intravenous (IV) platelet glycoprotein (GP) IIb/IIIa receptor inhibitors and stents markedly reduced both the early hazard and the 1-year mortality in diabetic patients undergoing PCI.[77,78] However, the introduction of clopidogrel, and especially of prasugrel and ticagrelor, has markedly reduced the indication for those agents. Accordingly, the value of GP IIb/IIIa in the era of potent $P2Y_{12}$ inhibition and of newer anticoagulants, such as bivalirudin, still needs to be defined. Because no trial has specifically addressed the value of different anticoagulants in the PCI/ACS setting in diabetic patients, the same recommendations are valuable as for the nondiabetic population. Anticoagulants of choice have included unfractionated heparin, enoxaparin, fondaparinux (with the addition of unfractionated heparin at the time of PCI), or bivalirudin.

LONG-TERM DIABETES MANAGEMENT

Adequate glycemic control remains of paramount importance in the management of diabetic patients. A meta-analysis of five RCTs that included 17,267 participants who received intensive glucose control and 15,362 who received conventional therapy showed a significant reduction in MI (OR, 0.86; 95% CI, 0.78 to 0.93) but not of stroke (OR, 0.93; 95% CI, 0.81 to 1.07) or CV mortality (OR, 0.98; 95% CI, 0.77 to 1.23).[79] Although hyperglycemia has been associated with CVD, and epidemiologic evidence links lower blood glucose levels to a decrease in CV events, the impact of good glycemic control on macrovascular events remains controversial—especially following publication of three large, long-term clinical studies of glucose control and macrovascular disease in patients with type 2 diabetes—the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Veterans Affairs Diabetes Trial (VADT).[80-82] Overall, these trials suggested no significant reduction in CVD outcomes with intensive glycemic control in these populations. However, in the ACCORD study, an unexplained increase in all-cause mortality in the intensive glycemic control group was detected.

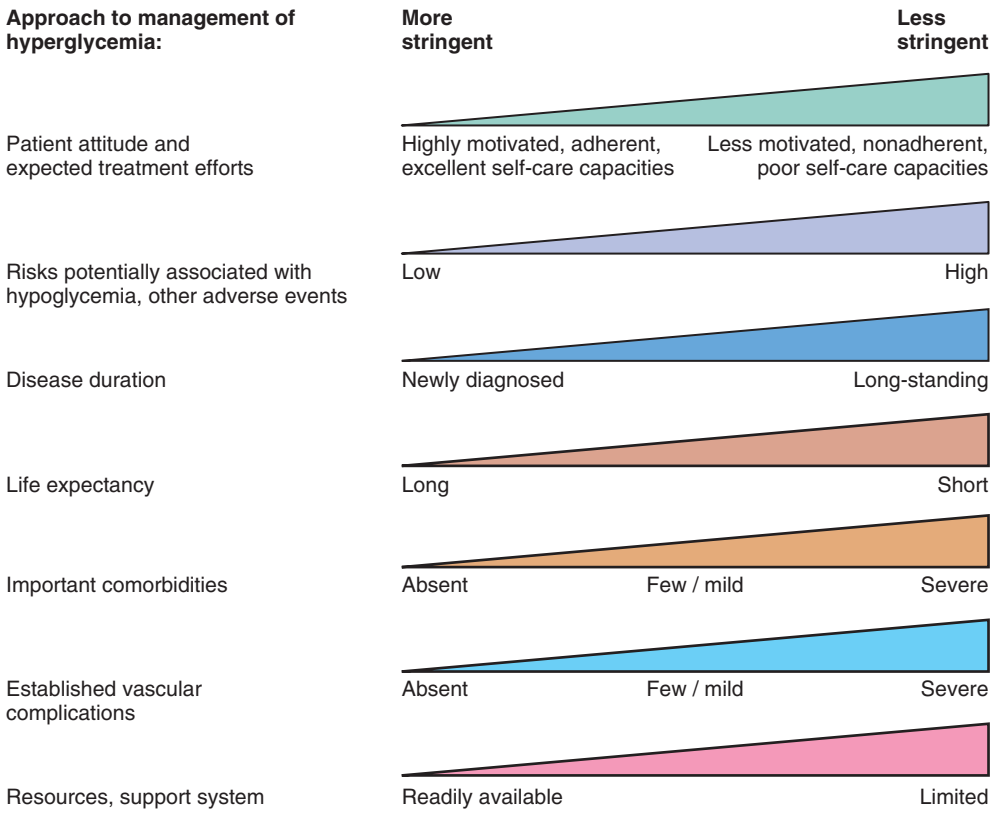


FIGURE 3-17 Depiction of the elements of decision making used to determine appropriate efforts to achieve glycemic targets. Greater concerns about a particular domain are represented by increasing height of the ramp. Thus characteristics/predicaments toward the left justify more stringent efforts to lower Hb_{A1c}, whereas those toward the right are compatible with less stringent efforts. Where possible, such decisions should be made in conjunction with the patient, reflecting his or her preferences, needs, and values. (From Inzucchi SE, Bergenstal RM, Buse JB, et al: Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association [ADA] and the European Association for the Study of Diabetes [EASD]. *Diabetes Care* 35:1364-1379, 2012.)

Hypothesized mechanisms include hypoglycemia, weight gain, rapid lowering of Hb_{A1c} level, and medication interactions.[83] All three trials were carried out in participants with established diabetes (mean duration 8 to 11 years) and either known CVD or multiple risk factors suggesting the presence of established atherosclerosis. Subset analysis suggest that a possible benefit from intensive glycemic control on CV outcomes may be observed in patients with a shorter duration of disease, better glucose control, younger age, no previous CV event, or fewer CV risk factors at the time of initiation of the intensified glucose control regimen.

Overall, the evidence for a CV benefit of intensive glycemic control primarily rests on long-term follow-up of study cohorts treated early in the course of type 1 and type 2 diabetes, as well as subset analyses of ACCORD, ADVANCE, and VADT. However, the mortality findings in ACCORD and subgroup analyses of VADT suggest that the risks of very aggressive glycemic control may outweigh its benefits in some patients, such as those with very long duration of diabetes, known history of severe hypoglycemia, advanced atherosclerosis, and advanced age or frailty. Certainly, care providers should be vigilant in preventing severe hypoglycemia in patients with advanced disease and should not aggressively attempt to achieve near-normal Hb_{A1C} levels in patients in whom such a target cannot be reasonably achieved easily and safely.[84] Glucose control in diabetic patients with CAD should be according to a patient-centered approach: the longer the diabetes disease duration, the older the patient, the more advanced the CAD, the more important the comorbidities, the less stringent the glucose control should be (Fig. 3-17).[84]

MULTIFACTORIAL INTERVENTION

Aggressive CV risk-factor modification, including optimal glycemic control, cigarette smoking cessation, control of blood pressure and cholesterol levels, and weight reduction and exercise, is an essential part of diabetes care. According to the 2013 ACC/AHA guidelines on cholesterol treatment, individuals with diabetes belong to a clinical category in which statin therapy is strongly recommended in primary prevention for low-density lipoprotein cholesterol (LDL-C) greater than 70 mg/dL.[13] Furthermore, high-intensity statin drug regimen should be considered in patients with diabetes and a risk of CVD of 7.5% or more over 10 years. In secondary prevention, a statin drug is strongly recommended, such as in those without diabetes. A recently published pooled data analysis from 5034 diabetic patients across the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE), BARI 2D, and FREEDOM studies showed that a significant proportion of patients with CAD did not reach recommended secondary prevention targets: only 18% of the COURAGE patients with diabetes, 23% of the participants in BARI 2D, and 8% of patients with diabetes in the FREEDOM study had a combined achievement for systolic blood pressure, LDL-C, smoking cessation, and Hb_{A1C} at 1 year of follow-up.[85] The ESC guidelines on diabetes made a strong recommendation for lifestyle modifications for the prevention of diabetes, such as smoking cessation, dietary counseling, an increased daily fiber intake, control of total and saturated fat intake, and moderate to vigorous physical activity of 150 minutes or more per week, including aerobic exercise and resistance training.[7]

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al: Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation* 129:e28–e292, 2014.
2. Danaei G, Finucane MM, Lu Y, et al: National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 378:31–40, 2011.
3. American Diabetic Association: National diabetes fact sheet, diabetes statistics. Available at http://www.Diabetes.Org/diabetes-basics/statistics. Accessed 14.6.10.
4. Morrish NJ, Wang SL, Stevens LK, et al: Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. *Diabetologia* 44(Suppl 2):S14–S21, 2001.
5. Mathers CD, Loncar D: Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 3:e442, 2006.
6. Goff DC, Jr, Lloyd-Jones DM, Bennett G, et al: 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 129:S49–S73, 2014.
7. American Diabetes Association: Standards of medical care in diabetes—2014. *Diabetes Care* 37(Suppl 1):S14–S80, 2014.
8. Ryden L, Grant PJ, Anker SD, et al: ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The task force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 34:3035–3087, 2013.
9. Roffi M, Topol EJ: Percutaneous coronary intervention in diabetic patients with non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 25:190–198, 2004.
10. Creager MA, Luscher TF, Cosentino F, Beckman JA: Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. *Circulation* 108:1527–1532, 2003.
11. Luscher TF, Creager MA, Beckman JA, Cosentino F: Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part II. *Circulation* 108:1655–1661, 2003.
12. Booth GL, Kapral MK, Fung K, Tu JV: Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet* 368:29–36, 2006.
13. Stone NJ, Robinson JG, Lichtenstein AH, et al: 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 129:S1–S45, 2014.
14. McKinlay J, Marceau L: US public health and the 21st century: diabetes mellitus. *Lancet* 356:757–761, 2000.
15. Preis SR, Hwang SJ, Coady S, et al: Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. *Circulation* 119:1728–1735, 2009.
16. Dale AC, Vatten LJ, Nilsen TI, et al: Secular decline in mortality from coronary heart disease in adults with diabetes mellitus: cohort study. *BMJ* 337:a236, 2008.
17. Ma J, Wang X, Wang Y, et al: The relationship between glycated hemoglobin and complexity of coronary artery lesions among older patients with diabetes mellitus. *PLoS ONE* 9:e91972, 2014.
18. Wackers FJ, Zaret BL: Detection of myocardial ischemia in patients with diabetes mellitus. *Circulation* 105:5–7, 2002.
19. Burgess DC, Hunt D, Li L, et al: Incidence and predictors of silent myocardial infarction in type 2 diabetes and the effect of fenofibrate: an analysis from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Eur Heart J* 31:92–99, 2010.
20. Albers AR, Krichavsky MZ, Balady GJ: Stress testing in patients with diabetes mellitus: diagnostic and prognostic value. *Circulation* 113:583–592, 2006.
21. Elkeles RS, Godsland IF, Feher MD, et al: Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients with type 2 diabetes: the PREDICT study. *Eur Heart J* 29:2244–2251, 2008.
22. Anand DV, Lim E, Hopkins D, et al: Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. *Eur Heart J* 27:713–721, 2006.
23. Bax JJ, Young LH, Frye RL, et al: Screening for coronary artery disease in patients with diabetes. *Diabetes Care* 30:2729–2736, 2007.
24. Young LH, Wackers FJ, Chyun DA, et al: Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA* 301:1547–1555, 2009.
25. Fihn SD, Gardin JM, Abrams J, et al: 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 126:e354–e471, 2012.
26. Task Force Members: 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 34:2949–3003, 2013.
27. Aronson D, Edelman ER: Revascularization for coronary artery disease in diabetes mellitus: angioplasty, stents and coronary artery bypass grafting. *Rev Endocr Metab Disord* 11:75–86, 2010.
28. Roffi M, Angiolillo DJ, Kappetein AP: Current concepts on coronary revascularization in diabetic patients. *Eur Heart J* 32:2748–2757, 2011.
29. Stettler C, Allemann S, Wandel S, et al: Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. *BMJ* 337:a1331, 2008.
30. Bangalore S, Kumar S, Fusaro M, et al: Outcomes with various drug eluting or bare metal stents in patients with diabetes mellitus: mixed treatment comparison analysis of 22,844 patient-years of follow-up from randomised trials. *BMJ* 345:e5170, 2012.
31. Kedhi E, Genereux P, Palmerini T, et al: Impact of coronary lesion complexity on drug-eluting stent outcomes in patients with and without diabetes mellitus: analysis from 18 pooled randomized trials. *J Am Coll Cardiol* 63:2111–2118, 2014.
32. Mahmud E, Bromberg-Marin G, Palakodeti V, et al: Clinical efficacy of drug-eluting stents in diabetic patients: a meta-analysis. *J Am Coll Cardiol* 51:2385–2395, 2008.
33. Windecker S, Serruys PW, Wandel S, et al: Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 372:1163–1173, 2008.
34. Stone GW, Rizvi A, Newman W, et al: Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med* 362:1663–1674, 2010.
35. Wijns W, Kolh P, Danchin N, et al: Guidelines on myocardial revascularization. *Eur Heart J* 31:2501–2555, 2010.
36. Levine GN, Bates ER, Blankenship JC, et al: 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 124:e574–e651, 2011.
37. Carson JL, Scholz PM, Chen AY, et al: Diabetes mellitus increases short-term mortality and morbidity in patients undergoing coronary artery bypass graft surgery. *J Am Coll Cardiol* 40:418–423, 2002.
38. Leavitt BJ, Sheppard L, Maloney C, et al: Effect of diabetes and associated conditions on long-term survival after coronary artery bypass graft surgery. *Circulation* 110(11 Suppl 1):II41–II44, 2004.
39. Sabik JF, 3rd, Blackstone EH, Gillinov AM, et al: Occurrence and risk factors for reintervention after coronary artery bypass grafting. *Circulation* 114:I454–I460, 2006.
40. Pevni D, Uretzky G, Mohr A, et al: Routine use of bilateral skeletonized internal thoracic artery grafting: long-term results. *Circulation* 118:705–712, 2008.
41. Dorman MJ, Kurlansky PA, Traad EA, et al: Bilateral internal mammary artery grafting enhances survival in diabetic patients: a 30-year follow-up of propensity score-matched cohorts. *Circulation* 126:2935–2942, 2012.
42. Yi G, Shine B, Rehman SM, et al: Effect of bilateral internal mammary artery on long-term survival: a meta-analysis approach. *Circulation* 130:539–545, 2014.
43. Taggart DP, Altman DG, Gray AM, et al: Randomized trial to compare bilateral vs. single internal mammary coronary artery bypass grafting: 1-year results of the Arterial Revascularisation Trial (ART). *Eur Heart J* 31:2470–2481, 2010.
44. Itagaki S, Cavallaro P, Adams DH, Chikwe J: Bilateral internal mammary artery grafts, mortality and morbidity: an analysis of 1 526 360 coronary bypass operations. *Heart* 99:849–853, 2013.
45. Lamy A, Devereaux PJ, Prabhakaran D, et al: Off-pump or on-pump coronary-artery bypass grafting at 30 days. *New Engl J Med* 366:1489–1497, 2012.
46. Frye RL, August P, Brooks MM, et al: A randomized trial of therapies for type 2 diabetes and coronary artery disease. *New Engl J Med* 360:2503–2515, 2009.
47. Kim LJ, King SB, 3rd, Kent K, et al: Factors related to the selection of surgical versus percutaneous revascularization in diabetic patients with multivessel coronary artery disease in the BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) trial. *JACC Cardiovasc Interv* 2:384–392, 2009.
48. Hannan EL, Racz MJ, Walford G, et al: Long-term outcomes of coronary-artery bypass grafting versus stent implantation. *New Engl J Med* 352:2174–2183, 2005.
49. Hannan EL, Wu C, Walford G, et al: Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. *New Engl J Med* 358:331–341, 2008.
50. Kapur A, Hall RJ, Malik IS, et al: Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization In Diabetes) trial. *J Am Coll Cardiol* 55:432–440, 2010.
51. Kappetein AP, Head SJ, Morice MC, et al: Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *Eur J Cardiothorac Surg* 43:1006–1013, 2013.
52. Banning AP, Westaby S, Morice MC, et al: Diabetic and nondiabetic patients with left main and/or 3-vessel coronary artery disease: comparison of outcomes with cardiac surgery and paclitaxel-eluting stents. *J Am Coll Cardiol* 55:1067–1075, 2010.
53. Head SJ, Davierwala PM, Serruys PW, et al: Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial. *Eur Heart J* 35:2821–2830, 2014.
54. Farkouh ME, Domanski M, Sleeper LA, et al: Strategies for multivessel revascularization in patients with diabetes. *New Engl J Med* 367:2375–2384, 2012.
55. Bangalore S, Toklu B, Feit F: Outcomes with coronary artery bypass graft surgery versus percutaneous coronary intervention for patients with diabetes mellitus: can newer generation drug-eluting stents bridge the gap? *Circ Cardiovasc Interv* 7:518–525, 2014.
56. Bhatt DL, Roe MT, Peterson ED, et al: Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE quality improvement initiative. *JAMA* 292:2096–2104, 2004.
57. Bartnik M, Ryden L, Ferrari R, et al: The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on Diabetes and the Heart. *Eur Heart J* 25:1880–1890, 2004.
58. Brogan GX, Jr, Peterson ED, Mulgund J, et al: Treatment disparities in the care of patients with and without diabetes presenting with non-ST-segment elevation acute coronary syndromes. *Diabetes Care* 29:9–14, 2006.
59. Donahoe SM, Stewart GC, McCabe CH, et al: Diabetes and mortality following acute coronary syndromes. *JAMA* 298:765–775, 2007.
60. O'Donoghue ML, Vaidya A, Afsal R, et al: An invasive or conservative strategy in patients with diabetes mellitus and non-ST-segment elevation acute coronary syndromes: a collaborative meta-analysis of randomized trials. *J Am Coll Cardiol* 60:106–111, 2012.
61. Hamm CW, Bassand JP, Agewall S, et al: ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 32:2999–3054, 2011.
62. 2012 Writing Committee Members: 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 126:875–910, 2012.
63. Kosiborod M, Rathore SS, Inzucchi SE, et al: Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. *Circulation* 111:3078–3086, 2005.
64. Roffi M, Radovanovic D, Erne P, et al: Gender-related mortality trends among diabetic patients with ST-segment elevation myocardial infarction: insights from a nationwide registry 1997–2010. *Eur Heart J Acute Cardiovasc Care* 2:342–349, 2013.
65. O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 127:e362–e425, 2013.
66. Malmberg K, Ryden L, Wedel H, et al: Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 26:650–661, 2005.
67. Ritsinger V, Malmberg K, Martensson A, et al: Intensified insulin-based glycaemic control after myocardial infarction: mortality during 20 year follow-up of the randomised Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI 1) trial. *Lancet Diabetes Endocrinol* 2:627–633, 2014.
68. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al: Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. *Diabetes* 54:2430–2435, 2005.
69. Angiolillo DJ, Bernardo E, Ramirez C, et al: Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment. *J Am Coll Cardiol* 48:298–304, 2006.
70. Bhatt DL, Fox KA, Hacke W, et al: Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *New Engl J Med* 354:1706–1717, 2006.
71. Yusuf S, Zhao F, Mehta SR, et al: Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *New Engl J Med* 345:494–502, 2001.
72. Angiolillo DJ, Badimon JJ, Saucedo JF, et al: A pharmacodynamic comparison of prasugrel vs. high-dose clopidogrel in patients with type 2 diabetes mellitus and coronary artery disease: results of the Optimizing anti-Platelet Therapy In diabetes MellitUS (OPTIMUS)-3 Trial. *Eur Heart J* 32:838–846, 2011.

73. Wiviott SD, Braunwald E, McCabe CH, et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes. *New Engl J Med* 357:2001–2015, 2007.
74. Gurbel PA, Bliden KP, Butler K, et al: Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 120:2577–2585, 2009.
75. Wallentin L, Becker RC, Budaj A, et al: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *New Engl J Med* 361:1045–1057, 2009.
76. James S, Angiolillo DJ, Cornel JH, et al: Ticagrelor vs. Clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the platelet inhibition and patient outcomes (PLATO) trial. *Eur Heart J* 31:3006–3016, 2010.
77. Bhatt DL, Marso SP, Lincoff AM, et al: Abciximab reduces mortality in diabetics following percutaneous coronary intervention. *J Am Coll Cardiol* 35:922–928, 2000.
78. Mehilli J, Kastrati A, Schuhlen H, et al: Randomized clinical trial of abciximab in diabetic patients undergoing elective percutaneous coronary interventions after treatment with a high loading dose of clopidogrel. *Circulation* 110:3627–3635, 2004.
79. Mannucci E, Monami M, Lamanna C, et al: Prevention of cardiovascular disease through glycemic control in type 2 diabetes: a meta-analysis of randomized clinical trials. *Nutr Metab Cardiovasc Dis* 19:604–612, 2009.
80. Gerstein HC, Miller ME, Byington RP, et al: Effects of intensive glucose lowering in type 2 diabetes. *New Engl J Med* 358:2545–2559, 2008.
81. Patel A, MacMahon S, Chalmers J, et al: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *New Engl J Med* 358:2560–2572, 2008.
82. Duckworth W, Abraira C, Moritz T, et al: Glucose control and vascular complications in veterans with type 2 diabetes. *New Engl J Med* 360:129–139, 2009.
83. Kahn SE: Glucose control in type 2 diabetes: still worthwhile and worth pursuing. *JAMA* 301:1590–1592, 2009.
84. Inzucchi SE, Bergenstal RM, Buse JB, et al: Management of hyperglycemia in type 2 diabetes: a patient-centered approach: Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 35:1364–1379, 2012.
85. Farkouh ME, Boden WE, Bittner V, et al: Risk factor control for coronary artery disease secondary prevention in large randomized trials. *J Am Coll Cardiol* 61:1607–1615, 2013.
86. Iakovou I, Schmidt T, Bonizzoni E, et al: Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 293:2126–2130, 2005.
87. Urban P, Gershlick AH, Guagliumi G, et al: Safety of coronary sirolimus-eluting stents in daily clinical practice: one-year follow-up of the e-Cypher registry. *Circulation* 113:1434–1441, 2006.
88. Kuchulakanti PK, Chu WW, Torguson R, et al: Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. *Circulation* 113: 1108–1113, 2006.
89. Machecourt J, Danchin N, Lablanche JM, et al: Risk factors for stent thrombosis after implantation of sirolimus-eluting stents in diabetic and nondiabetic patients: the EVASTENT Matched-Cohort Registry. *J Am Coll Cardiol* 50:501–508, 2007.
90. Daemen J, Wenaweser P, Tsuchida K, et al: Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* 369:667–678, 2007.
91. de la Torre-Hernandez JM, Alfonso F, Hernandez F, et al: Drug-eluting stent thrombosis: results from the multicenter Spanish registry ESTROFA (Estudio ESpanol sobre TROmbosis de stents FArmacoactivos). *J Am Coll Cardiol* 51:986–990, 2008.
92. Urban P, Abizaid A, Banning A, et al: Stent thrombosis and bleeding complications after implantation of sirolimus-eluting coronary stents in an unselected worldwide population: a report from the e-SELECT (Multi-Center Post-Market Surveillance) registry. *J Am Coll Cardiol* 57:1445–1454, 2011.

4 Prior Evaluation: Functional Testing and Multidetector Computed Tomography

MARIO J. GARCIA

KEY POINTS

- Functional tests such as stress electrocardiography (ECG), stress echocardiography, and stress nuclear perfusion imaging have limited accuracy for the detection of anatomic disease but provide important prognostic information.
- A normal exercise echocardiogram or myocardial perfusion imaging (MPI) result is associated with a low risk of cardiac events. The extent of stress-induced segmental wall motion and perfusion abnormalities helps to define which populations of patients will benefit most from revascularization and their incremental levels of risk.
- Positron emission tomography (PET) is one of the most sensitive methods for the identification of viable myocardium. The detection of gadolinium-delayed enhancement by cardiac magnetic resonance (CMR) perfusion imaging is the most sensitive method for identifying scarred, nonviable myocardium.
- A coronary computed tomography angiogram (CCTA) study that shows no stenosis virtually excludes the presence of coronary artery disease (CAD).
- Appropriate use of various imaging modalities depends on patient probability of disease, physician preference, and local imaging experience.
- American College of Cardiology/American Heart Association guidelines are intended to provide a practical standard to individual clinicians and patients when considering one of these procedures, based on any number of important local and patient-specific variables, while promoting optimal test utilization for the population at large.

Noninvasive testing in patients with known or suspected CAD is conducted to establish the diagnosis of coronary atherosclerosis as the cause of symptoms and/or to determine whether a patient would benefit from medical therapy and/or myocardial revascularization. Functional tests such as stress electrocardiography, stress echocardiography, and stress scintigraphic MPI attempt to quantify the presence of ischemia based on electrical, mechanical, and perfusion abnormalities. Over the last decade, CCTA has evolved as a noninvasive alternative to invasive catheterization for the evaluation of coronary anatomy. In general, anatomic tests such as CCTA have greater sensitivity for the detection of CAD, whereas functional tests have greater ability to predict benefit from revascularization. This chapter provides an overview of the methodology and interpretation of these tests with the objectives of providing guidelines for appropriate test selection and treatment.

STRESS TESTING

Anginal symptoms in patients with obstructive CAD are caused by an imbalance between myocardial oxygen supply and oxygen demand. Asymptomatic patients with CAD have normal resting blood flow even in the presence of epicardial coronary artery stenosis. Myocardial perfusion pressure and blood flow are maintained by compensatory dilation of the coronary arterioles. During stress, myocardial oxygen demand increases but myocardial blood flow cannot increase proportionally, which leads to the development of ischemia. Myocardial ischemia results in progressive metabolic and functional alterations that include electrical repolarization abnormalities and abnormal regional diastolic and systolic myocardial function. On these principles, different stress testing modalities attempt to quantify the burden of obstructive CAD based on the extent of myocardial hypoperfusion, ST-segment depression, and wall motion abnormalities. Stress may be accomplished by a number of methods that include exercise, pharmacologic maneuvers, and even mental tests. Whenever possible, exercise is the preferred modality because the information obtained may be more easily related to functional limitations. The choice between ECG versus echocardiography or MPI is often determined by local availability, costs, and patient characteristics. In general, specificity has been reported to be higher with stress echocardiography, and sensitivity is higher with MPI. Accordingly, many clinicians prefer stress echocardiography for individuals with a lower pretest probability of obstructive CAD and MPI for those with a higher probability. Although exercise ECG has lower sensitivity and specificity than stress imaging modalities, it is cost-effective and provides comparable prognostic information in patients who have a normal resting ECG and are able to exercise. One disadvantage of exercise ECG is that it cannot localize the ischemic region, which renders it less useful as a guide for targeting revascularization. Stress cardiac magnetic resonance (CMR) perfusion imaging can provide both perfusion and wall motion information with accuracy comparable to stress MPI; however, these modalities are currently limited to pharmacologic stress in selected reference centers.

Over the last two decades, the prognostic utility of stress testing has been increasingly recognized. Exercise capacity, heart rate response, and the extent of ST-segment depression, as well as wall motion and perfusion abnormalities, are powerful predictors of outcome. Patients with decreased exercise tolerance and chronotropic incompetence during exercise stress testing have worse outcomes independent of other factors. Chronotropic incompetence may be a marker of impaired autonomic dysfunction, which has been associated with angiographic severity of CAD and increased mortality.

Heart rate recovery is another index that appears to be related to autonomic tone. Unlike chronotropic incompetence, heart rate recovery is not significantly affected by the administration of beta-blockers. *Heart rate recovery* is calculated as the difference in heart rate at peak versus 1 minute after exercise; a value below 12 beats/minute is considered abnormal. Patients evaluated for suspected or known CAD with an abnormal heart rate recovery have a markedly increased mortality rate independent of other risk factors.[1] Although both impaired chronotropic response and heart rate recovery are powerful predictors of outcomes, it is unknown whether these are modifiable. Moreover, their association with mortality may be independent of the presence or severity of CAD; therefore they may have limited value in guiding therapeutic interventions.

Electrocardiography Stress Testing

Detection of ischemia by ECG stress testing relies on the development of abnormal repolarization that manifests as ST-segment depression during or immediately after exercise. Exercise ECG testing has modest diagnostic accuracy but remains a useful prognostic test. An index derived from the exercise ECG test that incorporates exercise time,

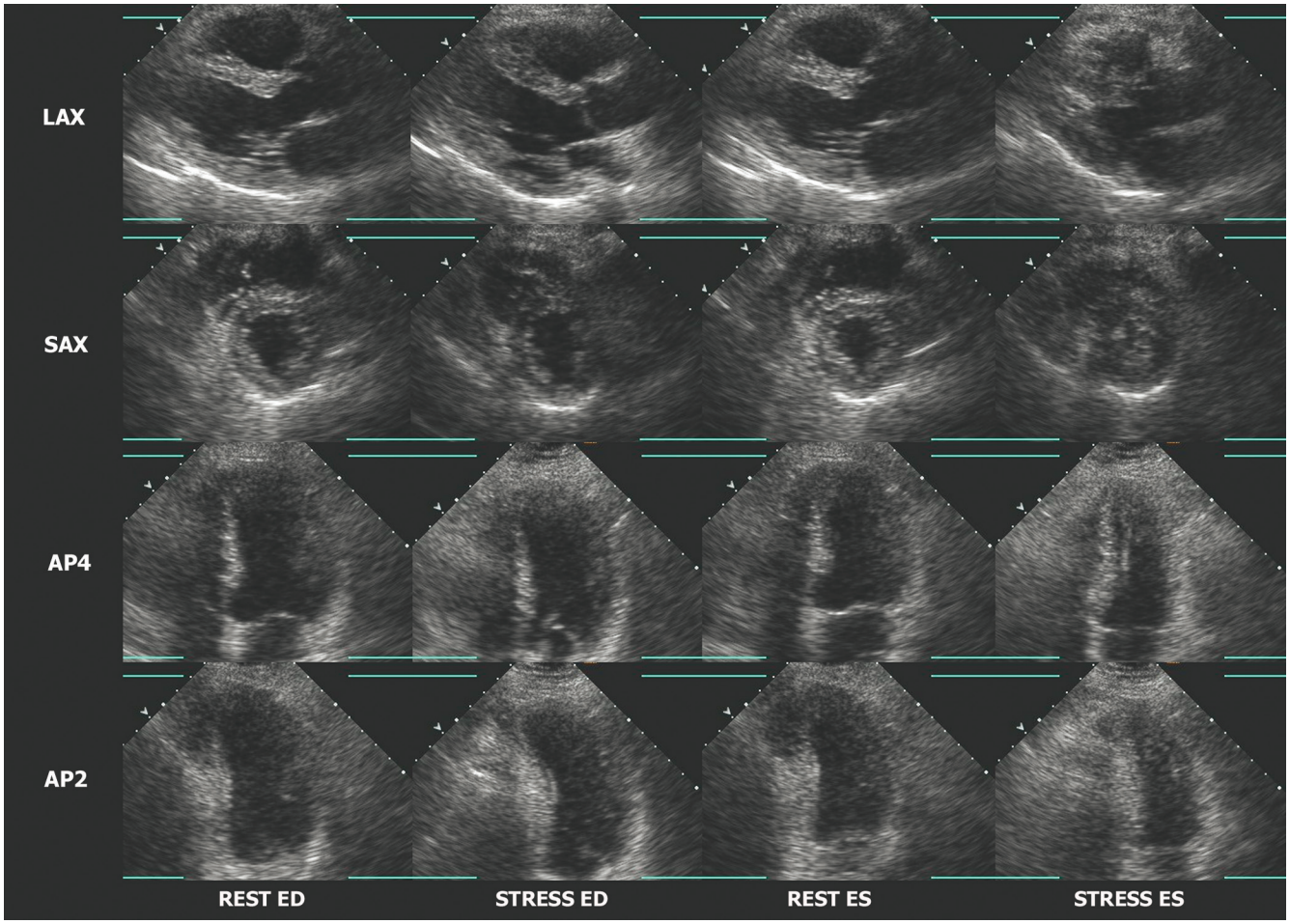


FIGURE 4-1 Normal stress echo response. Images obtained at end diastole (ED) and end systole (ES) at rest and immediately after exercise stress from the parasternal long axis (LAX), short axis (SAX), and apical four-chamber (AP4) and two-chamber (AP2) windows. Notice the decrease in end-systolic left ventricle cavity size after stress.

magnitude of ST-segment deviation, and angina—also known as the *Duke treadmill score*—has proven to be a powerful prognosticator of events.

Exercise time is measured based on the Bruce protocol and appears to be the most important determinant of prognosis.[2] The 5-year survival rates among patients categorized as low, intermediate, and high risk were initially reported at 97%, 91%, and 72%, respectively.

Stress Echocardiography

The interpretation of stress echocardiography is based on the identification of regional wall motion abnormalities induced by ischemia in the presence of obstructive CAD. The test has gained increasing acceptance following the introduction of digital acquisition, harmonic imaging, and contrast agents, all of which have incrementally contributed to increased image quality, reproducibility, and accuracy. In stress echocardiography, regional wall motion is assessed from parasternal long, parasternal short, and apical images using a 17-segment model of the left ventricle (LV).[3] Each segment is described as either normal, hypokinetic, akinetic, or dyskinetic, and the results of the individual segments are averaged to calculate a global wall motion score. The diagnosis of CAD is based on the detection of either resting or stress-induced regional wall motion abnormalities (Figs. 4-1 through 4-3). In most cases, a *resting* regional wall motion abnormality implies a prior myocardial infarction (MI), whereas a *stress-induced* regional wall motion abnormality implies ischemia caused by obstructive CAD.

Exercise Echocardiography

Exercise stress may be performed with a treadmill, a supine or prone bicycle, and even arm ergometry. Treadmill stress echocardiography is by far the most commonly used modality in the United States. Both treadmill and bicycle ergometry allow evaluation of important functional data such as exercise capacity, blood pressure response, hemodynamic responses to exercise that include the assessment of cardiac output and pulmonary pressures, and standard ECG ST-segment analysis. Several studies have reported sensitivities that range from 71% to 97% and specificities ranging from 64% to over 90%. The sensitivity of exercise echocardiography is lower for the detection of single-vessel CAD, in particular in the circumflex coronary artery distribution. Quite often, ischemia is only detected in the territory supplied by the most stenotic vessel in those patients with multivessel disease, especially if the test is discontinued at a submaximal workload.

Resting and/or exercise-induced wall motion abnormalities may occur in patients with cardiomyopathies, microvascular disease, severe hypertension (increased afterload), or valvular disease; they are often a cause of false-positive interpretations. Several stress echocardiographic variables have been shown to have important prognostic value in patients with known or suspected CAD. A low exercise wall motion score or a fall in exercise ejection fraction is highly predictive of an increased risk of adverse cardiac events. This prognostic value is equivalent to that of an MPI perfusion defect of more than 15%. The rate of cardiac events in individuals with a normal exercise echocardiogram has been reported in several studies to be less than 1% per year.

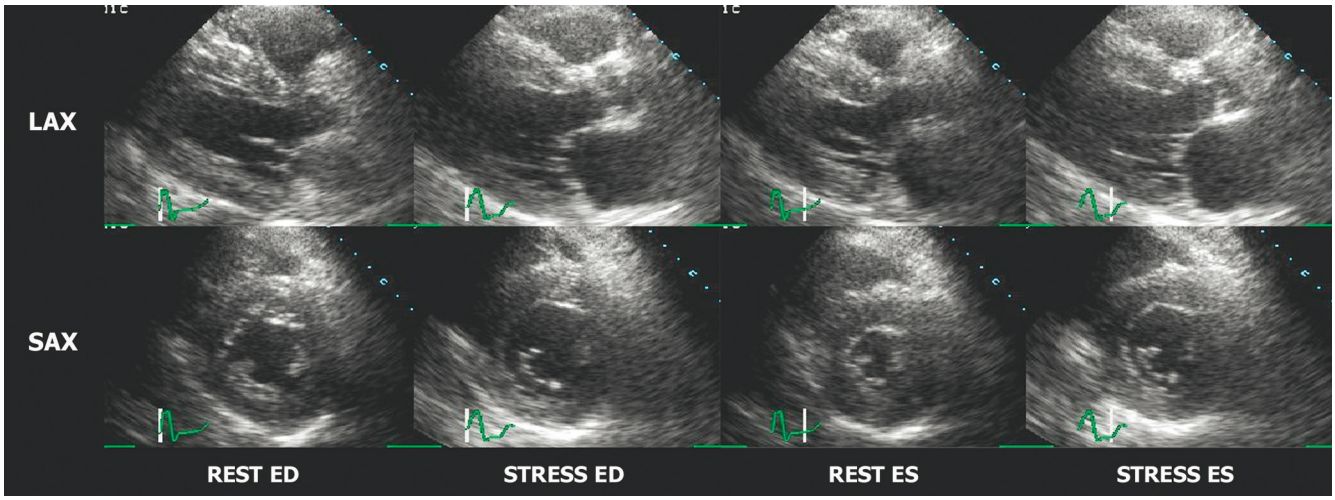


FIGURE 4-2 Abnormal stress echo response in a patient with severe multivessel coronary artery disease. Images obtained at end diastole (ED) and end systole (ES) at rest and immediately after exercise stress from the parasternal long axis (LAX) and short axis (SAX) windows. Notice the end-systolic dilatation of the left ventricle cavity.

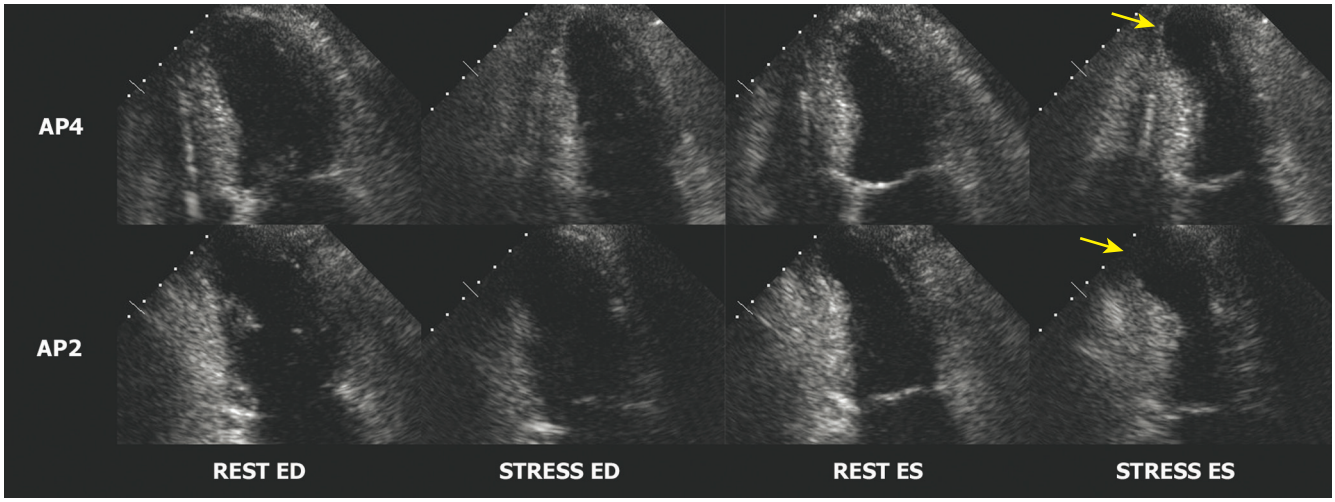


FIGURE 4-3 Abnormal stress echo response in a patient with severe stenosis of the mid–left anterior descending coronary artery. Images obtained at end diastole (ED) and end systole (ES) at rest and immediately after exercise stress from the apical four-chamber (AP4) and two-chamber (AP2) windows. Notice the relative end-systolic dilatation of the left ventricle apical segments (*arrows*).

Pharmacologic Stress Echocardiography

Intravenous (IV) dobutamine, dipyridamole, or adenosine may be used as pharmacologic stressors with echocardiography. Dobutamine is the most commonly used stressor in the United States. It is administered by continuous infusion at incremental rates starting from 5 μg/kg up to 50 μg/kg per minute. It is often complemented by handgrip exercise and/or IV atropine (0.5 to 2.0 mg) to increase heart rate. Dobutamine increases myocardial oxygen demand by increasing contractility and heart rate. Adenosine and dipyridamole are used in many centers in Europe and South America. These agents induce ischemia by coronary steal. The reported sensitivity and specificity of dobutamine echocardiography for the detection of obstructive CAD are equivalent to those reported for exercise echocardiography. The sensitivity is reduced in patients with concentric hypertrophy who experience cavity obliteration early during the test as well as in those who do not reach the target heart rate. Echocardiographic variables obtained during pharmacologic stress have also been shown to have significant prognostic value.[4] A normal dobutamine stress echocardiogram is associated with a low cardiac event rate in patients with suspected CAD and in those at clinically determined intermediate or high cardiac risk undergoing noncardiac surgery. The presence of stress-induced regional wall motion abnormalities, particularly when detected at low heart rates, is a strong predictor of cardiac events. Dobutamine echocardiography may be performed for risk assessment in patients after MI. In this setting, extensive resting regional wall motion abnormalities, stress-induced ischemia, absence of viability, and worsening LV function with stress are associated with an increased risk of adverse events.

CONTRAST PERFUSION IMAGING

Echocardiographic contrast agents consist of inert perfluorocarbon gases encapsulated in a biodegradable shell. Contrast microbubbles have a small diameter (<10 μ), which allows them to cross the pulmonary capillary bed. These agents are commercially available and have been approved for endocardial border definition in patients with

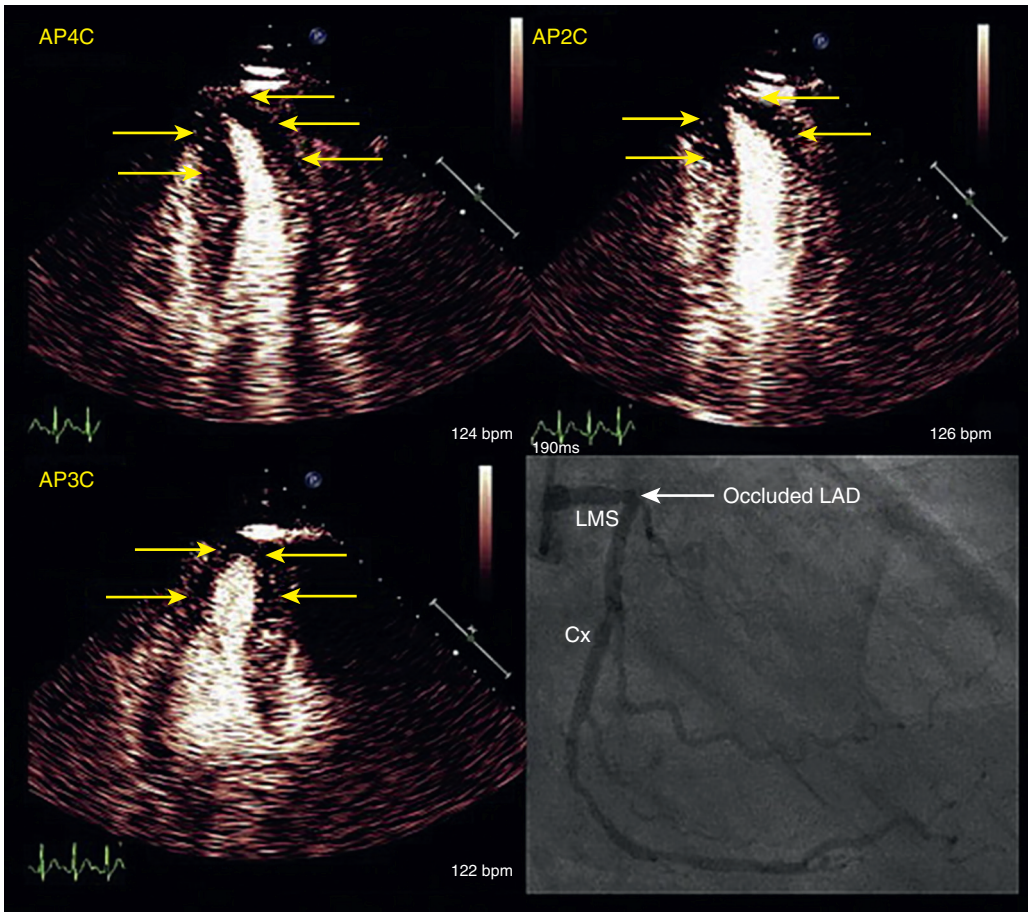


FIGURE 4-4 A 56-year-old male smoker with hypertension who reported chest pain underwent standard echocardiography (SE) and myocardial contrast echocardiography (MCE). SE showed a wall motion abnormality in only one segment (apical septum), but MCE revealed clear myocardium perfusion (MP) defects (*arrows*) in six segments in the apical four-chamber (AP4C), apical two-chamber (AP2C), and apical three-chamber (AP3C) views. Angiography (*bottom right*) revealed a completely occluded left anterior descending (LAD) coronary artery, which was successfully reopened. *Cx,* Circumflex artery; *LMS,* left main stem. (From Shah BN, Chahal NS, Bhattacharyya S, et al: The feasibility and clinical utility of myocardial contrast echocardiography in clinical practice: results from the incorporation of myocardial perfusion assessment into clinical testing with stress echocardiography study. *J Am Soc Echocardiogr* 27[5]:520-530, 2014.)

suboptimal echocardiographic images. When they are exposed to ultrasound, these microbubbles act as strong reflectors owing to their liquid-gas interface. Myocardial contrast echocardiography (MCE) may be used to evaluate myocardial perfusion. Because the LV myocardium has a dense capillary bed, the injection of contrast microbubbles results in myocardial enhancement proportional to the myocardial blood volume. During vasodilator stress in the presence of a flow-limiting stenosis, capillary blood flow and myocardial blood volume is reduced in the segments supplied by the stenotic vessel. This may be detected as either a delay in myocardial enhancement following contrast injection or a relative reduction in enhancement in ischemic compared with normal segments (Fig. 4-4).

Although early studies had shown excellent sensitivity and specificity for MCE,[5,6] subsequent multicenter trials have not been able to replicate these results. The first of these demonstrated sensitivity that ranged from 63% to 75% for MCE versus 63% to 76% for single photon emission computed tomography (SPECT) and specificity of 47% to 59% for MCE versus 53% to 76% for SPECT, but the study failed to meet some of the noninferiority end points.[7] The Real-Time Assessment of Myocardial Perfusion (RAMP-1 and -2) trials studied a total of 662 patients and compared MCE to SPECT using coronary angiography as the gold standard. The overall accuracy of MCE was 66% to 71%, and it was noninferior to the SPECT results, with sensitivity that ranged from 50% to 77% and specificity that ranged from 55% to 88%.[8]

The largest multicenter trial to date enrolled 628 subjects and compared MCE with SPECT in patients who also underwent coronary angiography. Higher sensitivity was obtained with MCE than with SPECT (75.2% vs. 49.1%, respectively), but specificity was lower (52.4% vs. 80.6%, respectively) for stenosis of 70% or greater. Similar findings were obtained for patients with 50% or greater stenosis. Sensitivity for detection of single-vessel disease and proximal disease for 70% or greater stenosis was higher for MCE, which may in part be due to the higher sensitivity of contrast echocardiography for the detection of microvascular abnormalities. These studies seem to agree that MCE demonstrates superior sensitivity but lower specificity for detection of CAD compared with SPECT in a population with a high incidence of cardiovascular (CV) risk factors and intermediate to high prevalence of CAD.[9]

Stress Scintigraphic Myocardial Perfusion Imaging

The assessment of myocardial perfusion imaging (MPI) by nuclear scintigraphic methods relies on the administration of a radionuclide isotope that is accumulated by the myocardium in proportion to blood flow. MPI is performed with either single-photon–emitting

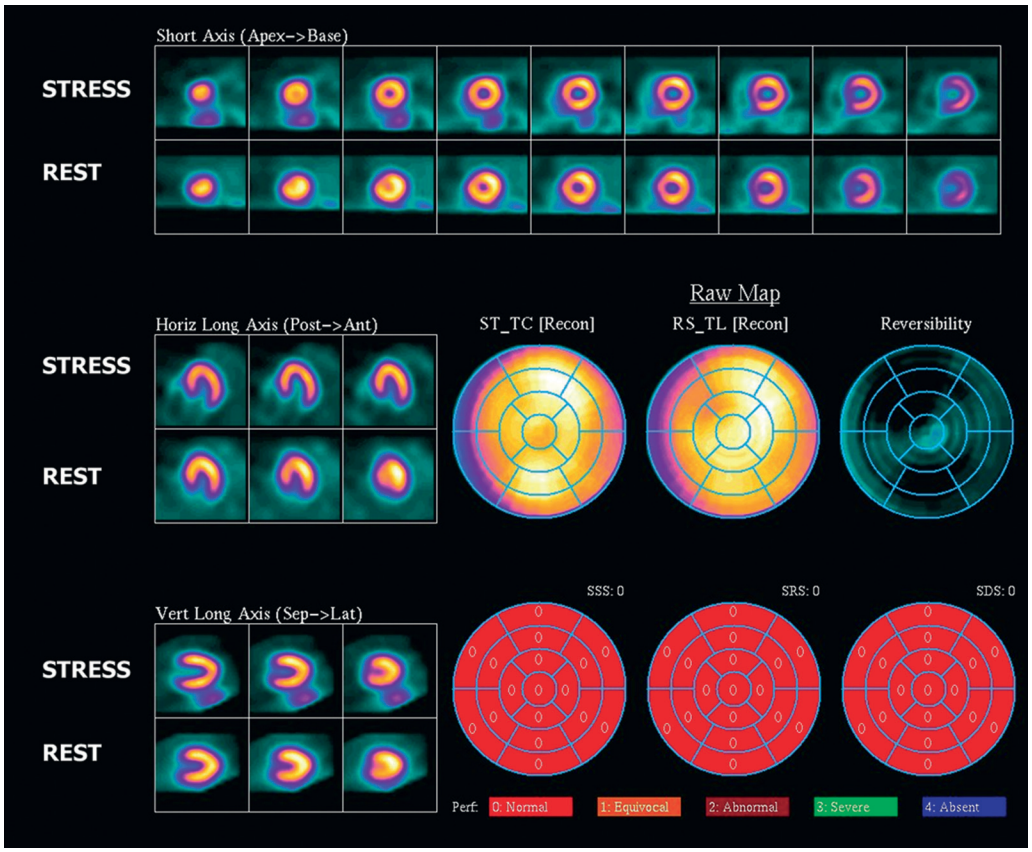


FIGURE 4-5 Single photon emission computed tomography (SPECT) technetium-99m sestamibi exercise stress study. Normal myocardial perfusion during stress and at rest are shown.

or dual-photon–emitting isotopes using SPECT or positron emission tomography (PET) imaging systems, respectively. Thallium-201, technetium-99m sestamibi, and technetium-99m tetrofosmin are isotopes commercially available for SPECT imaging. Currently, technetium-99m–based isotopes are preferred for their higher photon energy, which results in higher image quality, and their shorter half-life, which results in lower radiation exposure. In the past few years, there have been substantial advances in gamma camera technology. SPECT systems have been developed in which the traditional Anger camera is replaced with individual cesium iodide (CsI) scintillation crystals coupled to solid-state photodiodes or novel semiconductor-based detectors using cadmium–zinc telluride (CZT). They eliminate the need for conventional crystal and photomultiplier tubes by directly converting gamma radiation to an electronic pulse. CZT systems are significantly smaller than the traditional sodium iodide detectors and have shown improved efficiency, which makes it possible to obtain higher counts, thus improving signal-to-noise ratio and spatial resolution without increasing isotope dose or acquisition time. The most obvious direct benefit to patients is reduced radiation exposure because of the smaller doses of radioisotope required to obtain adequate counts. Several studies have been performed to compare these new solid-state cameras to those acquired by a conventional gamma camera. All of these studies reported comparable MPI quality with the benefit of significantly shorter image acquisition times. Some of these studies also evaluated left ventricular ejection fraction (LVEF) and volumes and reported similar results between the two cameras.[10-16]

PET imaging systems rely on the simultaneous detection of a pair of photons traveling in opposite directions. These photons travel toward detectors positioned around the subject, where they interact, become absorbed, and thus produce an electrical signal. The detector signals are processed by specialized coincidence circuitry. If the difference in the time of arrival of these photons is less than a predetermined value (typically <10 ns), a signal is recorded. Unlike SPECT imaging, PET imaging does not require collimation. Thus the efficiency of PET is several magnitudes greater and provides higher resolution, lower noise, and lower radiation exposure.

With either SPECT or PET cardiac perfusion studies, images are obtained after stress and at rest. For segmentation of the left ventricle, a 17-segment model is applied. Images are interpreted visually or by using automated quantification based on normalized data. Myocardial scar is determined by the presence of a relative perfusion defect (compared with the segment with the highest counts), which persists on both stress and resting images. Ischemia is determined by the presence of a perfusion defect on stress images that improves or resolves on the resting images (Figs. 4-5 through 4-8).

Exercise Scintigraphic Myocardial Perfusion Imaging

Exercise stress is well suited for SPECT MPI. At peak exercise, either on a treadmill or bicycle ergometer, patients are injected with the radioisotope. Acquisition of the stress images is performed after a few minutes to up to 1 hour after exercise, depending on the radioisotope used. Resting images are obtained before or after the exercise images following the administration of a separate dose of the isotope at rest. Different isotopes may be used for resting and for stress imaging—for example, thallium-201 injected at rest and technetium-99m sestamibi injected at peak stress. The mean reported sensitivity and specificity for exercise SPECT is 86% and 74%, respectively.[17] Most of the studies reported, however, are potentially subject to verification bias. Accordingly, true sensitivity may be overestimated and specificity underestimated. Sensitivity and specificity are higher for the detection of

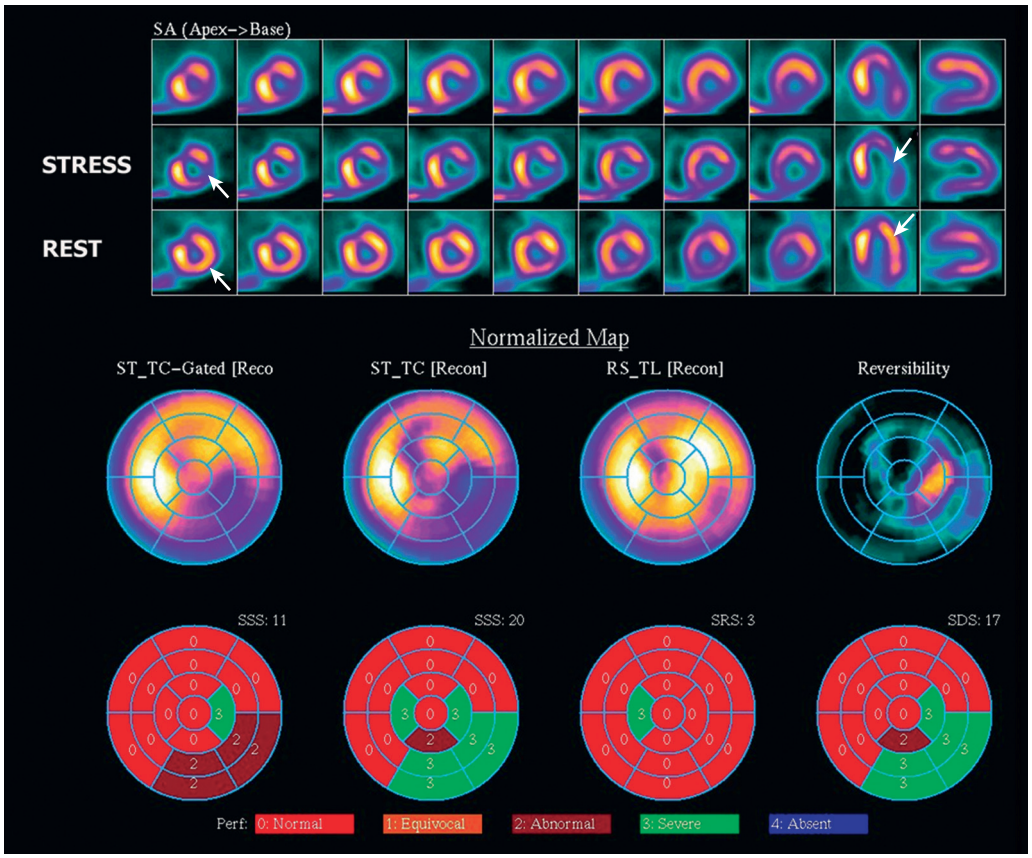


FIGURE 4-6 Single photon emission computed tomography (SPECT) technetium-99m sestamibi exercise stress study. A large myocardial perfusion defect is evident in the posterolateral walls during stress (*white arrows*) with complete reversibility on the resting study, indicating ischemia.

multivessel disease, followed by single-vessel disease in the left anterior descending (LAD) artery distribution, right coronary artery (RCA), and circumflex artery. False-positive results are often attributed to attenuation artifacts from large breasts in women and the diaphragm in obese individuals. Excessive bowel radioactivity may also result in false-positive or false-negative results. The introduction of ECG-gated SPECT imaging has allowed assessment of LV function in addition to perfusion. Studies have shown a good correlation for the assessment of LVEF between SPECT and other tomographic modalities.[18] However, LV volumes may be underestimated and ejection fraction overestimated in ventricles with a small LV cavity and hypertrophy of the walls because of partial volume effects. The accuracy of SPECT determination of LV volumes and ejection fraction is also limited in patients with extensive perfusion defects and LV aneurysms, where the entire geometry of the LV cavity cannot be defined. However, the additional information derived from regional systolic function in gated studies has improved the diagnostic accuracy of the test. Artifacts caused by soft tissue attenuation may be discriminated from true ischemia or scar by the demonstration of normal regional wall motion.

Another recent advancement in SPECT imaging has been the introduction of attenuation correction. Commercially available SPECT attenuation correction systems measure the nonhomogeneous attenuation distribution using external collimated radionuclide sources or computed tomography (CT) (hybrid systems). The application of attenuation correction in patients with excessive subdiaphragmatic activity corrects by enhancing the affected regions of the myocardium, such as the inferior and posterior LV walls. Several studies have shown significant improvements in specificity and modest improvements in sensitivity with the use of attenuation correction.[19,20]

Several studies have shown that a normal exercise stress SPECT study predicts a very low likelihood (<1%) of adverse events, such as cardiac death or MI, for at least 12 months and that this level of risk is independent of sex, age, symptom status, and even the presence of CAD. Therefore in those patients with abnormal scans—with baseline clinical characteristics such as diabetes or severe, extensive SPECT perfusion abnormalities—it is possible to define incremental levels of risk and to define which populations of patients will benefit most from revascularization.

Pharmacologic Scintigraphic Myocardial Perfusion Imaging

In the United States, many patients who are referred for evaluation of suspected or known CAD are unable to exercise. Both adenosine and dipyridamole are vasodilator agents that, in the absence of epicardial artery stenosis, increase myocardial blood flow three to five times over baseline. In the presence of a stenosis, a relative perfusion defect may be seen, indicating either failure to increase regional blood flow compared with myocardial segments supplied by a normal vessel or reduced myocardial blood flow due to coronary steal. For this reason, in some patients with multivessel disease and balanced ischemia, pharmacologic stress SPECT studies may appear normal. The average reported sensitivity and specificity of adenosine SPECT for the detection of CAD are similar to those of exercise SPECT studies, at 90% and 75%, respectively. With dipyridamole SPECT, sensitivity is similar (89%) but specificity is lower (65%). As previously discussed, verification bias may exaggerate true sensitivity and underestimate specificity. The sensitivities and specificities are also higher for multivessel than for single-vessel disease. Pharmacologic stress SPECT studies may also be performed with dobutamine. The mean reported sensitivity and specificity of this test are 82% and 75%, respectively. Unlike dobutamine echocardiography, monitoring of ischemia-induced functional abnormalities is difficult during SPECT MPI. For this reason, dobutamine is

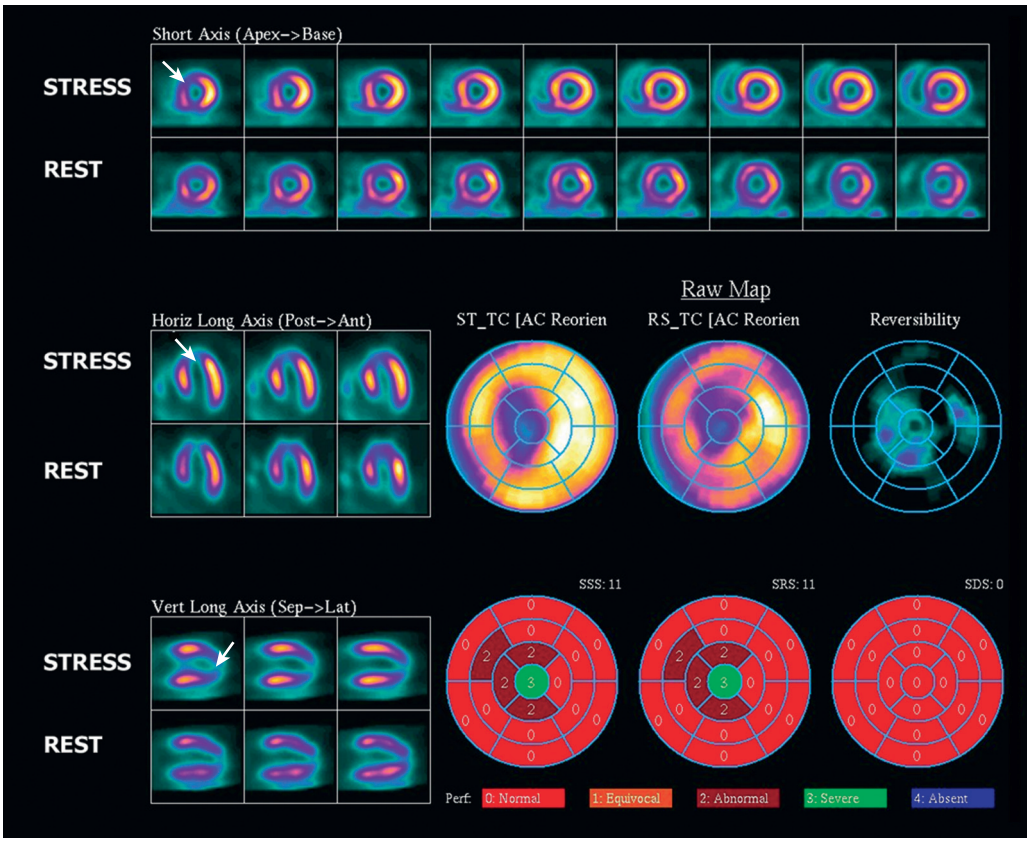


FIGURE 4-7 Single photon emission computed tomography (SPECT) technetium-99m sestamibi exercise stress study. A midsize myocardial perfusion defect is evident in the anteroseptal and apical walls during stress (*white arrows*) without reversibility on the resting study, indicating scar.

not a preferred stressor in most clinical instances. Pharmacologic SPECT is a powerful prognosticator in populations of patients with suspected CAD and in at-risk patients being evaluated prior to noncardiac surgery. The risk of death in patients with normal scans has been reported to be low, but it is higher than in patients with a negative result from exercise SPECT (1% to 3% per year). This probably reflects higher comorbidities in selected populations of patients who cannot exercise. In patients undergoing noncardiac surgery, a pharmacologic stress test has a significant negative predictive value (NPV) but a low positive predictive value (PPV). For that reason, it has been recommended that this test be used in populations at moderate risk, such as those with anginal symptoms, prior infarction, or diabetes. The role of stress MPI is well accepted for the evaluation of symptoms but has not been clearly established for screening asymptomatic patients at risk. In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, a randomized controlled trial (RCT) in which 1123 participants with type 2 diabetes and no symptoms of CAD were randomly assigned to be screened with adenosine stress MPI or not to be screened, the cardiac event rates were low and were not significantly reduced by MPI screening for myocardial ischemia over a follow-up period of 4.8 years.[21]

Pharmacologic stress imaging may also be performed with PET. Its higher spatial resolution, efficiency, and lower attenuation makes PET a superior method in certain patient groups, such as obese patients. Cardiac PET has also been validated for the quantitative assessment of regional myocardial perfusion, LV function, and viability. Current PET stress myocardial perfusion protocols require pharmacologic stress because of the short half-life of rubidium-82. Given that it can be produced on site without a cyclotron, from a column generator, this is the preferred radioisotope for the assessment of perfusion in clinical practice. Two other radioisotopes approved for cardiac PET use in the United States are nitrogen-13 ammonia (perfusion) and fluorine-18-2-fluoro-2-deoxyglucose (18F FDG; metabolic viability). A new PET myocardial perfusion tracer, fluorine-18-flurpiridaz (Flurpiridaz-18F), has recently been introduced. Owing to its smaller kinetic positron energy and consequently short positron range, an 18F-tagged agent can take the full advantage of PET spatial resolution. Flurpiridaz-18F has a long physical half-life and therefore does not require an on-site cyclotron. Phase I and II clinical studies have been completed with Flurpiridaz-18F, and phase III studies are ongoing.[22] In a phase II trial, PET MPI with Flurpiridaz-18F was safe and was superior to SPECT MPI for image quality, interpretative certainty, and overall CAD diagnosis.[23]

In patients with suboptimal SPECT results, follow-up cardiac PET has demonstrated superior accuracy. Most PET studies obtained in patients with a previous equivocal SPECT result are unequivocally classified as normal or mildly positive. PET is one of the most sensitive methods for the identification of myocardial viability in patients with ischemic LV dysfunction. PET defines *viable myocardium* as the presence of a perfusion/metabolism mismatch. Myocardial scar exhibits reduced uptake of both tracers, whereas ischemic viable myocardium shows preserved metabolic activity (Fig. 4-9). The extent of viability by PET has been shown in numerous studies as able to predict functional myocardial recovery after revascularization.

CARDIAC MAGNETIC RESONANCE IMAGING

CMR perfusion imaging has become a prominent modality in cardiovascular imaging because it provides both structural and functional heart disease assessment with high accuracy. It allows accurate determination of cardiac volume, flow quantification, and wall motion analysis both at stress and at rest. CMR myocardial perfusion studies

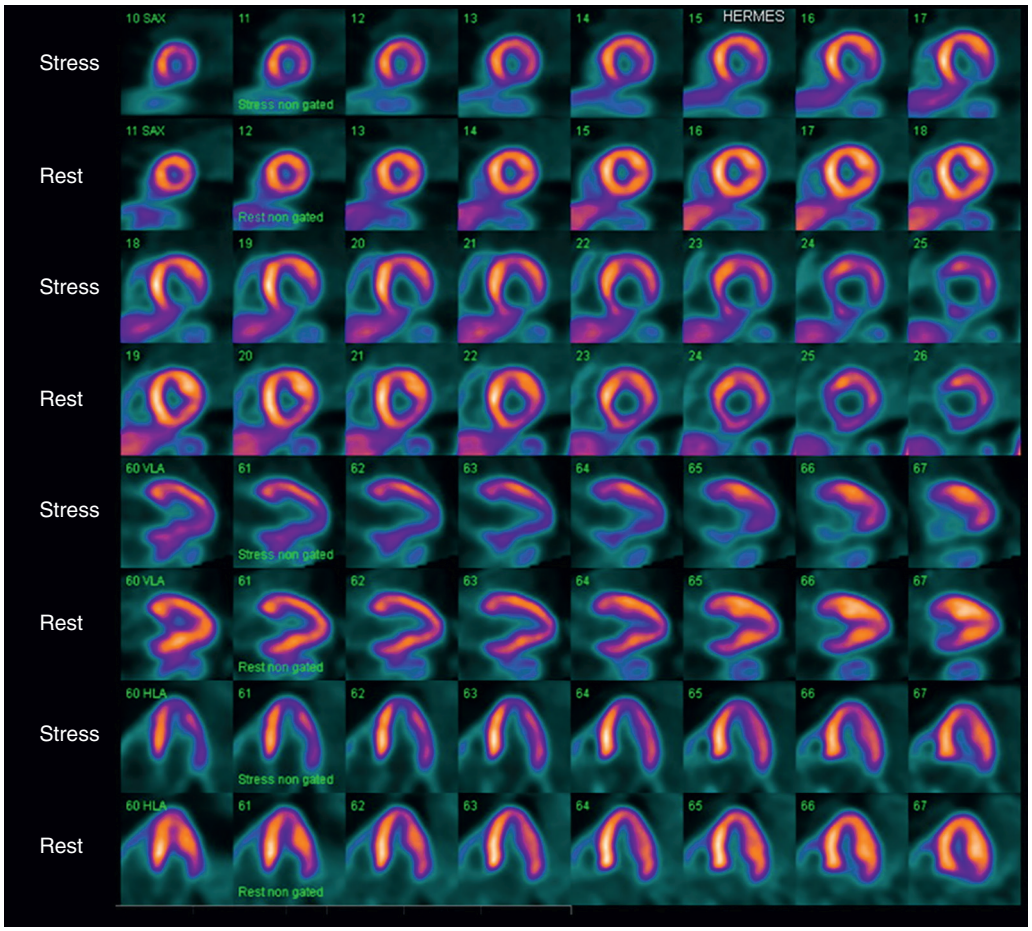


FIGURE 4-8 Positron emission tomography (PET) cardiac perfusion study using nitrogen-13 ammonia. This study shows a moderate-sized myocardial perfusion defect in the inferior wall during stress with complete reversibility on the rest study, indicating ischemia.

can also detect myocardial ischemia and can provide insight into the morphology of myocardial tissue. CMR perfusion imaging noninvasively differentiates causes, stages, and reversibility of myocardial injury. An emerging role for CMR perfusion imaging in the assessment of acute chest pain is that it can differentiate among the causes of chest pain such as ischemia, myocarditis, pericarditis, aortic dissection, or pulmonary embolism. Image quality is preserved even in obese patients, which makes this method ideal for obtaining technically difficult echocardiographic images.

Dobutamine Cardiac Magnetic Resonance

CMR perfusion imaging can evaluate global and regional LV function at rest and during bicycle ergometry or pharmacologic stress. Dobutamine is the most commonly used stressor for the evaluation of ischemia-induced regional wall motion abnormalities.

The average reported sensitivity and specificity for the detection of obstructive CAD are 89% and 84%, respectively. The protocols used are similar to those used in echocardiography for the evaluation of both ischemia and viability. One of the limitations of dobutamine CMR perfusion imaging is the inability to obtain accurate ECG monitoring of ST- segment deviation during the test. For this reason many centers have favored the use of vasodilator stress and CMR perfusion imaging.

Cardiac Magnetic Resonance Perfusion Imaging

An IV paramagnetic agent such as gadolinium diethyl triamine pentaacetic acid (DTPA) may be used to evaluate myocardial perfusion. Gadolinium DTPA is an extracellular agent that, during its first pass, will enhance the intravascular compartment; this is followed by extracellular deposition. Areas of fibrosis and scarring in the LV accumulate gadolinium over time and exhibit "delayed enhancement." Using a fast imaging protocol with steady-state precession (FISP)– based sequence, the first-pass enhancement of the myocardium may be visualized by CMR perfusion imaging in near real time. CMR perfusion imaging makes it possible to identify areas of myocardial hypoenhancement at rest in the presence of severely reduced myocardial blood flow (Fig. 4-10). In most circumstances, resting blood flow is normal in segments supplied by stenotic vessels owing to compensatory arteriolar vasodilation. However, adenosine or dipyridamole may induce ischemia in these cases by reducing myocardial perfusion pressure. The high spatial resolution of CMR perfusion imaging permits the visualization of nontransmural ischemia or infarction. In a recent multicenter study of patients undergoing cardiac catheterization for the evaluation of symptoms, CMR perfusion imaging was compared with SPECT MPI. Based on receiver operating characteristic (ROC) analysis, CMR perfusion imaging at the optimal gadolinium dose (0.1 mmol/kg) performed much like SPECT.[24] CMR perfusion imaging studies have also shown abnormal myocardial perfusion in patients with syndrome X and in others with microvascular dysfunction.[25] In addition, patients with a negative perfusion scan have a low likelihood (<1%) of a major cardiac event over the ensuing 2 years.[26-28]

Accumulating evidence dictates a shift from purely anatomic assessment of CAD to an objective functional assessment. Recent evidence with the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) and Deferred Stenting Versus Immediate Stenting to Prevent No or Slow Reflow (DEFER) trials have shown that

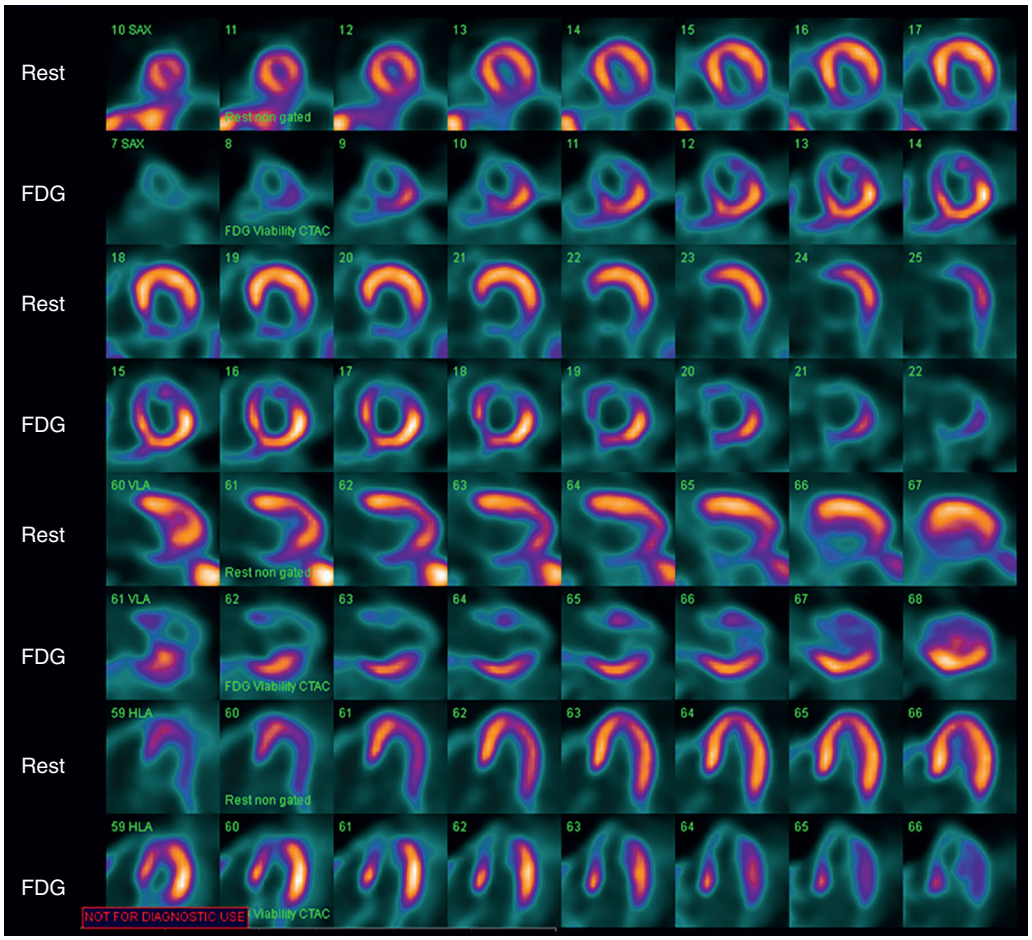


FIGURE 4-9 Positron emission tomography (PET) myocardial viability study obtained in a patient with ischemic left ventricle dysfunction. Resting ammonia images show an extensive inferior perfusion defect. The fluorodeoxyglucose (FDG) images show matched preserved metabolic activity that indicates hypoperfused but viable myocardium.

patients who undergo percutaneous coronary intervention (PCI) on stenotic lesions with positive fractional flow reserve (FFR) have an improved outcome compared with those who have intervention performed based on a visual estimation of lesion severity. The 2-year follow-up of the FAME trial shows a significant reduction in major cardiac events in patients guided by FFR. CMR perfusion imaging is a well-established modality for accurately detecting significant coronary stenosis when validated against FFR.[29,30]

Quantitative analysis of CMR perfusion images can be performed to determine the ratio of stress/resting blood flow or myocardial perfusion reserve (MPR). Studies have shown that in patients with obstructive CAD, MPR increases after PCI.[31] Delayed gadolinium-enhanced CMR perfusion imaging is a powerful technique for evaluating the presence of scar in patients with ischemic LV dysfunction. The extent of infarct transmurality as determined by CMR perfusion imaging predicts functional recovery in patients referred for revascularization (Fig. 4-11).[32] Coronary imaging also may be performed with CMR perfusion imaging. Although the method is well established for the evaluation of congenital coronary anomalies, it is less accurate for evaluating CAD. In a recent meta-analysis of 20 studies (989 patients) that comprised patients with suspected CAD assessed by MRI, mean sensitivity and specificity for the detection of obstructive CAD were 87.1% (confidence interval [CI], 83.0% to 90.3%) and 70.3% (CI, 58.8% to 79.7%)—considerably lower than the respective values found in a meta-analysis of 89 studies (7516 patients) assessed by CCTA (97.2% [95% CI, 96.2% to 98.0%] and 87.4% [CI, 84.5% to 89.8%]).[33]

MYOCARDIAL VIABILITY ASSESSMENT

Viability assessment is commonly sought prior to revascularization for ischemic heart disease. Many imaging modalities can assess the viability of ischemic myocardium; these include echocardiography, radionuclide imaging, and more recently, CMR perfusion imaging. Echocardiographic assessment traditionally depended on incremental low-dose dobutamine infusion and subsequent improvement of contractility or a lack thereof. Improvement in regional contractility at lower rates of dobutamine (5 to 10 μg/kg/min) in segments that are akinetic or hypokinetic at rest predicts functional recovery after revascularization, particularly when those same segments exhibit a reduction in contractility at high dobutamine rates (biphasic response). Patients with ischemic LV dysfunction and viable myocardium who undergo revascularization have better outcomes than those who are not revascularized or who have no evidence of viability regardless of revascularization. The sensitivity with which dobutamine echocardiography predicts recovery of function ranges between 74% and 88%; the specificity is between 73% and 87%. Compared with MPI, dobutamine stress echocardiography has higher specificity but lower sensitivity and overall similar accuracy for predicting functional recovery.[34] More recently, newer methods of characterizing ventricular function during stress echocardiography—namely, assessment of myocardial velocities and strain with tissue Doppler imaging (TDI) and speckle-tracking echocardiography (STE) and perfusion with MCE—have been developed and further investigated.[35-38]

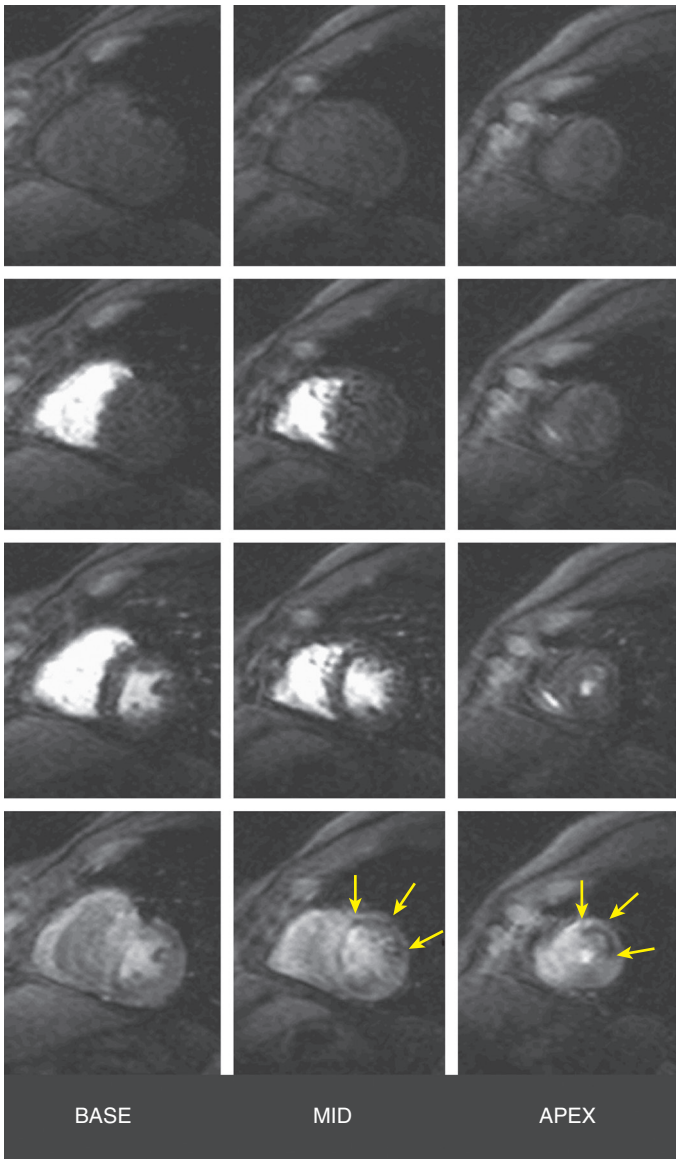


FIGURE 4-10 First-pass gadolinium diethylene triamine pentaacetic acid (DTPA) myocardial perfusion study. *From top to bottom:* Sequential cross-sectional images obtained at the base (*left*), middle, and apex (*right*). The first row of images was acquired before the arrival of contrast. The second row demonstrates the arrival of contrast in the right ventricle. The third row shows its arrival in the left ventricular cavity, and the fourth row shows enhancement of the myocardium. An area of subendocardial hypoenhancement is evident (*arrows*) in a patient with severe stenosis of a large marginal branch.

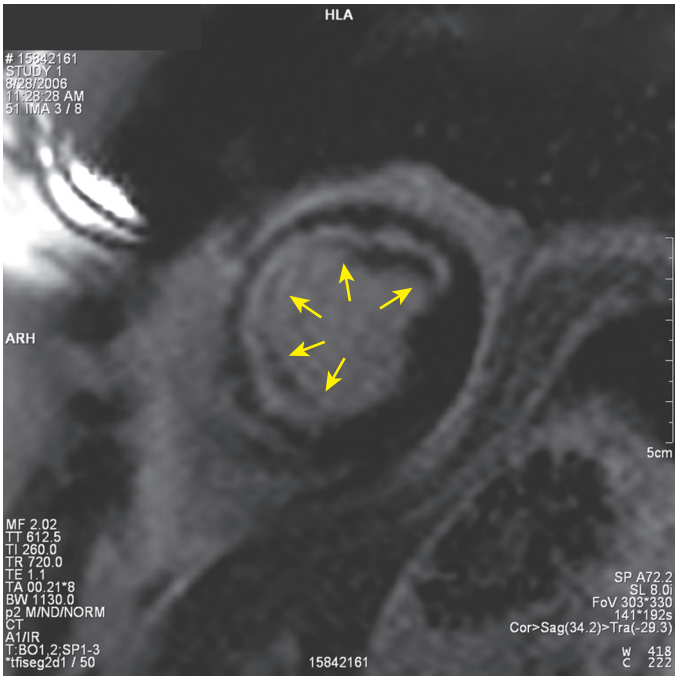


FIGURE 4-11 Mid–left ventricle cross-sectional image obtained 20 minutes after injection of gadolinium diethylene triamine pentaacetic acid (DTPA) demonstrates a large area of subendocardial fibrosis (the white rim is indicated by *arrows*) that involves 50% of the transmural thickness in the septum and anterior walls.

In radionuclide viability imaging, a number of isotopes—including thallium and technetium—have been used. However, a combination of SPECT and PET imaging has gained popularity because it characterizes both metabolism (PET) and perfusion (SPECT). Studies have shown that a metabolism/perfusion mismatch threshold greater than 5% identified patients who had significantly improved survival if treated by revascularization rather than optimal medical therapy (OMT) alone. A limitation of this technique is that it requires two tests, which increases the radiation dose to the patient.[39]

CMR perfusion imaging can determine myocardial viability measurement of end-diastolic wall thickness (EDWT), contractile response to low-dose dobutamine, and transmural extent of infarction on late gadolinium imaging by three methods. A recent meta-analysis of 24 prospective studies (N = 698) evaluated these three CMR perfusion imaging techniques and found that late gadolinium enhancement, using a 50% transmural extent of infarct, provided the greatest sensitivity and NPV, whereas low-dose dobutamine CMR perfusion imaging (Db-CMRI) yielded the highest specificity and PPV, as well as the greatest overall accuracy. EDWT showed good sensitivity but poor specificity.[40]

In general, techniques that detect presence (SPECT, PET, MCE) or absence of late gadolinium enhancement CMR perfusion imaging (LGE-CMRI) of cellular integrity are likely to be more sensitive but less specific than techniques that detect contractile reserve (dobutamine echocardiography [Db-E] and Db-CMRI) because a critical myocardial mass must be viable for a functional response to occur.

However, recent large trials that included the Heart Failure Revascularisation Trial (HEART),[41] Positron Emission Tomography and Recovery Following Revascularization (PARR-2) trial,[42] and most important, the Surgical Treatment for Ischemic Heart Failure (STICH) trial[43] have questioned the superiority of revascularization over OMT, as well as the benefit of viability assessment, in deciding between surgical versus medical therapy. In the STICH trial, viability assessment was an inclusion criterion, but this was dropped secondary to poor recruitment. Subsequently, 50% of patients underwent viability assessment at the discretion of their physician. The main finding of this trial was that revascularization did *not* improve overall survival in ischemic cardiomyopathy compared with OMT. The viability substudy showed that survival of patients with viability was significantly longer than that of patients without viability, but patients with viable myocardium who underwent coronary artery bypass grafting (CABG) did not show any survival benefit compared with those treated with OMT.[44] Although very informative, this trial raised a few concerns regarding its limitations. It only utilized SPECT and Db-E and did not use any of the other available modalities. Furthermore, patients who underwent viability testing were less likely to benefit from revascularization because they had significantly greater LV dysfunction, LV dilatation, and incidence

of previous MI. Each of the trials had limitations, and considerable debate remains about the role of revascularization and viability testing in these patients. Currently, the role of viability testing is to determine which patient with ischemic cardiomyopathy will have a potential for functional and clinical improvement. It can aid in better estimating the benefits of revascularization versus its risks. Even if evidence is insufficient to improve overall survival, it may help patients and physicians make better choices about revascularization therapies that could improve functional status.

Cardiac Computed Tomography

Cardiac computed tomography (CCT) has now been extensively validated as an accurate noninvasive method of evaluating the coronary anatomy. Technical advances available in modern scanners now make it possible to obtain adequate image quality in most patients. Image acquisition and interpretation can be performed very rapidly, which makes this technology suitable for the evaluation of ambulatory patients.

Coronary Artery Calcium Scoring

Coronary artery calcium (CAC) scoring quantifies coronary calcification using a radiographic density-weighted volume of high attenuation regions (>130 Hounsfield units). The prognostic value of CAC has been clearly established by Keelan and colleagues,[45] who demonstrated that a CAC Agatston score greater than 100 was an independent predictor (odds ratio [OR] 1.88) of cardiovascular outcomes (death and nonfatal MI) at 7 years' follow-up. Although very high calcium scores impart an approximately tenfold increased CV event risk, they do not always imply a tight coronary stenosis. The role of CAC for screening asymptomatic individuals is controversial, and the routine incorporation of this type of investigation into a comprehensive risk screening with C-reactive protein (CRP) and cholesterol measurements is still under debate. Some evidence supports the incorporation of CAC into the overall risk stratification of older individuals, using clinical algorithms such as the Framingham Risk Score. In the South Bay Heart Watch study,[46] a CAC greater than 300 was associated with a significant increase in cardiac event rates compared with that determined by clinical score alone. These data support the belief that CAC can improve risk prediction, especially among patients at intermediate Framingham risk, in whom clinical decision making is most difficult. Patients with low Framingham risk derive no significant additional benefit from CAC. Furthermore, it is costly to use CAC to improve cardiovascular risk prediction in populations with no cardiac symptoms who are at low risk. Some even suggest that its wide clinical implementation may in aggregate have a detrimental effect on the quality of life of screened populations.[47] However, in a published study of 6723 asymptomatic patients, CAC was shown to be the strongest predictor of cardiovascular death, nonfatal MI, angina, and revascularization (total events = 162) independent of race. In this study, the risk increased 7.7-fold in patients with a CAC score between 101 and 300 compared with 0 and 9.7-fold in patients with a score greater than 300.[48] The addition of CAC to MPI provides incremental value over and above myocardial perfusion findings.[40,49] In patients with normal stress perfusion, adding a CAC score can improve detection of CAD, particularly in patients with a high pretest likelihood, such as those with diabetes.[50]

Contrast-Enhanced Computed Tomography Coronary Angiography

Although the actual acquisition of a CCTA study takes less than 15 seconds, patient preparation and data interpretation require extensive training and extreme attention to detail. Patient selection is important because extensive coronary calcification and poor x-ray penetration in obese patients may compromise image quality. The frequency of artifacts related to diaphragmatic and/or cardiac motion has been significantly reduced with the newest wide detector coverage (128, 256, and 320 slice) scanners and dual-source imaging. However, most patients still require beta-blocker administration and cooperation with breath-holding instructions during the scan acquisition.

Over the last few years, significant attention has focused on excessive radiation exposure with medical imaging.[51] In response, and in collaboration with medical imaging leaders, the industry has implemented several strategies to reduce radiation dose during CCTA. These include reduction in the volume of coverage, use of lower peak x-ray–tube currents, and wider adoption of prospective ECG-gated acquisition. The use of prospective gating is very effective in reducing dose[52] but limits CCTA image acquisition to a predetermined brief phase of the cardiac cycle. Thus analysis of LV function cannot be performed when this acquisition mode is being used. Patients in whom functional analysis is required, or those with rapid or irregular heart rates who may require reconstruction of multiple cardiac phases for coronary vessel examination, should be imaged using conventional spiral retrospective ECG-gated acquisition, which requires higher overall radiation exposure. CCTA is very useful in assessing the origin and course of congenitally anomalous coronary arteries and the three-dimensional relationship of anomalous coronary arteries with the aorta and pulmonary arterial trunk.[53-55] Myocardial bridges and coronary arteriovenous fistulas can also be well visualized by CCTA.

Cardiac Computed Tomography Angiography to Evaluate Coronary Luminal Stenosis

Figures 4-12 and 4-13 are CCTA studies obtained from a patient with normal coronary arteries and another with severe multivessel disease. The corresponding invasive angiogram from the latter is shown in Figure 4-14. Several single-center and multicenter studies have examined the accuracy of CCTA for establishing the diagnosis of obstructive CAD. Most of these studies have been performed in patients referred for diagnostic coronary angiography based on clinical indications. The prevalence of obstructive CAD in patients enrolled in these studies ranged anywhere from 35% to 80%. Accuracy was defined in these studies based on segment-based, vessel-based, and/or patient-based analysis. *Segment-based analysis* has been restricted in many of these studies to segments greater than 1.5 mm or greater than 2 mm in diameter. In most studies, previously stented segments have been excluded. Either a greater than 50% or greater than 70% reduction in luminal diameter on invasive coronary angiography was used as the reference standard to adjudicate a positive result. On *vessel-based analysis,* a positive result was defined as the presence of one or more abnormal segments in the specific vessel's distribution. On *patient-based analysis,* a positive result was defined as one or more abnormal segments anywhere in the coronary arterial tree.

In a multicenter study[56] that enrolled 187 patients with high or intermediate risk with an Agatston calcium score below 600, 71% of segments were deemed evaluable on multidetector computed tomography (MDCT). All nonevaluable segments were censored to be positive because in clinical practice, they would also lead to the performance of angiography. The sensitivity, specificity, PPV, and NPV for detecting greater than 50% luminal stenoses in segment-based analysis were 89%, 65%, 13%, and 99%, respectively. In patient-based analysis, the sensitivity, specificity, PPV, and NPV were 98%, 54%, 50%, and 99%, respectively. The results of this study suggest that the clinical utility of CCTA, given its high NPV, lies primarily in the exclusion of obstructive CAD.

Prospective multicenter trials have demonstrated improved diagnostic characteristics of 64-slice CCTA in comparison to 16-slice CCTA.[57,58] The Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography (ACCURACY)[59] trial was a 15-center U.S.-based multicenter study that examined 230 patients who underwent CCTA prior to elective diagnostic coronary angiography. Researchers observed sensitivity, specificity, PPV, and NPV of CCTA to detect a 50% or greater stenosis (95%, 83%, 64%, and 99%, respectively) or a 70% or greater stenosis (94%, 83%, 48%, and 99%, respectively). It is likely that a discrepancy will always exist between CCTA and invasive coronary angiography for

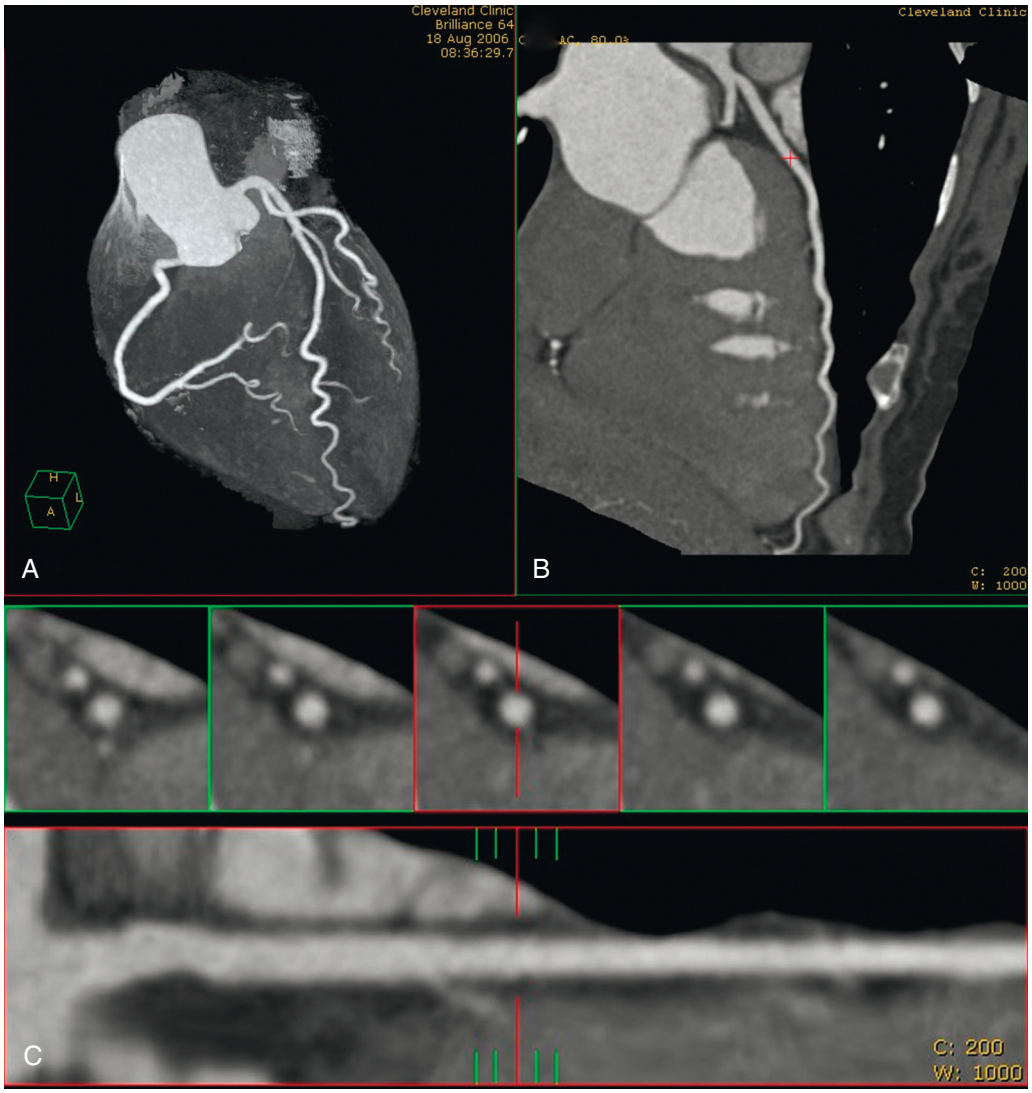


FIGURE 4-12 Multidetector computed tomography (MDCT) coronary angiography of normal coronary arteries. **A,** Volume-rendered maximum-intensity projection of the aortic root and coronary arteries. **B,** Curved multiplanar reconstruction of the left anterior descending (LAD) coronary artery. **C,** Series of cross-sectional images obtained from the mid-LAD at 1-mm intervals.

the quantitative assessment of luminal stenosis. Unlike angiography, CCTA provides data on both the lumen and vessel wall plaque. Thus the results of CCTA are more comparable with those of intravascular ultrasound (IVUS). In addition, CCTA provides an infinite number of projections because of its three-dimensional nature. Thus in many cases, a presumed "false-positive" CCTA finding may represent a "false-negative" coronary angiogram, in which adequate projections were not obtained. The prognostic utility of CCTA has been examined in several single-center studies. Among 169 low- to intermediate-risk patients who underwent both exercise treadmill testing and CCTA, the presence of obstructive (≥70%) stenosis was associated with both ST-segment depression (adjusted OR, 3.38; 95% CI, 1.32 to 8.64; P = .001) and elevated-risk Duke treadmill scores (adjusted OR, 4.67; 95% CI, 1.97 to 11.03; P < .001). In this study, a graded relationship was found between the extent and severity of CAD and the exercise time, as well as the likelihood of ST-segment depression. In another study of 163 low- to intermediate-risk patients who underwent both MPI and CCTA, the extent and severity of CAD as measured by a modified Duke coronary artery jeopardy score was independently associated with a severely abnormal MPI result (OR, 2.25; 95% CI, 1.12 to 4.41; P = .02) for the highest risk group as compared with those without disease.[60] In a multicenter study of 541 intermediate-probability patients referred for symptoms or CAD risk factors who prospectively underwent both CCTA and MPI, the annualized hard event rate was 1.8% in those with mild or no CAD versus 4.8% in those with 50% or greater stenosis by CCTA, and it was 1.1% in those with a normal MPS versus 3.8% in those with an abnormal MPS.[61] In multivariate analysis, CCTA-visualized obstructive plaque and abnormal MPS were independent predictors of late events after adjustment for clinical risk factors, with significantly improved prediction by the combined use of CCTA and MPI compared with either modality alone (log-rank test P value < .005). Over the study period, those with concordantly normal CCTA and MPS results had an annualized hard event rate of 1%; those with concordantly abnormal CCTA and MPS results had a hard event rate of 9.0%; and those with discordant CCTA and MPS results with either abnormal CCTA or abnormal MPS had event rates of 3.8% and 3.7%, respectively.

Second-generation 320-row CT scanners enable the acquisition of a full cardiac dataset within a single heartbeat. Image acquisition time is reduced from 8 to 12 seconds (64-slice CT) to 1 second. Such short image acquisition time allows the use of smaller contrast volumes and lower radiation doses to the patient, and it permits the inclusion of

patient populations previously considered unsuitable for CCTA imaging, such as patients with cardiac arrhythmias. The Coronary Artery Evaluation Using 320-Row Multidetector CT Angiography (CORE-320) pilot experience enrolled 64 subjects to assess radiation dose and image quality of the 320-row CT scanner. They found that only four subjects had limited image quality. Patient body mass index (BMI) was the strongest predictor of poor image quality.[62]

Ongoing large multicenter trials are attempting to unequivocally define how CCTA compares with usual-care functional testing with stress testing. One such trial, the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE), has completed enrollment of over 10,000 patients to determine whether an initial anatomic testing strategy using CCTA technology will reduce the primary end point (all-cause death, nonfatal MI, major periprocedural complications, or hospitalization for unstable angina) by 20% when compared with an initial functional testing strategy over a follow-up of 2.5 years.[63]

Although several studies have demonstrated the predictive value of low-density plaque components and eccentric remodeling, the benefit of CCTA in asymptomatic patients is not yet well established. In one study, 1000 asymptomatic patients underwent 64-slice CCTA as part of a general health evaluation; those with no plaque had no major adverse cardiac events (MACEs) over an average observation of 17 months (± 2), whereas 15 of the 215 individuals with any plaque had later unstable angina or underwent revascularization.[58,64] However, most events occurred within 90 days of the CCTA and were driven by revascularization procedures in this open-label trial. Furthermore, most events occurred in patients with an abnormal CAC, indicating that CCTA provided no significant incremental prognostic value in asymptomatic patients.

Accurate assessment of previously stented coronary vessels remains an important limitation of CCTA.[65] A noninvasive, accurate test for in-stent restenosis would be invaluable in patients with postinterventional chest pain. This is particularly true because the widespread use of drug-eluting stents reduces the incidence of in-stent restenosis, thus reducing the positive yield from repeated invasive coronary angiography. In a study that used 16-slice MDCT, only 126 of 232 stents (54%) could be evaluated.[60,66] Smaller stents in vessels less than 3 mm in diameter were harder to evaluate accurately, and internal luminal diameter is often underestimated. Studies performed with 64-slice scanners have shown improved sensitivity and specificity.[61,67]

FIGURE 4-13 Multidetector computed tomography (MDCT) coronary angiography of obstructive multivessel disease. **A,** Volume-rendered maximum-intensity projection of the aortic root and coronary arteries. **B,** Curved multiplanar reconstruction of the left circumflex (LCX) coronary artery. **C,** Series of cross-sectional images obtained from the mid-LCX at 1-mm intervals. *Arrows* indicate areas of severe stenosis caused predominantly by noncalcified (dark) atherosclerotic plaques.

Nevertheless, the ability to evaluate the lumen of stented vessels depends on the type and diameter of the stent. Practical delineation of in-stent stenosis remains difficult in stents with a diameter less than 3 mm, although CCTA is useful in the evaluation of coronary artery bypass grafts (Fig. 4-15).

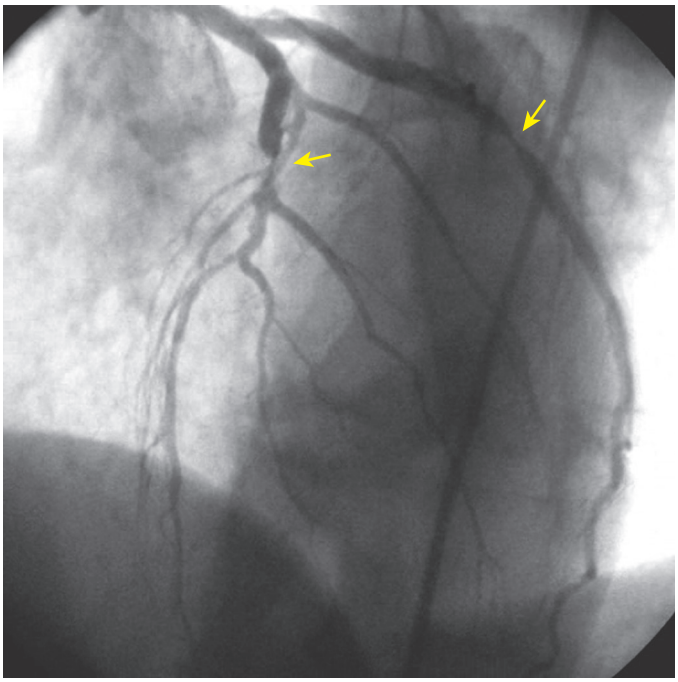


FIGURE 4-14 Angiographic left anterior projection of the left coronary artery and branches obtained by catheterization in the patient in Figure 4-13. *Arrows* indicate severe stenotic lesions in the left anterior descending and left circumflex coronary arteries.

In a study that used 64-slice scanners,[68] CCTA images of 138 grafts, native vessels, and anastomotic sites were compared with invasive coronary angiograms. The grafts included both venous and arterial bypass conduits. All the grafts were "evaluable" by CCTA, with sensitivity, specificity, PPV, and NPV of 100%, 94%, 92%, and 100%, respectively. Evaluation of the distal anastomosis is often limited by surgical clips, which constitute artifacts. Analysis of the native vessels is often more difficult in patients with previous CABG owing to poor runoff, more extensive calcification, and smaller lumen size. This can potentially limit the diagnostic utility of CCTA in this setting. In patients with previous CABG, CCTA should be considered as an alternative to invasive angiography when direct catheterization carries a risk, such as with suspected atheromas or when a high contrast load should be avoided. MDCT may also be useful in symptomatic patients with recent CABG in whom graft occlusion is suspected. CCTA is useful in defining the three-dimensional location of preexisting coronary grafts in relation to the chest wall in patients undergoing repeated sternotomy.

Guiding Interventions With Cardiac Computed Tomographic Angiography

Because of its three-dimensional capabilities, CCTA has great potential as a guide to interventions; it can define the anatomic course, caliber, and length of a diseased segment and the extent of calcification in patients with chronic total occlusion (CTO) of a coronary vessel.[69] In addition, MDCT images may be projected side by side with the fluoroscopy images in the catheterization laboratory.

Stress Myocardial Computed Tomography Perfusion Imaging

As previously discussed, CCTA has been shown by several multicenter studies to have excellent diagnostic accuracy in the detection and exclusion of significant CAD. However, one major limitation of coronary CT has been the inability to detect whether lesions are physiologically or functionally significant. Stress myocardial CT perfusion (CTP) imaging is a novel application of coronary CT in which the examination can provide both anatomic and physiologic assessment of coronary disease. A combined CCTA/CTP approach has been shown to

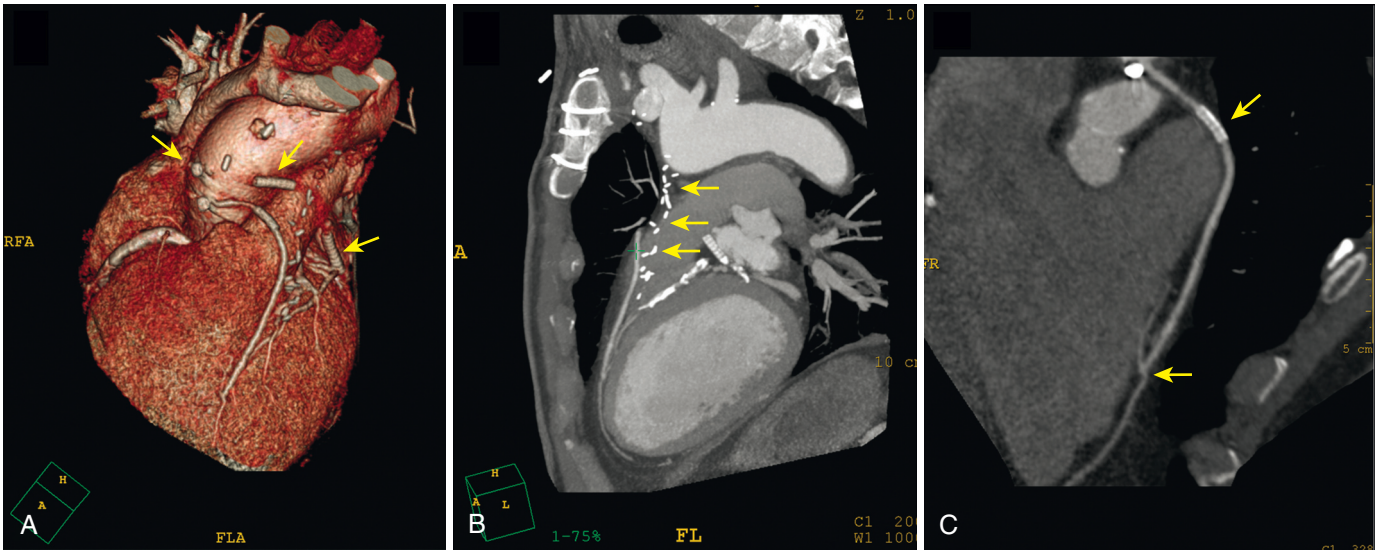


FIGURE 4-15 Multidetector computed tomography (MDCT) coronary angiography obtained in a patient with previous coronary artery bypass grafts. **A,** Volume-rendered projection of the heart shows the stump (*arrows*) of an occluded bypass to the circumflex coronary artery and stents previously deployed in this vessel. The graft is not visualized owing to the lack of contrast opacification. **B,** Oblique sagittal maximum-intensity projection shows a series of staples (*arrows*) that correspond to an occluded left internal thoracic graft to the left anterior descending (LAD) coronary artery. **C,** Curved multiplanar reconstruction of a saphenous vein bypass graft to the LAD. The *arrows* indicate a stent in the proximal segment and show the anastomosis to the distal LAD.

improve the diagnostic accuracy to detect functionally significant coronary lesions when compared with CCTA alone, at a dose comparable to nuclear perfusion exams.[70] During this exam, contrast attenuation differences in the myocardium are measured and compared during rest and stress. A direct relationship exists between the amount of iodinated contrast within the myocardium and myocardial attenuation in Hounsfield Units (HU). As such, a relative difference in myocardial perfusion can be visualized as differing attenuations; areas of myocardium with decreased blood flow would have a lower attenuation—a perfusion defect. Single-center studies have established that myocardial CTP imaging can help accurately diagnose CAD compared with various reference standards that include SPECT, invasive coronary angiography, MRI, and FFR.[71-73] The combination of CCTA and myocardial CTP imaging was validated in the multicenter diagnostic accuracy CORE-320 study.[74] This prospective multicenter study also provided the opportunity to independently validate the diagnostic performance of CTP imaging and SPECT in the diagnosis of anatomic CAD. Sixteen centers enrolled 381 patients, who underwent rest and adenosine stress CTP imaging and either exercise or pharmacologic stress SPECT before and within 60 days of coronary angiography. The per-patient sensitivity and specificity for the diagnosis of CAD (stenosis ≥50%) were 88% (202 of 229 patients) and 55% (83 of 152 patients), respectively, for CTP imaging and 63% (143 of 229 patients) and 67% (102 of 152 patients) for SPECT, with area under the ROC curve values of 0.78 (95% CI, 0.74 to 0.82) and 0.69 (95% CI, 0.64 to 0.74; $P = .001$). The sensitivity of CTP imaging for single-vessel and multivessel CAD was higher than that of SPECT, with sensitivities for left main, three-vessel, two-vessel, and one-vessel disease of 92%, 92%, 89%, and 83%, respectively, for CTP imaging and 75%, 79%, 68%, and 41%, respectively, for SPECT.[74]

Coronary Fractional Flow Reserve Computed Tomography

At present, the gold standard assessment of the physiologic significance of CAD is invasive FFR. Recently, a series of technologic innovations have advanced the possibility of CCTA to enable physiologic evaluation of CAD, thereby creating the potential of this test to provide an integrated anatomic-physiologic assessment of CAD. This advances the use of computational fluid dynamics to noninvasively calculate FFR from a typically acquired CCTA. Three prospective multicenter clinical studies have been conducted thus far to evaluate the diagnostic performance of fractional flow reserve computed tomography (FFRCT) using invasive FFR as the gold standard. In these trials, FFRCT was demonstrated as superior to CCTA stenosis severity–based diagnosis.[75-77] Furthermore, when comparing the susceptibility of FFRCT and CCTA visualized stenosis with reduced diagnostic performance in the presence of common CT artifacts—such as poor contrast opacification, high calcium content, and motion artifact—FFRCT demonstrated a robustness in accuracy that was not observed for CCTA stenosis.

The multicenter Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO) study[78] investigated 407 vessels from 252 patients at 17 centers to determine the diagnostic performance of FFRCT for lesions of intermediate stenosis severity. In this study, FFRCT was compared with invasive FFR, and the researchers found that for these lesions, accuracy, sensitivity, specificity, PPV, and NPV of FFRCT were 71%, 74%, 67%, 41%, and 90%, respectively; whereas accuracy, sensitivity, specificity, PPV, and NPV of CT stenosis were 63%, 34%, 72%, 27%, and 78%, respectively. FFRCT possesses high diagnostic performance for diagnosis of ischemia for lesions of intermediate stenosis severity. Notably, the high sensitivity and NPV suggest the ability of FFRCT to effectively and noninvasively rule out intermediate lesions that cause ischemia.

Coronary Computed Tomography Angiography in Acute Chest Pain

Acute chest pain is one of the leading presenting symptoms of patients who come to the emergency department (ED); it is responsible for more than 8 million visits annually in the United States alone. Only a minority of these patients will ultimately be diagnosed with cardiac ischemia, but most will be admitted to the hospital for investigations that cost $10 to $12 billion dollars annually in the United States.[79] Despite this effort and cost, up to 5% of acute coronary syndromes (ACSs) are missed.[80] To study the efficacy of CCTA in patients with acute chest pain, the Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography (ROMICAT) trial was conducted, in which a CCTA was performed in ED patients with chest pain and negative cardiac biomarkers. These researchers found excellent sensitivity and NPV (both 100% for the presence of any atherosclerotic plaque) to rule out ACS in 368 subjects.[81]

The effectiveness of CCTA in ruling out an ACS in the ED was studied in three large multicenter randomized trials. The Coronary Computed Tomography Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment (CT-STAT) study was performed on 699 subjects with acute chest pain but an inconclusive ED evaluation, and patients were randomly allocated to CCTA or MPI. These researchers found that CCTA resulted in a 54% reduction in time to diagnosis compared with MPI, and costs of care were 38% lower compared with those of standard testing. The diagnostic strategies revealed no difference in MACEs after normal index testing.

The ROMICAT II trial[82] was a large, multicenter randomized trial that enrolled 1000 patients with low to intermediate likelihood of an ACS. The study was powered to a primary end point of length of stay in the hospital; secondary end points included time to diagnosis, rate of discharge from the ED, and resource utilization. These researchers found that patients in the CCTA group had a shorter length of stay in the hospital, and almost four times as many patients were discharged directly from the ED without hospital admission (47% vs 12%). These two studies, CT-STAT and ROMICAT II, also confirmed the 6-month absence of MACEs in patients who had a normal CCTA examination.

A third large, randomized multicenter trial comprised 908 patients with a low (0-2) Thrombolysis in Myocardial Infarction (TIMI) score that were enrolled in a CCTA group and 462 patients that received traditional care. Similar to the ROMICAT II trial, the authors found that patients undergoing CT had a higher rate of discharge from the ED (50% vs. 23%) and a shorter length of stay in the hospital (difference 6.8 hr).[83]

The CT-STAT and ROMICAT studies outlined above also confirmed the excellent safety profile of CCTA use in the ED, as well as the absence or very low incidence of MACEs in patients who had a normal CCTA.

HYBRID IMAGING

Until the advent of CCTA, noninvasive imaging for the detection of CAD had mainly relied on functional imaging techniques to assess perfusion or wall motion abnormalities as indirect evidence of CAD. Functional imaging has been proven to be very valuable in determining prognosis and establishing the need for revascularization. However, neither echocardiography, MPI, nor CMR stress testing can establish the presence of mild to moderate CAD. Moreover, decisions regarding revascularization cannot rely solely on functional imaging without knowledge of the coronary anatomy. CCTA is capable of providing detailed information about the coronary anatomy that includes luminal stenosis and wall plaque. Because of the latter, it may establish the presence of atherosclerosis even earlier than invasive coronary angiography. However, the technique is limited in spatial and temporal resolution, making the differentiation between moderate and severe luminal stenosis difficult in most cases. In a study of 114 patients who underwent both MPI and CCTA, 90% of patients with no visualized plaque by CCTA had normal MPS, 45% with any plaque visualized by CCTA had abnormal MPI results, and only 50% with any greater than 50% plaque by CCTA had abnormal MPI results.[69,84] The rationale for the development of PET-CT or SPECT-CT hybrid systems is that in many patients, a knowledge of both coronary anatomy and extent of

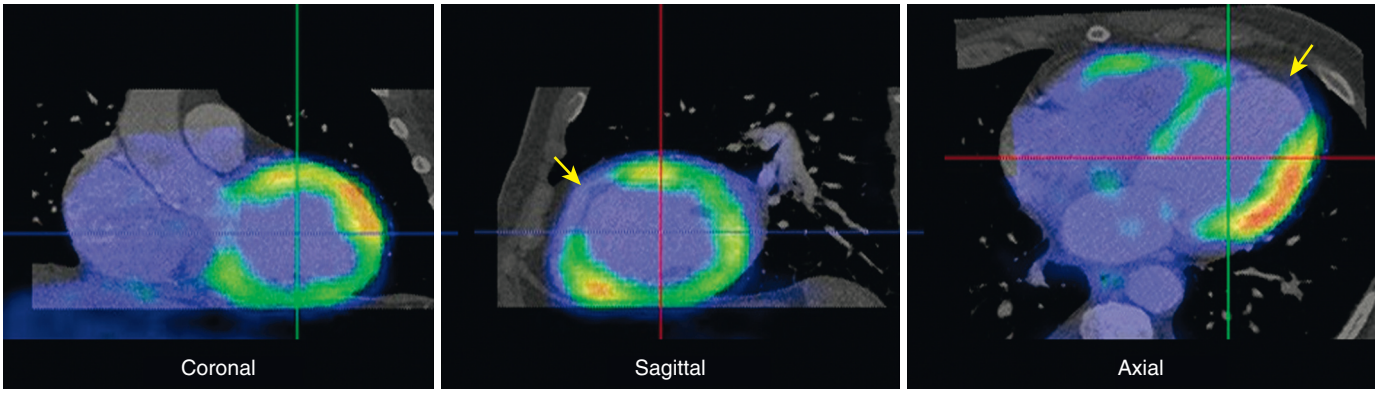


FIGURE 4-16 Hybrid imaging. Fusion of anatomic multidetector computed tomography (MDCT) and functional images (positron emission tomography [PET] rubidium-82) in a patient with a large apical myocardial infarction (*arrows*). Notice the thinning of the myocardium, which matches the lack of perfusion.

TABLE 4-1 Multimodality Detection and Risk Assessment of Ischemic Heart Disease Appropriate Use Criteria: Symptomatic Patients

	Indication Text	Exercise ECG	Stress RNI	Stress Echo	Stress CMR	Calcium Scoring	CCTA	Invasive Coronary Angiography
1	Low pretest probability of CAD, ECG interpretable, *and* able to exercise	A	R	M	R	R	R	R
2	Low pretest probability of CAD, ECG uninterpretable, *or* unable to exercise	–	A	A	M	R	M	R
3	Intermediate pretest probability of CAD, ECG uninterpretable, *and* able to exercise	A	A	A	M	R	M	R
4	Intermediate pretest probability of CAD, ECG uninterpretable, *or* unable to exercise	–	A	A	A	R	A	M
5	High pretest probability of CAD, ECG interpretable, *and* able to exercise	M	A	A	A	R	M	A
6	High pretest probability of CAD, ECG uninterpretable, *or* unable to exercise	–	A	A	A	R	M	A

From Wolk MJ, Bailey SR, Doherty JU, et al: ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 63(4):380-406, 2014.
A, Appropriate; *CAD,* coronary artery disease; *CCTA,* coronary computed tomography angiography; *CMR,* cardiac magnetic resonance; *ECG,* electrocardiogram; *Echo,* echocardiography; *M,* may be appropriate; *R,* rarely appropriate; *RNI,* radionuclide imaging.

ischemia is needed to make management decisions. Hybrid systems consist of an MDCT and either a SPECT or a PET camera mounted next to each other and sharing the same patient table. This facilitates the registration of functional and anatomic data in three-dimensional space (Fig. 4-16). In oncology, the use of hybrid PET-CT systems has largely replaced the use of either modality alone. The benefit of integrating anatomic and functional data is clear, given the small size and large possible volume of distribution of metastatic tumors. However, in cardiology, the development of the technology has advanced before a clinical need has been clearly established.

APPROPRIATE USE CRITERIA

The clinical scenario is most often the deciding factor between anatomic and functional imaging. Anatomy is most helpful to exclude disease in asymptomatic or low-likelihood patients, whereas function may be most helpful in symptomatic patients. The American College of Cardiology Foundation, along with key specialty and subspecialty societies, conducted an appropriate use review of common clinical presentations for stable ischemic heart disease (SIHD) for which to consider use of stress testing and anatomic diagnostic procedures.

Tables 4-1 and 4-2 are intended to provide a practical guide to individual clinicians and patients when considering one of these procedures based on any number of important local and patient-specific variables, such as symptoms and global risk scores, while promoting optimal test utilization for the population at large.[85]

RADIATION EXPOSURE RELATIVE HEALTH RISKS

Over the last decade, the medical community has raised awareness about the potential health care risks associated with radiation exposure from medical imaging. Even though most of the evidence that supports an increased lifetime incidence of cancer has been obtained from observational studies from overexposed children and adolescents, cardiac imaging organizations and the medical industry have introduced safer technologies and practices to reduce such risk. Table 4-3 provides a comparison of the typical radiation exposure and the estimated excess mortality risk attributed to the various tests discussed in this chapter. The reader should understand that these estimates use data from atomic bomb survivors and assume a linear relationship between level of exposure and risk. The validity of the linear relationship theory has not been established; therefore the true risk associated with low levels of radiation exposure is unknown. Moreover, radiation dose estimates vary widely according to the equipment, protocol, isotopes, and patient characteristics.

TABLE 4-2 Multimodality Detection and Risk Assessment of Ischemic Heart Disease Appropriate Use Criteria: Asymptomatic Patients

	Indication Text	Exercise ECG	Stress RNI	Stress Echo	Stress CMR	Calcium Scoring	CCTA	Invasive Coronary Angiography
7	Low global CHD risk regardless of ECG interpretability and ability to exercise	R	R	R	R	R	R	R
8	Intermediate global CHD risk ECG interpretable *and* able to exercise	M	R	R	R	M	R	R
9	Intermediate global CHD risk ECG uninterpretable *or* unable to exercise	–	M	M	R	M	R	R
10	High global CHD risk ECG interpretable *and* able to exercise	A	M	M	M	M	M	R
11	High global CHD risk ECG uninterpretable *or* unable to exercise	–	M	M	M	M	M	R

From Wolk MJ, Bailey SR, Doherty JU, et al: ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 63(4):380-406, 2014.
A, Appropriate; *CCTA,* coronary computed tomography angiography; *CHD,* coronary heart disease; *CMR,* cardiac magnetic resonance; *ECG,* electrocardiogram; *Echo,* echocardiography; *M,* may be appropriate; *R,* rarely appropriate; *RNI,* radionuclide imaging.

TABLE 4-3 Estimated Radiation Exposure and Excess Lifetime Cancer Risk Attributable to Common Noninvasive Cardiac Diagnostic Studies

Modality	System	Protocol	Isotope	Isotope Dose (mCi)	Effective Dose (mSv)	Excess All-Cancer Risk	Excess Fatal Cancer Risk
SPECT-MPI	Anger	Rest-stress	Thallium-201	4.5	31.4	0.31%	0.16%
		Rest-stress	Thallium-201 Technetium-99m sestamibi	3.5/25	29.2	0.29%	0.15%
		Rest-stress	Technetium-99m sestamibi	37.5	11.3	0.11%	0.06%
		Stress only	Technetium-99m sestamibi	27.5	7.9	0.08%	0.04%
	Solid State	Rest-stress	Technetium-99m sestamibi	20	5.8	0.06%	0.03%
		Stress only	Technetium-99m sestamibi	12.5	3.6	0.04%	0.02%
PET-MPI		Rest-stress	Rubidium-82	100	13.5	0.14%	0.07%
		Rest-stress	13N-ammonia	30	2.5	0.03%	0.01%
		Rest-stress	Flurpiridaz-18F	10	7	0.07%	0.04%
PET-Metabolism			18F-FDG	10	7	0.07% 0.00%	0.04% 0.00%
CT-CAC score		Retrospective			3	0.03%	0.02%
		Prospective			1	0.01%	0.01%
CT-CCTA		Nongated			18	0.18%	0.09%
		Retrospective			12	0.12%	0.06%
		Prospective			3	0.03%	0.02%

From Einstein AJ, Moser KW, Thompson RC, et al: Radiation dose to patients from cardiac diagnostic imaging. *Circulation* 116:1290-1305, 2007; Slomka PJ, Berman DS, Germano G: New cardiac cameras: single-photon emission CT and PET. *Semin Nucl Med* 44:232-251, 2014; and Nuclear Science: A Guide to the Nuclear Science Wall Chart, Contemporary Physics Education Project (CPEP), 2003. Available online at www2.lbl.gov/abc/wallchart/guide.html.
CAC, Coronary artery calcium; *CCTA,* cardiac computed tomography angiography; *CT,* computed tomography; *FDG,* fluorodeoxyglucose; *MPI,* myocardial perfusion imaging; *PET,* positron emission tomography; *SPECT,* single photon emission computed tomography.

CONCLUSIONS

The objectives of noninvasive cardiac imaging in patients with known or suspected CAD are to provide confirmatory evidence that CAD has been the cause of symptoms and to offer guidance for the appropriate selection of medical therapy and/or revascularization. In most cases, the extent of anatomic CAD is directly related to the extent and severity of stress-induced myocardial perfusion abnormalities. However, abnormal myocardial perfusion may also be associated with vascular dysfunction in the setting of nonobstructive CAD. Conversely, normal myocardial perfusion may be present in patients with obstructive CAD with increased collateral flow. Hence, because the objective of myocardial revascularization is to reduce myocardial ischemia, it may be concluded that the results of functional imaging tests are more important to guide therapeutic decisions in patients with known or suspected CAD.

In patients who have been evaluated by both MPI and CCTA, the frequency of inducible ischemia is 0%, 5%, 33%, 54%, and 86% for CCTA stenosis of 0%, 0% to 60%, 60% to 70%, 70% to 80%, and greater than 80%, respectively ($P < .0001$).[59] Thus when severe ischemia is present and a false-positive result is unlikely, the likelihood of obstructive CAD is high. The additional information provided by CCTA in such cases is minimal in terms of dictating patient management. On the other hand, real-world experience has shown that a significant proportion of patients who are evaluated by functional tests have inconclusive, false-positive, or false-negative results. Thus anatomic demonstration of CAD by CCTA may play an important role as a less expensive and safer alternative to diagnostic invasive coronary angiography in these cases.

A meta-analysis of comparative studies performed with 64-slice CCTA demonstrated diagnostic sensitivities and specificities of 94% (93% to 97%) and 85% (80% to 90%).[86] From these studies it is clear

that the strengths of CCTA are its high sensitivity and high NPV, which exceeds 95%.[87] These characteristics suggest that CCTA would be most useful as a first diagnostic test for excluding obstructive CAD in low- to intermediate-risk patients. Furthermore, with the advent and technological advances of CT and magnetic resonance imaging (MRI) to diagnose the functional significance of coronary lesions, these modalities are being used with more frequency and confidence in diagnosing and managing coronary lesions.

In comparison with CCTA, MPI has a lower sensitivity—in the range of 85% to 90%[88]—and it is even lower for the detection of single-vessel CAD. The rate of false-positive MPI scans has been reduced with the use of technetium-99m radioisotopes, attenuation-correction algorithms, and the incorporation of gated LVEF and regional wall motion analysis. The result has been improved specificity in the range of 80% to 90%.[88-90] Specificity is also very high with stress echocardiography. The sensitivity of CTP imaging for single-vessel and multivessel CAD was higher than that of SPECT, and studies have shown that MRI stress perfusion performs just as well. Therefore the strengths of functional stress imaging tests are their higher specificity and PPV. Accordingly, stress imaging would be most useful as a first diagnostic test for confirming obstructive CAD in intermediate- to high-risk patients. The clinical scenario is most often the deciding factor between anatomic and functional imaging, and appropriateness criteria have been established to guide individual clinicians when considering these procedures. Several ongoing prospective multicenter trials are seeking to determine the utility of anatomic versus functional imaging tests in specific clinical scenarios.

REFERENCES

1. Cole CR, Blackstone EH, Pashkow FJ, et al: Heart-rate recovery immediately after exercise as a predictor of mortality. *New Engl J Med* 341(18):1351–1357, 1999.
2. Nishime EO, Cole CR, Blackstone EH, et al: Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA* 284(11):1392–1398, 2000.
3. Quinones MA, Douglas PS, Foster E, et al: ACC/AHA clinical competence statement on echocardiography: a report of the American College of Cardiology/American Heart Association/American College of Physicians-American Society of Internal Medicine Task Force on Clinical Competence. *J Am Coll Cardiol* 41(4):687–708, 2003.
4. Sicari R, Pasanisi E, Venneri L, et al: Stress echo results predict mortality: a large-scale multicenter prospective international study. *J Am Coll Cardiol* 41(4):589–595, 2003.
5. Shimoni S, Zoghbi WA, Xie F, et al: Real-time assessment of myocardial perfusion and wall motion during bicycle and treadmill exercise echocardiography: comparison with single photon emission computed tomography. *J Am Coll Cardiol* 37(3):741–747, 2001.
6. Elhendy A, O'Leary EL, Xie F, et al: Comparative accuracy of real-time myocardial contrast perfusion imaging and wall motion analysis during dobutamine stress echocardiography for the diagnosis of coronary artery disease. *J Am Coll Cardiol* 44(11):2185–2191, 2004.
7. Wei K, Crouse L, Weiss J, et al: Comparison of usefulness of dipyridamole stress myocardial contrast echocardiography to technetium-99m sestamibi single-photon emission computed tomography for detection of coronary artery disease (PB127 Multicenter Phase 2 Trial results). *Am J Cardiol* 91(11):1293–1298, 2003.
8. Senior R, Monaghan M, Main ML, et al: Detection of coronary artery disease with perfusion stress echocardiography using a novel ultrasound imaging agent: two Phase 3 international trials in comparison with radionuclide perfusion imaging. *Eur J Echocardiogr* 10(1):26–35, 2009.
9. Senior R, Moreo A, Gaibazzi N, et al: Comparison of sulfur hexafluoride microbubble (SonoVue)-enhanced myocardial contrast echocardiography with gated single-photon emission computed tomography for detection of significant coronary artery disease: a large European multicenter study. *J Am Coll Cardiol* 62(15):1353–1361, 2013.
10. Esteves FP, Raggi P, Folks RD, et al: Novel solid-state-detector dedicated cardiac camera for fast myocardial perfusion imaging: multicenter comparison with standard dual detector cameras. *J Nucl Cardiol* 16(6):927–934, 2009.
11. Herzog BA, Buechel RR, Katz R, et al: Nuclear myocardial perfusion imaging with a cadmium-zinc-telluride detector technique: optimized protocol for scan time reduction. *J Nucl Med* 51(1):46–51, 2010.
12. Buechel RR, Herzog BA, Husmann L, et al: Ultrafast nuclear myocardial perfusion imaging on a new gamma camera with semiconductor detector technique: first clinical validation. *Eur J Nucl Med Mol Imaging* 37(4):773–778, 2010.
13. Sharir T, Ben-Haim S, Merzon K, et al: High-speed myocardial perfusion imaging initial clinical comparison with conventional dual detector Anger camera imaging. *JACC Cardiovasc Imaging* 1(2):156–163, 2008.
14. Gambhir SS, Berman DS, Ziffer J, et al: A novel high-sensitivity rapid-acquisition single-photon cardiac imaging camera. *J Nucl Med* 50(4):635–643, 2009.
15. Ben-Haim S, Kacperski K, Hain S, et al: Simultaneous dual-radionuclide myocardial perfusion imaging with a solid-state dedicated cardiac camera. *Eur J Nucl Med Mol Imaging* 37(9):1710–1721, 2010.
16. Sharir T, Slomka PJ, Hayes SW, et al: Multicenter trial of high-speed versus conventional single-photon emission computed tomography imaging: quantitative results of myocardial perfusion and left ventricular function. *J Am Coll Cardiol* 55(18):1965–1974, 2010.
17. Underwood SR, Anagnostopoulos C, Cerqueira M, et al: Myocardial perfusion scintigraphy: the evidence. *Eur J Nucl Med Mol Imaging* 31(2):261–291, 2004.
18. Ioannidis JP, Trikalinos TA, Danias PG: Electrocardiogram-gated single-photon emission computed tomography versus cardiac magnetic resonance imaging for the assessment of left ventricular volumes and ejection fraction: a meta-analysis. *J Am Coll Cardiol* 39(12):2059–2068, 2002.
19. Hendel RC, Berman DS, Cullom SJ, et al: Multicenter clinical trial to evaluate the efficacy of correction for photon attenuation and scatter in SPECT myocardial perfusion imaging. *Circulation* 99(21):2742–2749, 1999.
20. Links JM, Becker LC, Rigo P, et al: Combined corrections for attenuation, depth-dependent blur, and motion in cardiac SPECT: a multicenter trial. *J Nucl Cardiol* 7(5):414–425, 2000.
21. Young LH, Wackers FJ, Chyun DA, et al: Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA* 301(15):1547–1555, 2009.
22. Nakazato R, Berman DS, Alexanderson E, Slomka P: Myocardial perfusion imaging with PET. *Imaging Med* 5(1):35–46, 2013.
23. Berman DS, Maddahi J, Tamarappoo BK, et al: Phase II safety and clinical comparison with single-photon emission computed tomography myocardial perfusion imaging for detection of coronary artery disease: flurpiridaz F 18 positron emission tomography. *J Am Coll Cardiol* 61(4):469–477, 2013.
24. Schwitter J, Wacker CM, van Rossum AC, et al: MR-IMPACT: comparison of perfusion-cardiac magnetic resonance with single-photon emission computed tomography for the detection of coronary artery disease in a multicentre, multivendor, randomized trial. *Euro Heart J* 29(4):480–489, 2008.
25. Panting JR, Gatehouse PD, Yang GZ, et al: Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *New Engl J Med* 346(25):1948–1953, 2002.
26. Jahnke C, Nagel E, Gebker R, et al: Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. *Circulation* 115(13):1769–1776, 2007.
27. Pilz G, Jeske A, Klos M, et al: Prognostic value of normal adenosine-stress cardiac magnetic resonance imaging. *Am J Cardiol* 101(10):1408–1412, 2008.
28. Hartlage G, Janik M, Anadiotis A, et al: Prognostic value of adenosine stress cardiovascular magnetic resonance and dobutamine stress echocardiography in patients with low-risk chest pain. *Int J Cardiovasc Imaging* 28(4):803–812, 2012.
29. Watkins S, McGeoch R, Lyne J, et al: Validation of magnetic resonance myocardial perfusion imaging with fractional flow reserve for the detection of significant coronary heart disease. *Circulation* 120(22):2207–2213, 2009.
30. Lockie T, Ishida M, Perera D, et al: High-resolution magnetic resonance myocardial perfusion imaging at 3.0-Tesla to detect hemodynamically significant coronary stenoses as determined by fractional flow reserve. *J Am Coll Cardiol* 57(1):70–75, 2011.
31. Al-Saadi N, Nagel E, Gross M, et al: Noninvasive detection of myocardial ischemia from perfusion reserve based on cardiovascular magnetic resonance. *Circulation* 101(12):1379–1383, 2000.
32. Kim RJ, Wu E, Rafael A, et al: The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *New Engl J Med* 343(20):1445–1453, 2000.
33. Schuetz GM, Zacharopoulou NM, Schlattmann P, Dewey M: Meta-analysis: noninvasive coronary angiography using computed tomography versus magnetic resonance imaging. *Ann Intern Med* 152(3):167–177, 2010.
34. Bax JJ, Poldermans D, Elhendy A, et al: Sensitivity, specificity, and predictive accuracies of various noninvasive techniques for detecting hibernating myocardium. *Curr Probl Cardiol* 26(2):147–186, 2001.
35. Li DY, Hao J, Xia Y, et al: Clinical usefulness of low-dose dobutamine stress real-time myocardial contrast echocardiography for detection of viable myocardium. *J Clin Ultrasound* 40(5):272–279, 2012.
36. Fernandes DR, Tsutsui JM, Bocchi EA, et al: Qualitative and quantitative real time myocardial contrast echocardiography for detecting hibernating myocardium. *Echocardiography* 28(3):342–349, 2011.
37. Rosner A, Avenarius D, Malm S, et al: Persistent dysfunction of viable myocardium after revascularization in chronic ischaemic heart disease: implications for dobutamine stress echocardiography with longitudinal systolic strain and strain rate measurements. *Eur Heart J Cardiovasc Imaging* 13(9):745–755, 2012.
38. Ran H, Zhang PY, Fang LL, et al: Clinic value of two-dimensional speckle tracking combined with adenosine stress echocardiography for assessment of myocardial viability. *Echocardiography* 29(6):688–694, 2012.
39. Uebleis C, Hellweger S, Laubender RP, et al: The amount of dysfunctional but viable myocardium predicts long-term survival in patients with ischemic cardiomyopathy and left ventricular dysfunction. *Int J Cardiovasc Imaging* 29(7):1645–1653, 2013.
40. Romero J, Xue X, Gonzalez W, Garcia MJ: CMR imaging assessing viability in patients with chronic ventricular dysfunction due to coronary artery disease: a meta-analysis of prospective trials. *JACC Cardiovasc Imaging* 5(5):494–508, 2012.
41. Cleland JG, Calvert M, Freemantle N, et al: The Heart Failure Revascularisation Trial (HEART). *Eur J Heart Fail* 13(2):227–233, 2011.
42. Beanlands RS, Nichol G, Huszti E, et al: F-18-fluorodeoxyglucose positron emission tomography imaging-assisted management of patients with severe left ventricular dysfunction and suspected coronary disease: a randomized, controlled trial (PARR-2). *J Am Coll Cardiol* 50(20):2002–2012, 2007.
43. Velazquez EJ, Lee KL, Deja MA, et al: Coronary-artery bypass surgery in patients with left ventricular dysfunction. *New Engl J Med* 364(17):1607–1616, 2011.
44. Bonow RO, Maurer G, Lee KL, et al: Myocardial viability and survival in ischemic left ventricular dysfunction. *New Engl J Med* 364(17):1617–1625, 2011.
45. Keelan PC, Bielak LF, Ashai K, et al: Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. *Circulation* 104(4):412–417, 2001.
46. Greenland P, LaBree L, Azen SP, et al: Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA* 291(2):210–215, 2004.
47. O'Malley PG, Greenberg BA, Taylor AJ: Cost-effectiveness of using electron beam computed tomography to identify patients at risk for clinical coronary artery disease. *Am Heart J* 148(1):106–113, 2004.
48. Detrano R, Guerci AD, Carr JJ, et al: Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *New Engl J Med* 358(13):1336–1345, 2008.
49. Schenker MP, Dorbala S, Hong EC, et al: Interrelation of coronary calcification, myocardial ischemia, and outcomes in patients with intermediate likelihood of coronary artery disease: a combined positron emission tomography/computed tomography study. *Circulation* 117(13):1693–1700, 2008.
50. Anand DV, Lim E, Hopkins D, et al: Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. *Euro Heart J* 27(6):713–721, 2006.
51. Hausleiter J, Meyer T, Hermann F, et al: Estimated radiation dose associated with cardiac CT angiography. *JAMA* 301(5):500–507, 2009.
52. Raff GL, Chinnaiyan KM, Share DA, et al: Radiation dose from cardiac computed tomography before and after implementation of radiation dose-reduction techniques. *JAMA* 301(22):2340–2348, 2009.
53. Taylor AJ, Byers JP, Cheitlin MD, Virmani R: Anomalous right or left coronary artery from the contralateral coronary sinus:

"high-risk" abnormalities in the initial coronary artery course and heterogeneous clinical outcomes. *Am Heart J* 133(4):428–435, 1997.
54. Shi H, Aschoff AJ, Brambs HJ, Hoffmann MH: Multislice CT imaging of anomalous coronary arteries. *Eur Radiol* 14(12):2172–2181, 2004.
55. Memisoglu E, Hobikoglu G, Tepe MS, et al: Congenital coronary anomalies in adults: comparison of anatomic course visualization by catheter angiography and electron beam CT. *Catheter Cardiovasc Interv* 66(1):34–42, 2005.
56. CATSCAN Study Investigators: Accuracy of 16-row multidetector computed tomography for the assessment of coronary artery stenosis. *JAMA* 296(4):403–411, 2006.
57. Miller JM, Rochitte CE, Dewey M, et al: Diagnostic performance of coronary angiography by 64-row CT. *New Engl J Med* 359(22):2324–2336, 2008.
58. Meijboom WB, Weustink AC, Pugliese F, et al: Comparison of diagnostic accuracy of 64-slice computed tomography coronary angiography in women versus men with angina pectoris. *Am J Cardiol* 100(10):1532–1537, 2007.
59. Lin FY, Saba S, Weinsaft JW, et al: Relation of plaque characteristics defined by coronary computed tomographic angiography to ST-segment depression and impaired functional capacity during exercise treadmill testing in patients suspected of having coronary heart disease. *Am J Cardiol* 103(1):50–58, 2009.
60. Lin F, Shaw LJ, Berman DS, et al: Multidetector computed tomography coronary artery plaque predictors of stress-induced myocardial ischemia by SPECT. *Atherosclerosis* 197(2):700–709, 2008.
61. van Werkhoven JM, Schuijf JD, Gaemperli O, et al: Prognostic value of multislice computed tomography and gated single-photon emission computed tomography in patients with suspected coronary artery disease. *J Am Coll Cardiol* 53(7):623–632, 2009.
62. Yoneyama K, Vavere AL, Cerci R, et al: Influence of image acquisition settings on radiation dose and image quality in coronary angiography by 320-detector volume computed tomography: the CORE320 pilot experience. *Heart Int* 7(2):e11, 2012.
63. Douglas PS, Hoffmann U, Lee KL, et al: PROspective Multicenter Imaging Study for Evaluation of chest pain: Rationale and design of the PROMISE trial. *Am Heart J* 167(6):796–803 e1, 2014.
64. Choi EK, Choi SI, Rivera JJ, et al: Coronary computed tomography angiography as a screening tool for the detection of occult coronary artery disease in asymptomatic individuals. *J Am Coll Cardiol* 52(5):357–365, 2008.
65. Gilard M, Cornily JC, Rioufol G, et al: Noninvasive assessment of left main coronary stent patency with 16-slice computed tomography. *Am J Cardiol* 95(1):110–112, 2005.
66. Hong C, Chrysant GS, Woodard PK, Bae KT: Coronary artery stent patency assessed with in-stent contrast enhancement measured at multi-detector row CT angiography: initial experience. *Radiology* 233(1):286–291, 2004.
67. Leber AW, Knez A, von Ziegler F, et al: Quantification of obstructive and nonobstructive coronary lesions by 64-slice computed tomography: a comparative study with quantitative coronary angiography and intravascular ultrasound. *J Am Coll Cardiol* 46(1):147–154, 2005.
68. Ropers D, Pohle FK, Kuettner A, et al: Diagnostic accuracy of noninvasive coronary angiography in patients after bypass surgery using 64-slice spiral computed tomography with 330-ms gantry rotation. *Circulation* 114(22):2334–2341, 2006.
69. Ehara M, Terashima M, Kawai M, et al: Impact of multislice computed tomography to estimate difficulty in wire crossing in percutaneous coronary intervention for chronic total occlusion. *J Invasive Cardiol* 21(11):575–582, 2009.
70. George RT, Arbab-Zadeh A, Miller JM, et al: Adenosine stress 64- and 256-row detector computed tomography angiography and perfusion imaging: a pilot study evaluating the transmural extent of perfusion abnormalities to predict atherosclerosis causing myocardial ischemia. *Circulation Cardiovasc Imaging* 2(3):174–182, 2009.
71. George RT, Arbab-Zadeh A, Miller JM, et al: Computed tomography myocardial perfusion imaging with 320-row detector computed tomography accurately detects myocardial ischemia in patients with obstructive coronary artery disease. *Circulation Cardiovasc Imaging* 5(3):333–340, 2012.
72. Blankstein R, Shturman LD, Rogers IS, et al: Adenosine-induced stress myocardial perfusion imaging using dual-source cardiac computed tomography. *J Am Coll Cardiol* 54(12):1072–1084, 2009.
73. Bettencourt N, Chiribiri A, Schuster A, et al: Direct comparison of cardiac magnetic resonance and multidetector computed tomography stress-rest perfusion imaging for detection of coronary artery disease. *J Am Coll Cardiol* 61(10):1099–1107, 2013.
74. George RT, Mehra VC, Chen MY, et al: Myocardial CT perfusion imaging and SPECT for the diagnosis of coronary artery disease: a head-to-head comparison from the CORE320 multicenter diagnostic performance study. *Radiology* 272(2):407–416, 2014.
75. Koo BK, Erglis A, Doh JH, et al: Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. *J Am Coll Cardiol* 58(19):1989–1997, 2011.
76. Min JK, Leipsic J, Pencina MJ, et al: Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA* 308(12):1237–1245, 2012.
77. Norgaard BL, Leipsic J, Gaur S, et al: Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol* 63(12):1145–1155, 2014.
78. Nakazato R, Park HB, Berman DS, et al: Noninvasive fractional flow reserve derived from computed tomography angiography for coronary lesions of intermediate stenosis severity: results from the DeFACTO study. *Circulation Cardiovasc Imaging* 6(6):881–889, 2013.
79. Tatum JL, Jesse RL, Kontos MC, et al: Comprehensive strategy for the evaluation and triage of the chest pain patient. *Ann Emerg Med* 29(1):116–125, 1997.
80. Pope JH, Aufderheide TP, Ruthazer R, et al: Missed diagnoses of acute cardiac ischemia in the emergency department. *New Engl J Med* 342(16):1163–1170, 2000.
81. Hoffmann U, Bamberg F, Chae CU, et al: Coronary computed tomography angiography for early triage of patients with acute chest pain: the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. *J Am Coll Cardiol* 53(18):1642–1650, 2009.
82. Hoffmann U, Truong QA, Schoenfeld DA, et al: Coronary CT angiography versus standard evaluation in acute chest pain. *New Engl J Med* 367(4):299–308, 2012.
83. Litt HI, Gatsonis C, Snyder B, et al: CT angiography for safe discharge of patients with possible acute coronary syndromes. *New Engl J Med* 366(15):1393–1403, 2012.
84. Schuijf JD, Wijns W, Jukema JW, et al: Relationship between noninvasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging. *J Am Coll Cardiol* 48(12):2508–2514, 2006.
85. Wolk MJ, Bailey SR, Doherty JU, et al: ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 63(4):380–406, 2014.
86. Janne d'Othee B, Siebert U, Cury R, et al: A systematic review on diagnostic accuracy of CT-based detection of significant coronary artery disease. *Euro J Radiol* 65(3):449–461, 2008.
87. Budoff MJ, Achenbach S, Blumenthal RS, et al: Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation* 114(16):1761–1791, 2006.
88. Mieres JH, Shaw LJ, Arai A, et al: Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. *Circulation* 111(5):682–696, 2005.
89. Fricke E, Fricke H, Weise R, et al: Attenuation correction of myocardial SPECT perfusion images with low-dose CT: evaluation of the method by comparison with perfusion PET. *J Nucl Med* 46(5):736–744, 2005.
90. Duvall WL, Croft LB, Corriel JS, et al: SPECT myocardial perfusion imaging in morbidly obese patients: image quality, hemodynamic response to pharmacologic stress, and diagnostic and prognostic value. *J Nucl Cardiol* 13(2):202–209, 2006.

Intracoronary Pressure and Flow Measurements

5

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KEY POINTS

- Evaluation of patients with stable ischemic heart disease necessitates that the operator define ischemia-producing coronary lesions. Angiography alone is often insufficient as a singular tool, and adjunctive stress testing often is not regionally specific enough to extrapolate to an individual coronary stenosis. Fractional flow reserve (FFR) has been proven to be an accurate detector of the ability of a given stenosis to produce myocardial ischemia, and as such, it is an invaluable adjunct to the modern-day catheterization lab.
- A coronary stenosis that does not produce an "ischemic" FFR has been shown to have a favorable long-term outcome when treated with medical therapy. Outcomes are not significantly improved with coronary revascularization.
- Percutaneous coronary intervention (PCI) of only those lesions that are physiologically significant, as shown by FFR, has been prospectively demonstrated to be clinically and economically superior to angiography-guided PCI in patients with multivessel coronary artery disease (CAD).
- FFR is a highly useful adjunctive modality in guiding decision making within the catheterization lab for common angiographic dilemmas, including side-branch stenoses, left main CAD, or multivessel disease.
- At this time, indices obtained without coronary hyperemia are under investigation to increase use of in-lab physiologic lesion assessment, and outcome studies are in progress.

The goal of PCI is the relief of ischemia and restoration of coronary blood flow. The treatment of coronary stenosis with stenting improves exercise tolerance, reduces antiischemic medications, and improves survival in patients with ST-elevation myocardial infarction (STEMI). However, in patients with stable CAD, stent placement is of no benefit if the angiographic stenoses are not responsible for ischemia.

The rationale for physiologic lesion assessment is simple: for lesions of intermediate severity, the angiogram cannot be relied on exclusively to direct coronary revascularization.[1] Coronary angiography produces two-dimensional (2-D) luminograms, a silhouette image of the three-dimensional (3-D) vascular lumen in a given projection. Angiography does not truly identify atherosclerosis, a disease within the vessel wall, but instead provides a "shadow" without intraluminal details sufficient to characterize a plaque. Furthermore, the eccentric shapes of plaques do not permit the observer to determine whether such an opening is limiting coronary blood flow. The accurate identification of both "normal" and "diseased" vessel segments by angiography further complicates the determination of a lesion's significance in the setting of diffuse CAD, which cannot easily be seen on an angiogram. Angiographic artifacts that include contrast streaming, branch overlap, vessel foreshortening, calcifications, and ostial origins further make the interpretation of some luminal narrowings unreliable. Despite numerous attempts to improve the angiographic imaging of complex anatomy, the angiographer is still confronted by a visual dilemma in which no single view or multiple views can provide an answer. Moreover, even sophisticated imaging modalities such as densitometry, rotational angiography, and computed tomography angiography (CTA) with 3-D reconstruction (without the computational fluid-dynamic addition of FFR computed tomography [FFR-CT]) do not reliably reflect the physiologic significance of a given lesion.[2]

FUNDAMENTAL CONCEPTS OF CORONARY BLOOD FLOW

Coronary blood flow can increase from a resting level to a maximum (i.e., coronary reserve), depending on increases in myocardial oxygen demand or in response to neurogenic or pharmacologic hyperemic stimuli. Normally, large epicardial vessel resistance to blood flow is negligible. Most of the regulation of coronary flow occurs in the myocardial precapillary arteriolar resistance vessels. In a normal adult artery that supplies normal myocardium, coronary blood flow can increase more than threefold. However, several conditions—including left ventricular hypertrophy, myocardial ischemia, and diabetes—can affect the microcirculation, blunting the maximal absolute increase in coronary flow or increasing resting flow above the expected level for myocardial oxygen demand at rest. The regulation of coronary vasomotor tone and the influence of several mechanisms such as α-adrenoreceptor–mediated vasoconstriction have been extensively reviewed elsewhere and are beyond the scope of this chapter.[3] A significant atherosclerotic stenosis produces epicardial conduit resistance and, depending on flow, loss of distal pressure. In response to the loss of perfusion pressure and flow to the distal (poststenotic) vascular bed, the small resistance vessels dilate to maintain satisfactory basal flow appropriate for myocardial oxygen demand. Viscous friction, flow separation forces, and turbulence at the site of the stenosis produce energy loss at the stenosis (Fig. 5-1). Energy (heat) is extracted, which reduces pressure distal to the stenosis and thereby produces a pressure gradient between the proximal and distal arterial regions. The pressure loss or pressure gradient increases with increasing coronary flow in a curvilinear manner.[4] An absolute poststenotic myocardial perfusion pressure threshold exists, below which myocardial ischemia may be easily induced.

Coronary Flow and Flow Reserve

As the severity of an epicardial stenosis increases, maximal coronary flow becomes attenuated, and coronary flow reserve (CFR) decreases. CFR, the ratio of maximal to basal arterial flow, is a combined measure of the capacity of the major resistance components—the epicardial coronary artery and the supplied vascular bed—to achieve maximal blood flow in response to hyperemic stimulation. Although there is no true "normal CFR," a higher CFR implies that both epicardial and microvascular bed resistances are low (i.e., normally low resistance; Fig. 5-2). However, a lower CFR (<2.0) does not indicate which component is affected, a fact that limits the clinical applicability of this measurement for lesion assessment. Although early studies in animals and humans indicated an absolute "normal" range for CFR of 3.5 to 5, the CFR in adult patients undergoing cardiac catheterization with chest pain syndromes and CAD risk factors with "angiographically normal" vessels was 2.7 (SD ± 0.6), suggesting a degree of patient variability and microvascular disease.

CFR may be reduced in patients with normal coronary arteries and either essential hypertension or aortic stenosis, in part related to

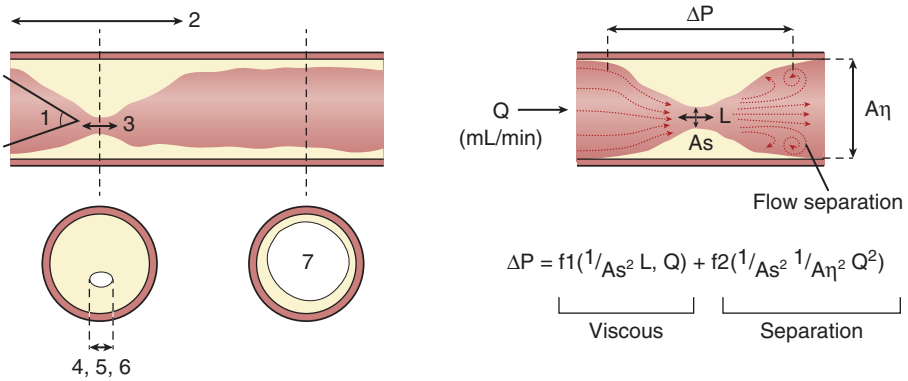


FIGURE 5-1 *Left:* Diagram of coronary stenosis showing seven factors that produce resistance to flow: (1) entrance angle; (2) diseased segment length; (3) stenosis length; (4-6) shape factors of lumen area (minimum lumen diameter, minimum lumen area, eccentricity of stenosis); and (7) area of reference vessel. *Right:* Total pressure loss across a stenosis is derived from two sources: the frictional losses along the leading edge of the stenosis and the inertial losses stemming from the sudden expansion, which causes flow separation and eddies (exit losses). *Frictional losses* are linearly related to flow by Poiseuille's law, and *inertial losses* (exit losses) increase with the square of the flow (Bernoulli's law). The total change in pressure gradient (ΔP) is the sum of the two: the loss coefficients, *f1* and *f2,* are functions of stenosis geometry and rheologic properties of blood (viscosity and density). The graphic representation of this equation results in a quadratic relationship, in which the curvilinear shape demonstrates the presence of nonlinear exit losses. If no stenosis is present, the second term is zero, and the curve becomes a straight line (with a positive slope that depends on the diameter of the vessel, based on Poiseuille's law). *Aη,* Area of the normal segment; *As,* area of the stenosis; *L,* length; *Q,* flow. (Redrawn from Kern MJ, Samady H: Current concepts of integrated coronary physiology in the catheterization laboratory. *J Am Coll Cardiol* 55(3):173-185, 2010.)

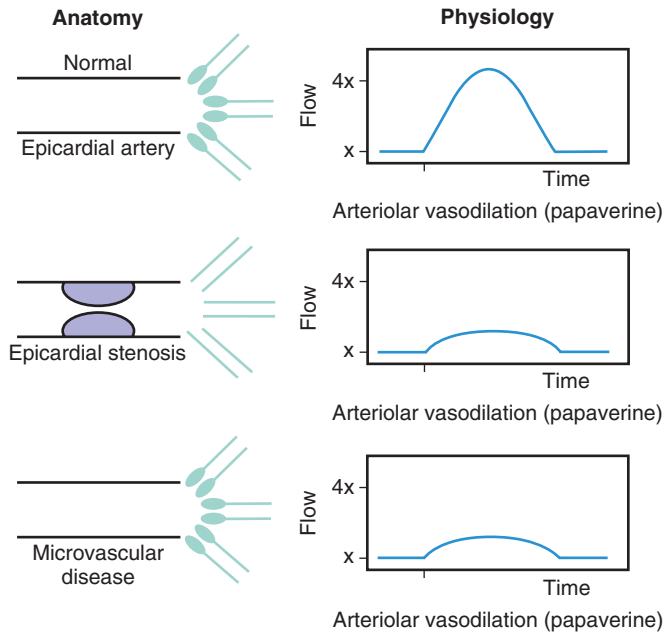


FIGURE 5-2 Schematic representation of coronary flow reserve findings. *Top panel:* A normal artery without any epicardial stenosis or microvascular disease demonstrates the ability to significantly increase coronary flow when a hyperemic agent is given. *Middle panel:* An artery with significant epicardial stenosis that blunts the ability to increase flow over baseline. *Bottom panel:* The same finding of an artery unable to increase its flow rate. However, the reason in this case is not epicardial stenosis but severe microvascular disease. (Redrawn from Wilson RF, Lascon DD: A clinician's guide to assessing the physiologic significance of arterial stenoses. *Cathet Cardiovasc Diagn* 29:93-98, 1993.)

myocardial hypertrophy and an abnormal microvasculature. Furthermore, CFR can be altered by changes in basal and hyperemic flows, both of which are influenced by hemodynamics, loading conditions, and contractility. For example, tachycardia increases basal flow and decreases hyperemic flow, thus reducing CFR by 10% for each 15-beat increase in heart rate. In clinical terms, CFR is best used to assess the microcirculation in the absence of epicardial artery narrowings.

Intracoronary Pressure Measurements and Fractional Flow Reserve

As the limitations of invasive CFR were recognized, the development of pressure-sensor guidewires yielded a new concept of lesion assessment. As is the case from the earlier discussion regarding coronary flow, resistance to blood flow in a normal epicardial coronary artery is negligible, with virtually no energy loss as blood traverses the vessel. The aortic pressure thus remains constant throughout the conduit—including all branch vessels, regardless of their size—in the absence of epicardial disease. In the case of epicardial coronary narrowing, the resistance to flow and associated energy loss results in a pressure drop and is proportional to flow. To maintain resting myocardial perfusion at a constant level, a decrease in myocardial resistance compensates for any resistance of flow caused by the epicardial narrowing. The pressure ratio between normal and poststenotic pressure at constant maximal flow can represent an index of the physiologic consequences of a given coronary narrowing on the myocardium. Pressure measurements, made across a lesion during maximal hyperemia, are termed the *myocardial fractional flow reserve*, a concept introduced in 1993 by Pijls and colleagues.[5] FFR is the ratio of the maximal myocardial blood flow in the presence of a stenosis relative to expected normal flow in the absence of a stenosis, and it can be expressed as a fraction of its normal expected value if there were no lesion. Derived from pressure data alone for the myocardium, FFR measurement is based on several assumptions regarding translesional pressure measured during maximal hyperemia.[6] The proposed equations have been derived from a theoretic model of the coronary circulation and have been validated experimentally in instrumented dogs, and later in humans, by comparison with myocardial flow measured by positron emission tomography (PET).[7] During maximal hyperemia (induced pharmacologically),

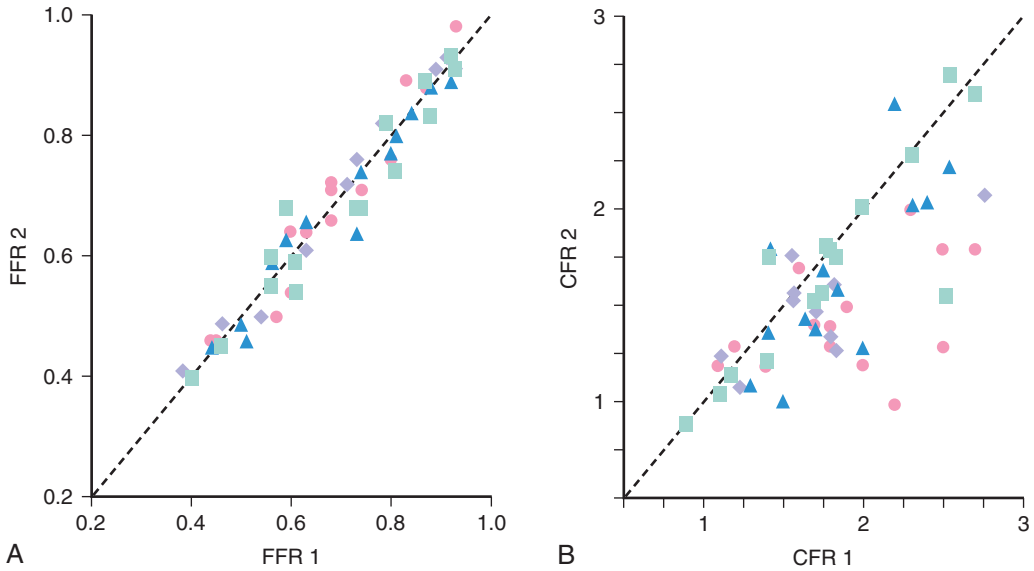


FIGURE 5-3 **A,** Reproducibility of fractional flow reserve (FFR) by serial measurements in a multicenter study of 325 patients in whom FFR was measured twice within a 10-minute interval. **B,** Reproducibility of coronary flow reserve (CFR) in the same patients. *Blue boxes* represent baseline conditions. *Violet diamonds* represent changes in blood pressure induced by infusion of nitroprusside. *Blue triangles* represent changes in heart rate induced by pacing. *Pink circles* represent changes in contractility induced by infusion of dobutamine. Despite variations in heart rate of 40%, blood pressure of 35%, and contractility of 50%, FFR but not CFR was unaffected by these changes. (Data from De Bruyne B, Bartunek J, Sys SU, et al: Simultaneous coronary pressure and flow velocity measurements in humans: feasibility, reproducibility and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index and fractional flow reserve. *Circulation* 94:1842-1849, 1996.)

coronary resistance is at the lowest level and remains constant, so that flow is directly related to the measured pressure. The total myocardial blood flow (Qn) in an area served by a coronary artery with a stenosis is the sum of the flow through the stenosis (Qs) and the collateral flow (Qc). *Fractional flow reserve* is then simply defined as the ratio of the measured flow (Qs) to the maximal flow that should be present without any stenosis (Qn):

$$Qs = (Pd - Pv) \div R$$

and

$$Qn = (Pa - Pv) \div R$$

where *Pd* is distal coronary pressure, *Pa* is aortic pressure, *Pv* is venous pressure (or right atrial pressure), and *R* is resistance of the myocardial vascular bed. In this model, *Pv* is assumed to be negligible hence

$$FFR = Qs \div Qn = [(Pd - Pv) \div R] \div [(Pa - Pv) \div R]$$

Given maximal hyperemia, resistance becomes constant and "near zero" in both the numerator and denominator, thus

$$FFR = Pd \div Pa \text{ when measured at hyperemia.}$$

FFR can thus be estimated as the ratio of the mean distal coronary blood pressure to the mean aortic blood pressure. Because each myocardial territory serves as its own control, FFR is a lesion-specific index. Furthermore, because FFR is measured only at maximal hyperemia, it is independent of microcirculation, heart rate, blood pressure, and other hemodynamic variables.

Unlike most other physiologic indexes, FFR has a normal value of 1.0 for every patient and every coronary artery. FFR has high reproducibility and low intraindividual variability (Fig. 5-3). Moreover, unlike CFR, FFR is independent of sex or CAD risk factors, such as hypertension and diabetes, and has less variability with common doses of adenosine. De Bruyne and associates[8] demonstrated that in humans, FFR is independent of hemodynamic conditions. Changes in heart rate affected by pacing, changes in contractility affected by dobutamine infusion, and changes in blood pressure affected by nitroprusside infusion did not alter FFR. The coefficient of variation between two consecutive measurements was 4.2%, which is lower than the 17.7% for CFR measured with a Doppler wire.

METHODOLOGY OF CORONARY PRESSURE MEASUREMENT

General Setup and Guidewire Manipulation

The measurement of coronary pressure is similar to performing an angioplasty in that a sensor guidewire is passed through an angioplasty Y-connector attached to a guiding catheter, with anticoagulation (intravenous [IV] heparin) given beforehand. To minimize measurement variability caused by vessel spasm, intracoronary (IC) nitroglycerin (100 to 200 μg) is given before the guidewire is advanced into the artery. For coronary pressure measurements, a guidewire with a pressure sensor can be utilized to measure distal coronary pressure (St. Jude Medical, Minneapolis, MN; Volcano Therapeutics, Rancho Cordova, CA). The angioplasty sensor guidewires have mechanical properties close to standard "workhorse" guidewires and have a pressure sensor located 3 cm from the tip, at the junction of the radiopaque and radiolucent portions of the wire. The wire tip can be shaped to facilitate delivery to the distal vessel. Recently, a novel 0.022″ pressure-sensing monorail microcatheter (the Navvus microcatheter from ACIST Medical Systems, Eden Prairie, MN) has been made available to measure distal coronary pressure over any 0.014″ standard guidewire of the operator's choice. The microcatheter has a pressure sensor associated with a marker that sends its signal via a fiberoptic pathway to the table-mounted analyzer (Fig. 5-4, *C*).

All currently available systems have an "auto zero" feature that activates when the guidewire/catheter is connected to the analyzer. This signal should be zeroed against the "zero" from the guiding catheter transducer. The sensor is then introduced and positioned at the tip of the guiding catheter, where the guiding catheter and wire pressures are equalized (or normalized)—a step that electronically assimilates both pressure signals so that they are identical. Next, the sensor

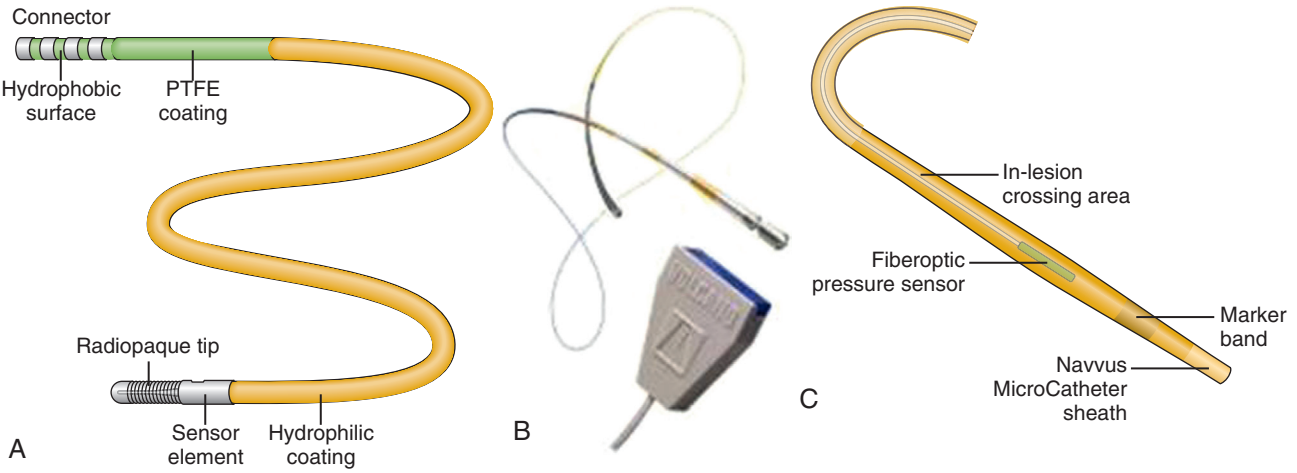


FIGURE 5-4 **A,** Certus wire from St Jude Medical. **B,** Volcano Verrata Wire. **C,** Acist Navvus microcatheter. *PTFE,* Polytetrafluoroethylene.

is advanced down the vessel and across the stenosis (or to the most distal part of the coronary artery for assessment of serial lesions or diffuse disease). A pharmacologic hyperemic stimulus (e.g., adenosine, discussed later) is then administered through the guiding catheter, or it can be given by IV infusion. The mean and phasic pressure signals are continuously recorded, and at peak hyperemia—represented by the steady-state nadir, or lowest, distal pressure once stable-hyperemia is reached—the FFR is calculated as noted earlier (Fig. 5-5).

To study the distribution of abnormalities along a diseased coronary artery (with serial lesions or diffuse disease), the pressure sensor can be pulled back slowly during intravenously induced hyperemia. Simultaneously observing the location of the wire by fluoroscopy and the pressure tracings can pinpoint the location of hemodynamically significant atherosclerotic abnormalities. On pulling back the pressure sensor in a vessel with diffuse but not focal obstructions, gradual pressure recovery along the course of the vessel can be observed. In contrast, a vessel with a focal stenosis will demonstrate an abrupt increase in pressure proximal to the lesion. By moving the sensor back and forth, the exact location of a pressure drop, representing a focal obstruction to flow, can be determined. FFR is often measured using 6-French guiding catheters, but 5-French guides and diagnostic catheters as small as 4 French have been successfully used. In general, the smaller the lumen of the catheter, the greater care the operator must take at flushing the catheter to optimally achieve an accurate aortic pressure signal (Pa). As with any technique in the catheterization lab, attention to detail is required to reduce inaccuracies in the measurement of FFR. A more complete description of the application and nuances of coronary pressure measurements can be found elsewhere.[9]

Safety of Intracoronary Sensor Wire Measurements

Qian and coworkers[10] examined the safety of IC Doppler wire measurements in 906 patients. Of these, 15 patients (1.7%) had severe transient bradycardia after administration of IC adenosine, 14 in the right coronary artery (RCA) and 1 in the left coronary artery (LCA). Nine patients (1%) had coronary spasm during passage of the Doppler guidewire, five in the RCA and four in the left anterior descending (LAD) coronary artery. Two patients (0.2%) had ventricular fibrillation (VF) during the procedure. Hypotension with bradycardia and ventricular asystole occurred in one patient. Transplant recipients had more of these complications than did patients undergoing either diagnostic or interventional procedures. All complications were easily managed, and no long-term adverse consequences were observed. These data support the safe clinical practice of sensor-wire measurements with IC adenosine.

Pharmacologic Hyperemic Stimuli

Maximal coronary hyperemia is required for in-lab coronary physiologic lesion assessment (Table 5-1). The most widely used maximal vasodilator agent at this time is adenosine. Hyperosmolar ionic and low-osmolar nonionic contrast media do not produce maximal vasodilation. Nitrates increase volumetric flow, but because these agents also dilate the epicardial conductance vessels, the increase in coronary flow velocity is less than with adenosine or papaverine. IC nitroprusside has similar hyperemic effects compared with IC adenosine. Papaverine is no longer used for IC hyperemic stimulation because of the occasional Q-T interval prolongation and associated ventricular tachycardia (VT) or VF.

Adenosine

A principal advantage of adenosine is that it has a short half-life, with a return to basal flow within 30 to 60 seconds after cessation of infusion. Adenosine is benign in a wide range of dosages (IC and IV). Typically, IV adenosine will result in about a 10% drop in mean arterial pressure (MAP) and may be accompanied by symptoms of chest burning. IC adenosine down the dominant coronary artery will result in atrioventricular (AV) block at high enough doses that it will result in a significant, although transient, decline in MAP.

IV adenosine has the advantages of simplicity and weight-adjusted dosing (140 µg/kg/min) and is required for the evaluation of ostial lesions or for the assessment of diffuse disease during pull-back recordings. IV administration, however, tends to have a higher incidence of side effects such as flushing, chest tightness, bronchospasm, nausea, and transient AV block or bradycardia compared with IC dosing. It should also be noted that all the validation studies utilizing IV adenosine administered this infusion through a central vein. Administration through a peripheral vein may be accompanied by a long latent period before the onset of hyperemia without a clear-cut stability of the hyperemic phase.

IC adenosine appears to be equivalent to IV infusion for determination of FFR in most patients. Jeremias and colleagues[11] examined differences in FFR between IC adenosine (15 to 20 µg in the RCA or 18 to 24 µg in the LCA) and IV adenosine (140 µg/kg/min) in 52 patients with 60 lesions and found a strong linear relationship between IC and IV adenosine (regression coefficient [r] = 0.978, $P <$ .001). The mean measurement difference for FFR was 0.004 (SD ± 0.03). A small random scatter in both directions of FFR was noted in 8.3% of stenoses, where the IC adenosine FFR value was 0.05 greater than the IV adenosine FFR value, suggesting a suboptimal IC hyperemic response for which a repeated, higher IC adenosine dose may be helpful. Changes in heart rate and blood pressure were significantly greater with IV adenosine. Two patients with IV adenosine, but none

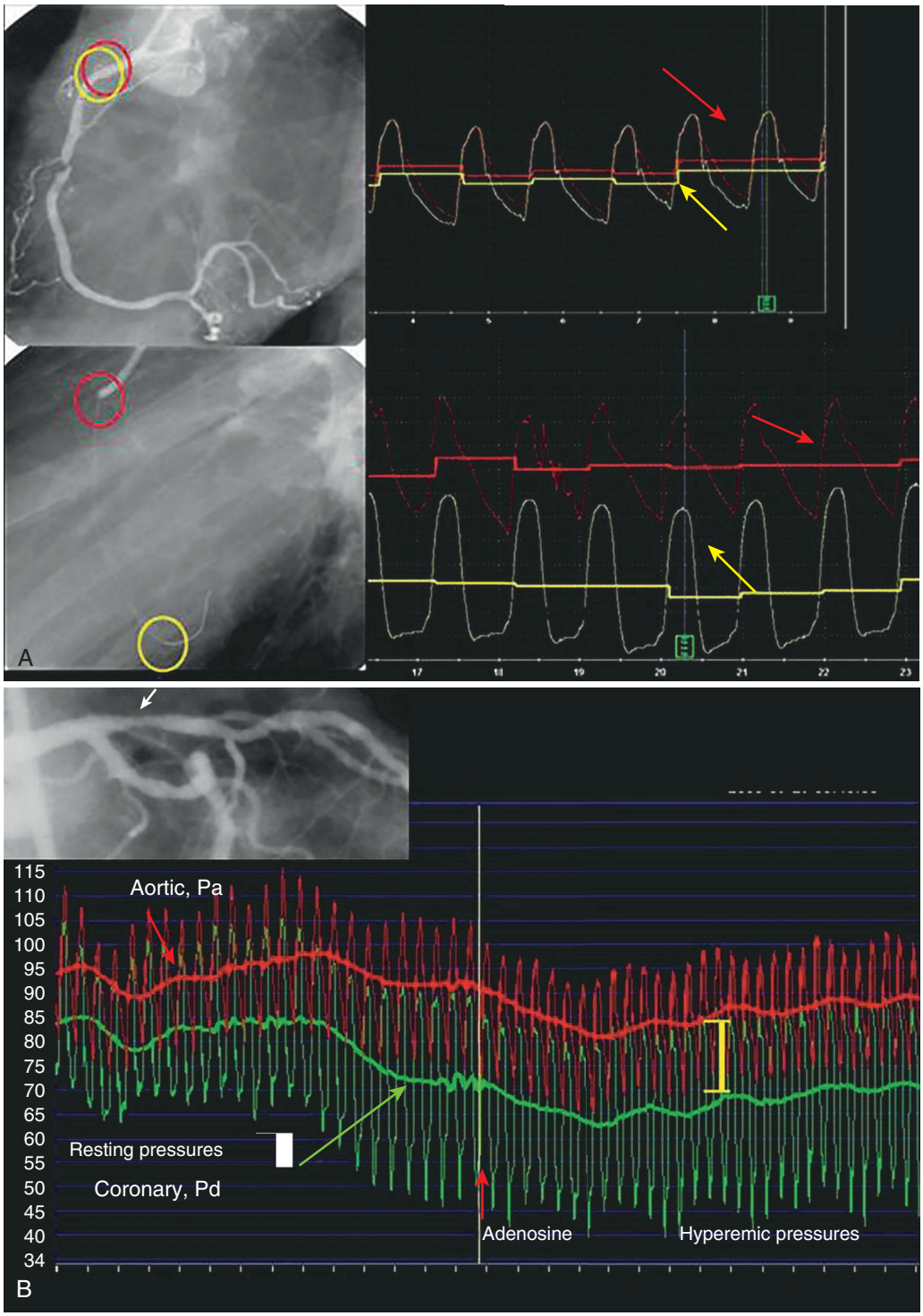


FIGURE 5-5 **A,** *Top:* The guidewire sensor and guide catheter (*red and yellow circles*) are shown in the proximal right coronary artery with corresponding pressures depicted on the right, showing "equalization" of pressures. *Bottom:* The guidewire has been advanced across the right coronary artery lesion and now is in the distal vessel with corresponding pressure loss as depicted on the right. **B,** Fractional flow reserve (FFR) measurement across a proximal left anterior descending coronary artery lesion. The *red* pressure tracing is aortic guide catheter pressure, and the *green* tracing is coronary wire pressure. Adenosine is started, and the tracings from right to left reflect the changes over time. At the *yellow bar,* which reflects the lowest distal coronary pressure divided by aortic pressure (Pd/Pa) at steady state, the FFR is computed. FFR = Pd/Pa, or 65/90 (0.72).

with IC adenosine, had side effects such as bronchospasm and nausea. Despite these doses being correlated with hyperemic effects of IV adenosine, many operators use IC doses that are significantly greater to ensure maximal hyperemia is achieved.

Regadenoson

Regadenson is a low-affinity α-2A adenosine receptor agonist that causes coronary vasodilation and increased myocardial blood flow and has been reported to be equivalent to adenosine. It selectively targets

TABLE 5-1 Pharmacologic Characteristics of Agents Used for Induction of Hyperemia

Drug	Dose	Plateau (sec)	Half-Life (min)	Side Effects	Comments
Papaverine IC	15 mg LCA 10 mg RCA	30-60	2	Transient Q-T interval prolongation, torsades de pointes	Rarely used
Adenosine IV	140 µg/kg/min	60-120	1-2	Decreased blood pressure (10% to 15%), chest burning	Avoid in patients with history of bronchospasm
Adenosine IC	50-120 µg LCA 30-60 µg RCA	5-10	0.5-1	Transient AV block when injected into the dominant artery	Must repeat with escalating doses to ensure that maximal hyperemia is reached
Dobutamine IV	20-40 µg/kg/min	60-120	3-5	Tachycardia, increase in blood pressure	May induce ischemia
Nitroprusside IC	0.3-0.9 µg/kg	20	1	Decreased blood pressure (20%)	
Regadenoson IV	0.4 mg	30	2-4*	Tachycardia	Exact length of hyperemia and ability to repeat bolus not studied in the cardiac catheterization lab for FFR

*Half-life is triphasic, with second phase lasting ~30 mins and third phase lasting ~2 hrs.
AV, Atrioventricular; *FFR,* fractional flow reserve; *IC,* intracoronary; *IV,* intravenous; *LCA,* left coronary artery; *RCA,* right coronary artery.

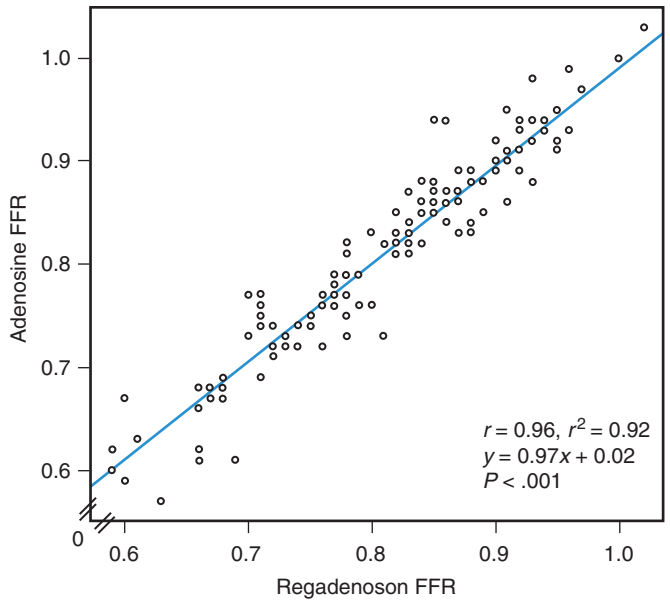


FIGURE 5-6 Linear regression analysis of intrapatient fractional flow reserve (FFR) measured with an intravenous (IV) adenosine infusion and IV regadenoson bolus. (From Stolker JM, Guzman L, Zenni MM, et al: TCT-626 comparison of intravenous adenosine infusion and regadenoson bolus for calculating fractional flow reserve: results of a pooled analysis. *J Am Coll Cardiol* 62[18 S1]:B190, 2013.)

the α-2A receptor in coronary arteries and therefore has fewer adverse effects compared with adenosine. Regadenoson has a longer half-life of 2 to 3 minutes in the initial phase, 30 minutes in the intermediate phase, and 2 hours in the terminal phase, and it may prove to be easier to use. With a single infusion bolus of regadenoson (0.4 mg), maximum coronary hyperemia is achieved and maintained equivalent to that achieved with a constant infusion of adenosine. However, questions regarding the amount of time that hyperemia persists after this bolus and whether a similar hyperemic effect can be achieved with a second bolus demand further investigation. At this time, regadenoson is a useful agent for simple measurement of FFR (Fig. 5-6).[12-14]

Dobutamine

Bartunek and associates[15] examined FFR in response to IC adenosine and IV dobutamine (10 to 40 µg/kg/min) in 22 patients with single-vessel CAD. Peak dobutamine infusion produced similar distal coronary pressures and pressure ratios (Pd/Pa, 60 ± 18 and 59 ± 18 mm Hg; FFR, 0.68 ± 0.18 and 0.68 ± 0.17, respectively; all P = not significant [NS]). An additional bolus of IC adenosine given at peak dobutamine in nine patients failed to change the FFR. As shown by angiography, high-dose IV dobutamine did not modify the area of the epicardial stenosis and, much like adenosine, it fully exhausted myocardial resistance regardless of inducible left ventricular dysfunction.

Sodium Nitroprusside

IC nitroprusside may be an alternative to IC adenosine. Parham and associates[16] examined coronary blood flow velocity, heart rate, and blood pressure in unobstructed LAD arteries in 21 patients at rest, after IC adenosine (boluses of 30 to 50 µg), and after three serial doses of IC nitroprusside (boluses of 0.3, 0.6, and 0.9 µg/kg). IC nitroprusside produced equivalent coronary hyperemia with a longer duration (~25%) compared with IC adenosine. IC nitroprusside (0.9 µg/kg) decreased systolic blood pressure by 20% with minimal change in heart rate, whereas IC adenosine had no effect on these parameters. FFR measurements with IC nitroprusside were identical to those obtained with IC adenosine (r = 0.97). In doses commonly used for the treatment of the no-reflow phenomenon, IC nitroprusside can produce sustained coronary hyperemia without detrimental systemic hemodynamics. Sodium nitroprusside also appears to be a suitable hyperemic stimulus for coronary physiologic measurements.

Clinical Validation of Intracoronary Pressure Measurements

To define the threshold of FFR below which inducible ischemia is present, Pijls and colleagues[6] and De Bruyne and colleagues[17] conducted independent but parallel and complementary investigations. Pijls' group studied 60 patients accepted for single-vessel percutaneous transluminal coronary angioplasty (PTCA) who had a positive (abnormal or ischemic) exercise test in the preceding 24 hours. FFR was measured before and 15 minutes after PTCA, and the exercise test was repeated after 1 week. If the second exercise test had reverted to normal after PTCA, FFR values were associated with inducible ischemia. All except two FFR measurements greater than 0.74 were not associated with ischemia, and all FFR measurements of 0.74 or less were related to inducible ischemia. In normal coronary arteries, FFR was 0.98 (SD ± 0.03). De Bruyne's group studied FFR in 60 patients who each had one isolated lesion in one major coronary artery and a maximal exercise test 6 hours before catheterization. ST-segment depression was compared with FFR, APV_{max} (average peak velocity at maximal hyperemia), and APV_{rest}. Intersections of sensitivity and specificity curves were at 87%, 83%, and 75%, respectively, for FFR of 0.66, $ÄPV_{max}$ of 31 mm Hg, and $ÄPV_{rest}$ of 12 mm Hg. No abnormal test was present for FFR greater than 0.72. FFR has also been compared with the results of dobutamine echocardiography in 75 patients with normal left

ventricular function and single-vessel CAD; the degree of dobutamine-induced dyssynergy correlated significantly with the quantitative coronary angiography (QCA) data, but the correlation was markedly better with FFR. All but one patient with an FFR greater than 0.75 had a normal stress test result.

Among the most important validations of FFR is that of Pijls and colleagues,[18] who compared FFR with the unique ischemic standard of common noninvasive testing modalities in 45 patients with moderate coronary stenoses and chest pain syndromes. When the FFR was less than 0.75 (21 patients), reversible myocardial ischemia was demonstrated unequivocally on at least one noninvasive test (bicycle exercise testing, thallium scintigraphy, stress echocardiography with dobutamine), and all these positive test results were reversed after PTCA or coronary artery bypass grafting (CABG). In 21 of 24 patients with an FFR greater than 0.75, all of the tests showed no demonstration of ischemia, and no revascularization procedure was performed. Importantly, no revascularization was required after 14 months of follow-up. The sensitivity of FFR in the identification of reversible ischemia was 88%, the specificity was 100%, the positive predictive value (PPV) was 100%, the negative predictive value (NPV) was 88%, and the accuracy was 93%.

Fractional Flow Reserve and Myocardial Perfusion Imaging

Magnetic resonance (MR) myocardial perfusion imaging (MPI) with IV adenosine (140 µg/kg/min) and a first-pass 0.1 mmol/kg gadolinium bolus has been shown to correlate well with FFR in detecting reversible ischemia. When tested against an FFR less than 0.75 in 103 patients with angina (300 coronary artery segments), MRMPI had a high sensitivity (91%), specificity (94%), PPV (91%), and NPV (94%) for detecting functionally significant coronary heart disease.[19]

PET-CT MPI shows poor concordance with FFR in identifying ischemic territories. In a study of 67 patients (201 vascular territories) with angiographic two-vessel or three-vessel coronary disease, PET-CT and FFR detected identical ischemic territories in only 42% of patients. In the remaining patients, PET-CT tended to significantly underestimate or overestimate the number of ischemic regions compared with FFR.[20]

Managing conflicting data when noninvasive stress imaging, such as nuclear perfusion imaging, and FFR produce different results creates uncertainty in the mind of the interventionalist. In such cases, the operator must reevaluate his or her level of confidence in the accuracy of both test modalities. For nuclear perfusion imaging, a number of common conditions can produce false-positive and false-negative results. For FFR, certain rare situations produce false-positive results and almost none produce false-negative results. As recommended by the American College of Cardiology (ACC)/American Hospital Association (AHA)/ Society for Cardiovascular Angiography and Interventions (SCAI) guidelines, use of FFR is a class III indication when the clinical scenario, angiogram, and ischemic test are concordant. Otherwise, the FFR serves to alleviate uncertainty when the clinical and testing data are at odds with one another. If the operator—for whatever reason—elects to use FFR, this decision should be based on FFR's ability to precisely define the ischemic potential of a stenosis in question.

Table 5-2 summarizes the comparison between ischemic stress testing and coronary physiologic measurements.

Fractional Flow Reserve and Angiography

Multiple studies have shown only a modest correlation between angiographic severity and FFR. In the largest study to date, Toth and associates[21] reported on over 4000 intermediate lesions in which a slight yet statistically significant correlation was found between percent diameter stenosis as measured by QCA and FFR, with an r value of 0.38 ($P <$ .001). A 50% or greater diameter stenosis had mediocre overall sensitivity (61%), specificity (67%), and diagnostic accuracy (64%) for predicting an FFR of less than 0.80. Using a stenosis diameter of 70% or greater, the measure became highly specific (98%) but poorly sensitive

TABLE 5-2 Summary of Correlation Between Noninvasive Stress Test Results and Physiologic Measurements

Index	Ischemic Test	N	BCV	Accuracy (%)
FFR	SPECT	763	0.74-0.78	75-95
	DSE	58	0.67-0.75	90
CFR	SPECT	704	1.7-2	75-92
	DSE	58	2	87-88
rCFR	SPECT	260	0.64-0.75	75-92
	DSE	28	0.75	81

BCV, Best cut-off value (defined as the value with the highest sum of sensitivity and specificity); *CFR,* coronary flow reserve; *DSE,* dobutamine stress echocardiography; *FFR,* fractional flow reserve; *N,* number of patients; *rCFR,* relative coronary flow reserve; *SPECT,* single photon emission tomography.

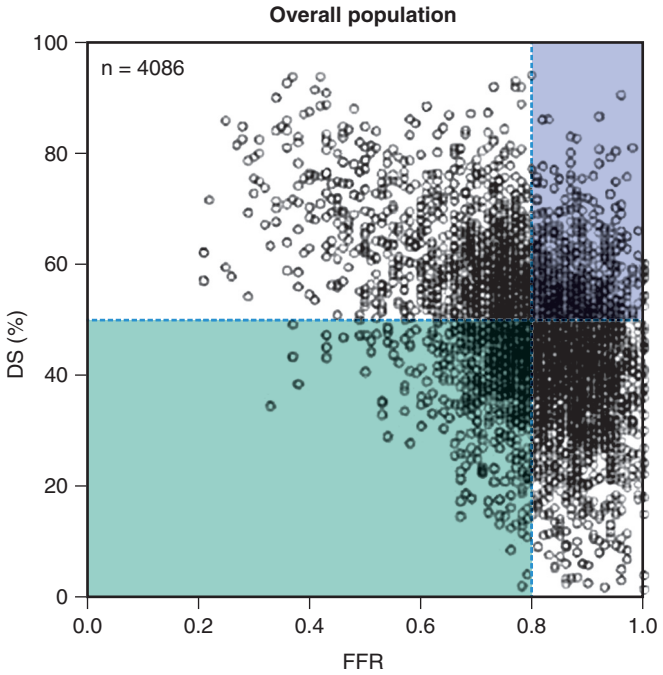


FIGURE 5-7 Correlation between percent diameter stenosis (DS) and fractional flow reserve (FFR). (Toth G, Hamilos M, Pyxaras S, et al: Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. *Eur Heart J* 35[40]:2831-2838, 2014.)

(13%), with a net decrease in the overall diagnostic accuracy for detecting functionally significant lesions. Their data also showed that the optimal diagnostic threshold of stenosis diameter was markedly lower in coronary segments that supply a larger myocardial area because FFR depends to some extent on the downstream mass. In particular, left main stenoses were often underestimated by the classical 50% diameter cutoff compared with FFR (Fig. 5-7).

Intracoronary Physiologic Measurements, Intravascular Ultrasound, and Optical Coherence Tomography Measurements

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) offer a high degree of anatomic detail that can aid the operator in making clinical decisions. The cross-sectional lumen area measured by these techniques (i.e., minimal luminal area [MLA]) has been proposed as a surrogate measurement of the functional significance of a given stenosis. However, in clinical practice, the anatomic measurements are more complementary than they are similar to FFR because FFR is a physiologic assessment, whereas IVUS and OCT are tools to measure vessel anatomy and lesion morphology. IVUS and OCT are

highly accurate for vessel sizing and for confirming stent expansion and strut apposition.

A study to compare IVUS, QCA, and FFR in 42 patients with 51 stenoses also demonstrated that QCA alone was not accurate in determining physiologic lesion significance assessed by either IVUS or FFR.[22] A correlation was found between IVUS minimal lumen area (MLA) less than 3 mm^2 and stenosis cross-sectional area (CSA) greater than 60% with a measured FFR less than 0.75 (IVUS sensitivity 83%, specificity 92%). Several IVUS studies have compared FFR with IVUS measurements, for example, MLA. Takagi and colleagues[23] found that most MLA values less than 4 mm^2 were associated with an FFR of less than 0.75, although several patients had a nonischemic FFR. The reason for this variance is that resistance to flow is based on various anatomic factors (entrance angle, length, MLA, eccentricity), of which MLA is only one. A 4-mm^2 MLA may limit flow in a large proximal vessel segment but will not impair flow in a smaller segment of the same artery. For assessment of the left main coronary artery (LMCA), unlike FFR, the IVUS threshold of "treat" or "do not treat" changes. Various IVUS MLAs have been reported to be the cut-off value, ranging from 5.9 to 7 mm^2 for treatment decisions.[24] Most IVUS thresholds are derived from clinical outcomes, with different areas from different studies. The poor correlation between MLA and FFR can be understood from a review of the factors that produce pressure loss across a stenosis. The loss of pressure across a stenosis can be computed from the two factors that produce the resistance to flow, viscous friction (factor 1 is coefficient of friction; factor 2 is coefficient of flow separation), and the energy loss in the coefficient of flow separation and reconstitution to laminar flow. Factor 1 (*f1*) is not only proportional to the inverse of the cross-sectional area squared but also directly proportional to the length of the narrowing:

$$\Delta P = \underbrace{f_1(1/As^2\ \ell, Q)}_{\text{Viscous}} + \underbrace{f_2(1/As^2\ 1/A\eta^2\ Q^2)}_{\text{Separation}}$$

where *P* is the pressure drop across a stenosis, *As* is the minimal cross-sectional stenosis area (MCSa), and *Q* is blood flow (velocity) through the tube. Unlike IVUS, FFR represents the net myocardial blood flow across the stenosis supplying the specific myocardial bed. For example, a 70% stenosis in a vessel subtending a small diagonal or a previously infarcted midanterior descending territory will have less physiologic impact compared with an identical lesion in a midanterior descending territory subtending a normal anterior wall region because of the significantly higher flow requirements. Thus it is not uncommon to encounter a visual-functional mismatch, wherein the angiography or IVUS measurements do not correspond with the FFR and the clinician's impression of lesion significance; also, the use of IVUS to determine lesion significance has not been shown to have a strong correlation with FFR or perfusion imaging.

Furthermore, the recent Fractional Flow Reserve and Intravascular Ultrasound Relationship Study (FIRST) demonstrated that using IVUS-MLA to guide intervention in intermediate lesions by calculation of the MLA was limited in accuracy (64% sensitivity and specificity) and highly variable based on reference vessel characteristics.[25] Previous work has varied greatly when defining an MLA that denotes functional significance, and currently the routine use of IVUS in place of FFR is not recommended.[26] Johnson and coworkers[27] summarize the results of 25 IVUS or OCT imaging studies correlated to FFR and note that the best cut-off value (BCV) for MLA ranged from 1.8 mm^2 to 4.0 mm^2 (excluding the left main BCVs of 4.8 to 5.9 mm^2) with areas under the curve ranging from 0.63 to 0.90. However, although it is true that MLA greater than 4 mm^2 had an FFR greater than 0.8 in 91% of cases with a strong negative correlation, an MLA less than 4 mm^2 had poor correlation to FFR, with most studies reporting a roughly 50% chance of having an FFR less than 0.8 (Figs. 5-8 and 5-9).[28]

Given these caveats, operators should gain confidence in the higher-resolution anatomic data derived from modalities such as IVUS and OCT while utilizing FFR (as discussed below) to determine the physiologic significance of a given epicardial coronary stenosis and guide treatment decision making.

OPTICAL COHERENCE TOMOGRAPHY AND INTRAVASCULAR ULTRASOUND IMAGES WITH FFR

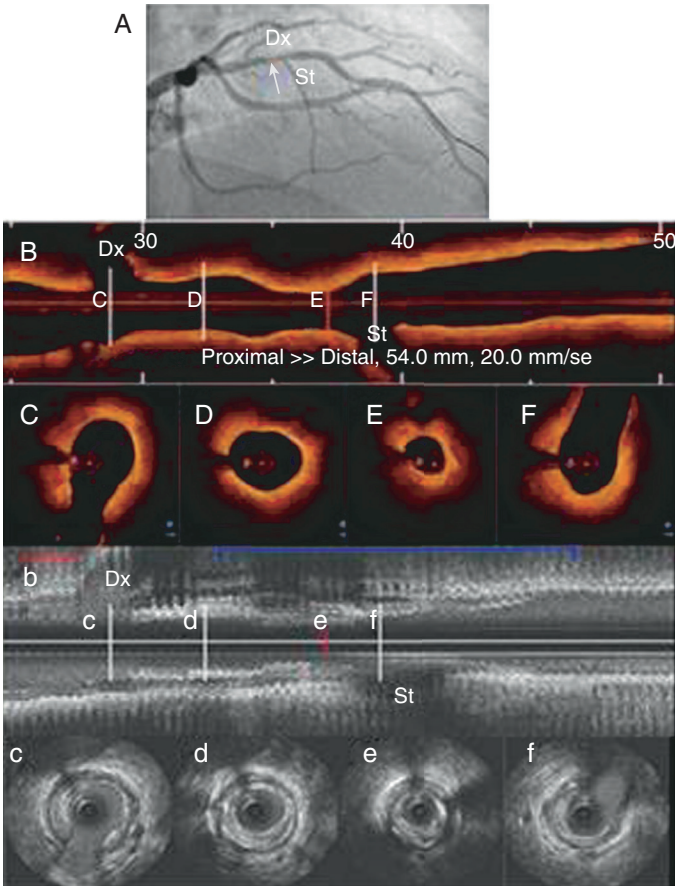


FIGURE 5-8 Matching of optical coherence tomography (OCT) and intravascular ultrasound (IVUS) pullbacks. **A,** Angiographic view shows an intermediate stenosis in the mid–left anterior descending coronary artery (*yellow arrow*). Distal to the lesion is a septal branch (St), proximal to the lesion is a diagonal branch (Dx). **B,** Longitudinal OCT and IVUS reconstructions show the two side branches (St and Dx) and the stenosis. Corresponding cross-sectional OCT and IVUS images: **C,** Diagonal branch; **D,** Reference cross section; **E,** Minimum luminal area; **F,** Septal branch. FFR, fractional flow reserve. (From Gonzalo N, Escaned J, Alfonso F, et al: Morphometric assessment of coronary stenosis relevance with optical coherence tomography: a comparison with fractional flow reserve and intravascular ultrasound. *J Am Coll Cardiol* 59[12]:1080-1089, 2012.)

CLINICAL OUTCOMES WITH FRACTIONAL FLOW RESERVE–GUIDED PERCUTANEOUS CORONARY INTERVENTION

Three prospective randomized trials have demonstrated the safety and efficacy of using FFR to guide PCI, and these form the basis of the evidence that supports incorporating FFR into daily use in the catheterization lab. The first was Fractional Flow Reserve to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis called the DEFER study (DEFER) trial,[29] which randomized 325 patients with stable ischemic heart disease and an intermediate angiographic lesion. FFR was performed on all the lesions in question; those with an FFR less than 0.75 were treated with PCI and those with an FFR of 0.75 or greater were eligible for randomization to either PCI or medical therapy (i.e., deferral of angioplasty). The patients who received PCI

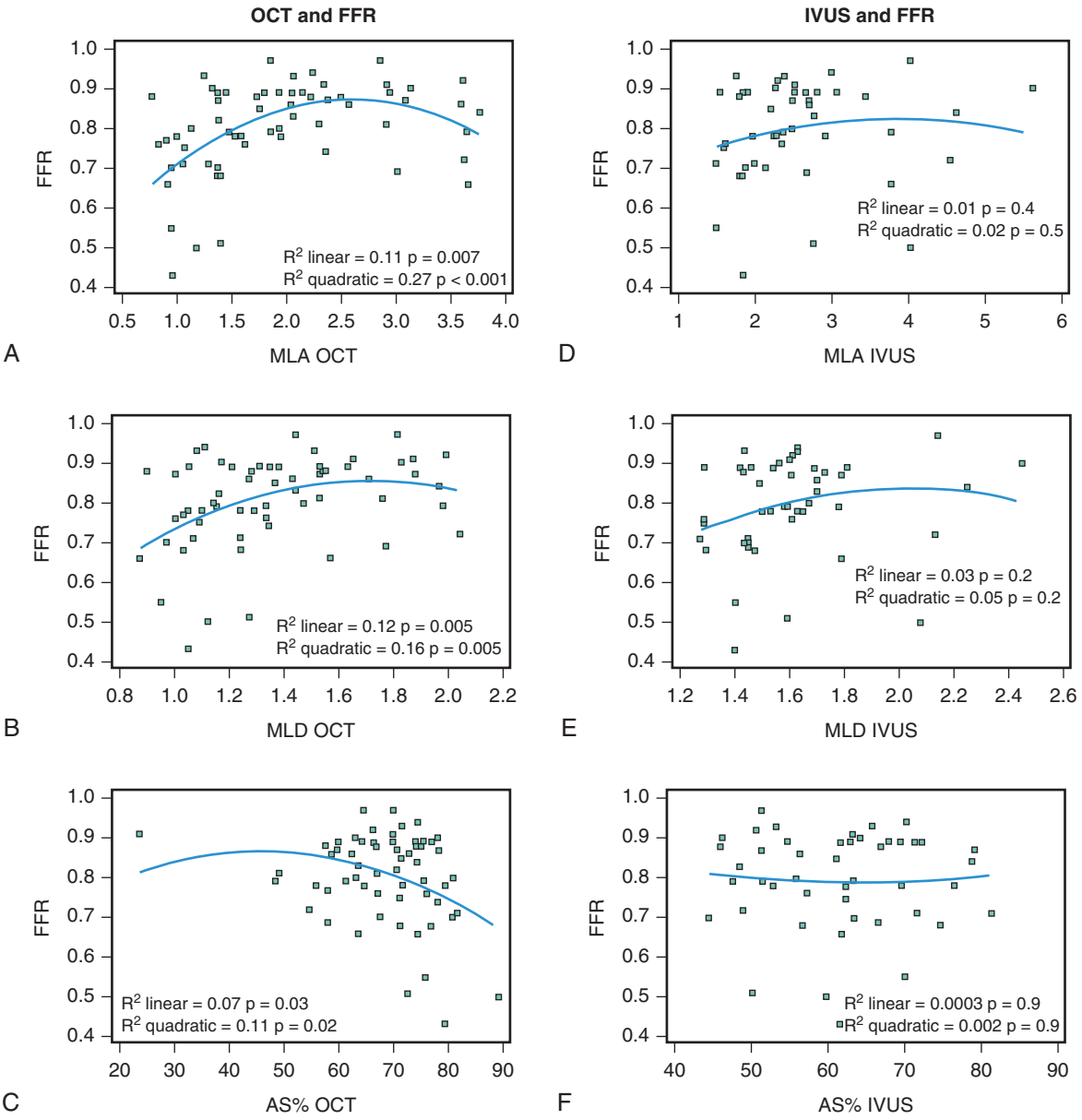


FIGURE 5-9 Relation between FFR and OCT and IVUS measurements. **A** to **C,** Fractional flow reserve (FFR) and optical coherence tomography (OCT) measurements. **D** to **F,** FFR and intravascular ultrasound (IVUS) measurements. *AS%,* Percent area stenosis; *IVUS,* intravascular ultrasound; *MLA,* minimum lumen area; *MLD,* minimum lumen diameter; *OCT,* optical coherence tomography. (From Gonzalo N, Escaned J, Alfonso F, et al: Morphometric assessment of coronary stenosis relevance with optical coherence tomography: a comparison with fractional flow reserve and intravascular ultrasound. *J Am Coll Cardiol* 59[12]:1080-1089, 2012.)

for an FFR less than 0.75 comprised a reference group, and all patients were followed for 5 years. Outcomes are shown in Figure 5-10.

The Fractional Flow Reserve Versus Angiography for Guiding Coronary Intervention (FAME) trial[30] was a prospective randomized trial that enrolled 1005 patients with multivessel CAD (at least two vessels with a 50% angiographic stenosis). Patients were randomized to a strategy of revascularization: the angiographically guided group had a drug-eluting stent placed in all prospectively identified lesions, and the FFR-guided group had a drug-eluting stent placed in only those lesions that produced an FFR of less than 0.80. The primary end point was a combined end point of death, nonfatal myocardial infarction (MI), and repeat revascularization at 1 year. Outcomes are shown in Figure 5-11.

The Fractional Flow Reserve–Guided PCI Versus Medical Therapy in Stable Coronary Disease (FAME 2) trial[31] enrolled 1220 patients with angiographic disease in one, two, or three vessels that was suitable for PCI. After performing FFR, all patients with lesions that had an FFR less than 0.80 were randomized to either receive PCI or medical therapy. A composite of death from any cause, nonfatal MI, or unplanned hospitalization leading to urgent revascularization during a 2-year follow-up was the primary end point. Outcomes are shown in Figure 5-12.

The following is a discussion of the major findings from these trials.

Deferring Percutaneous Coronary Intervention for Nonsignificant Fractional Flow Reserve

From the DEFER study, we learned that at 5 years, the risk of death or MI was no different between the deferred and treated (performed)

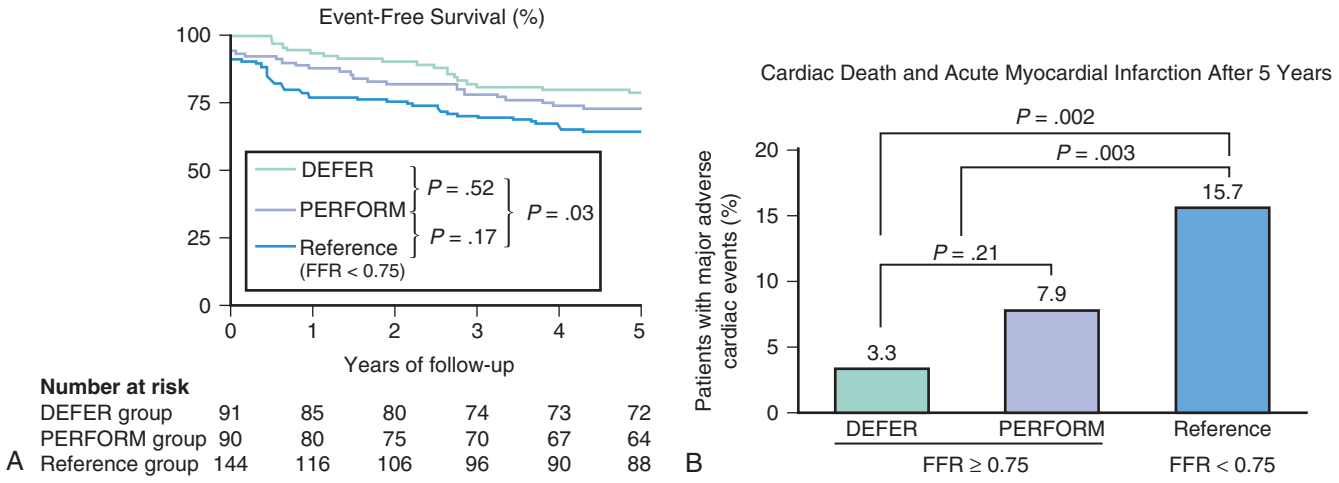


FIGURE 5-10 Graphs showing the 5-year results from the DEFER trial. **A,** Kaplan-Meyer freedom from events for three treatment groups. **B,** Overall event rates for the three groups. The y-axis depicts the percentage of patients with major adverse cardiac events (MACEs): death, myocardial infarction, coronary artery bypass surgery, or percutaneous coronary intervention. The DEFER group ($n = 91$) consisted of those patients found to have an intermediate coronary stenosis in which the measured fractional flow reserve (FFR) was greater than 0.75, and no angioplasty was performed (MACE = 20%). The PERFORM group ($n = 90$) consisted of those patients with an intermediate coronary stenosis with FFR values greater than 0.75 in whom angioplasty was performed (MACE = 28%). The reference group ($n = 144$) comprised patients whose lesions had measured FFR values less than 0.75 in whom angioplasty was performed (MACE = 37%). (From Pijls NH, van Schaardenburgh P, Manoharan G, et al: Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol* 49(21):2105-2111, 2007.)

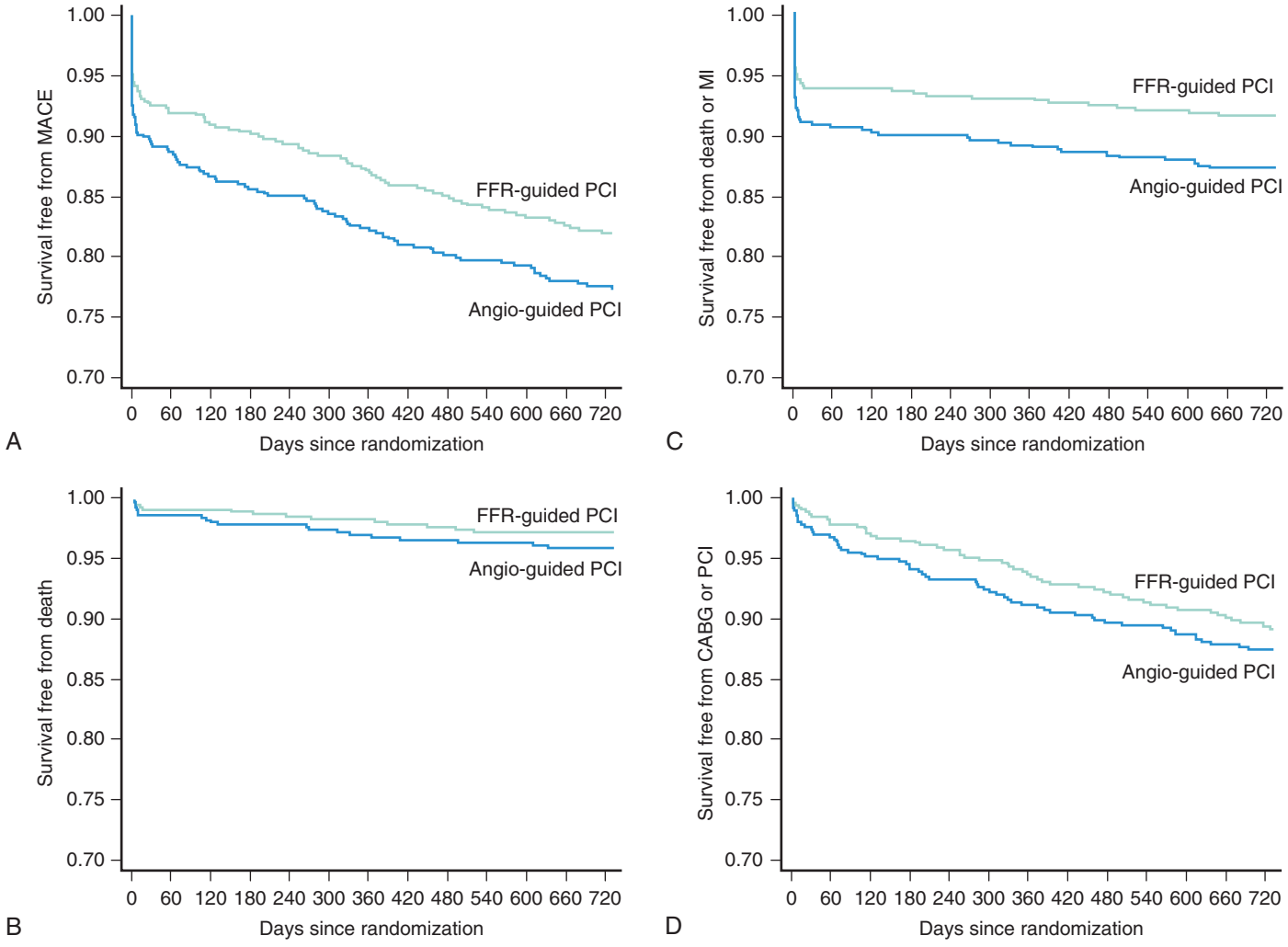


FIGURE 5-11 Two-year Kaplan-Meier curves show individual and combined outcomes of the patients from the FAME trial. **A,** Freedom from major adverse cardiac events (MACEs). **B,** Overall survival. **C,** Freedom from death or myocardial infarction (MI). **D,** Freedom from revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). FFR, fractional flow reserve. (From Tonino PA, De Bruyne B, Pijls NH, et al: Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Eng J Med* 360[3]:213-224, 2009.)

groups (3.3% vs. 7.9%).[29] Furthermore, the end point was much more frequently encountered in the group with the significant FFR and subsequent revascularization (15.7%), suggesting that lesions with an FFR of 0.75 or greater had a very good 5-year prognosis that was not improved with PCI. Specifically, in the group with deferred revascularization, three cardiac deaths and no MIs were reported over the course of the 5-year follow-up, and in the group that received PCI (despite an FFR > 0.75), two cardiac deaths and six MIs were reported during the same period.

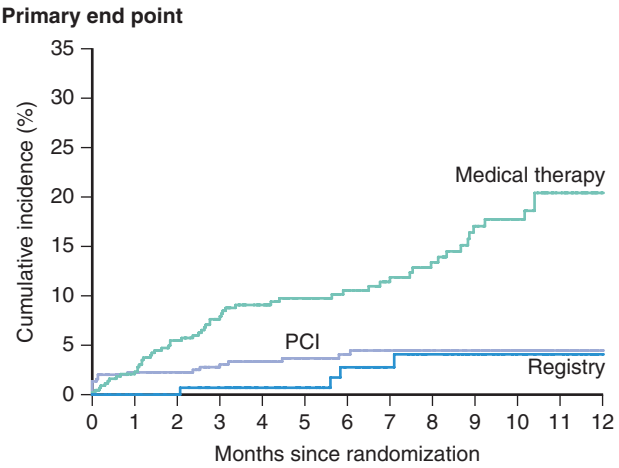


FIGURE 5-12 FAME 2 asked the question, Is optimal medical therapy (OMT) better than percutaneous coronary intervention (PCI) plus OMT for patients with abnormal fractional flow reserve (FFR; i.e., ischemia)? Kaplan-Meier curves for FAME 2 patients show that medical therapy had a more than tenfold incidence of major adverse cardiac events (MACEs) compared with the PCI group, which was similar to the nonischemic registry group. (From De Bruyne B, Pijls NH, Kalesan B, et al: Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 367[11]:991-1001, 2012.)

In a more complex group of patients with multivessel lesions, in the FAME trial, there were 513 lesions with an FFR greater than 0.80 (i.e., deferred PCI) in 509 patients. In a 2-year follow-up, nine late MIs were reported, of which eight were related to either a stent in another lesion or a new lesion, and thus a 0.2% rate of late MI was reported in FFR-negative lesions that did not receive a stent. Furthermore, of those same 513 lesions in 509 patients, 53 repeat revascularizations were reported. However, 37 of those involved restenosis in a stent or a new lesion. This left only 10 lesions that had clearly progressed over the 2 years needing revascularization—a rate of 2%.

Finally, the FAME 2 trial had a registry arm that consisted of those lesions that had FFR values greater than 0.80. These patients had a low rate of the primary end point of death (0), MI (1.8%), or urgent revascularization (2.4%) throughout the follow-up period. This group represents one of the most recent randomized cohorts with no PCI and "modern" medical therapy, but it still reproduces consistent findings compared with patients enrolled in the DEFER trial in the late 1990s.

Taken together, these data strongly support the hypothesis that lesions in patients with stable CAD whose FFR is nonphysiologically significant (i.e., >0.80) have an exceptionally good prognosis without PCI, and the recommendation is that these lesions receive treatment with OMT alone.

Percutaneous Coronary Intervention Versus Medical Therapy for Significant Fractional Flow Reserve

FAME 2 studied 764 lesions with an angiographic stenosis of greater than 50% that had a corresponding FFR less than 0.80 (mean of 0.68 ± 0.15). Within this cohort were 3 deaths (0.7%), 14 MIs (3.2%), and 49 urgent revascularization (11.1%) end points. In the corresponding group that received revascularization for these FFR-significant lesions, only 1 death occurred (0.2%), 15 MIs were reported (3.4%), and 7 patients needed urgent revascularization (1.6%). A landmark analysis (Fig. 5-13) suggested a higher rate of acute coronary syndromes (ACSs) in the medical-therapy arm starting 1 week after randomization. These data strongly suggest that lesions with abnormal FFR values do not have the good long-term prognosis that those with normal FFR values have and that PCI of these lesions significantly improves patient outcomes.

End point	PCI	Medical therapy	Relative risk (95% CI)	*P* value	*P* value for interaction
	Number of events/total number (%)				
Primary end point					< .001
≤7 days	9/447 (2.0)	4/441 (0.9)	2.24 (0.69–7.31)	0.17	
8 days to maximum follow-up	10/427 (2.3)	52/428 (12.2)	0.17 (0.09–0.35)	< .001	
Death or myocardial infarction					0.003
≤7 days	8/447 (1.8)	1/441 (0.2)	7.99 (0.99–64.57)	0.04	
8 days to maximum follow-up	7/428 (1.6)	16/431 (3.7)	0.42 (0.17–1.04)	0.053	
Death					—
≤7 days	0/447	0/441			
8 days to maximum follow-up	1/436 (0.2)	3/432 (0.7)	0.33 (0.03–3.17)	0.37	
Myocardial infarction					0.007
≤7 days	8/447 (1.8)	1/441 (0.2)	7.99 (0.99–64.57)	0.04	
8 days to maximum follow-up	7/428 (1.6)	13/431 (3.0)	0.52 (0.21–1.32)	0.16	
Urgent revascularization					0.09
≤7 days	2/447 (0.5)	4/441 (0.9)	0.49 (0.09–2.70)	0.45	
8 days to maximum follow-up	5/434 (1.2)	45/428 (10.5)	0.10 (0.04–0.26)	< .001	

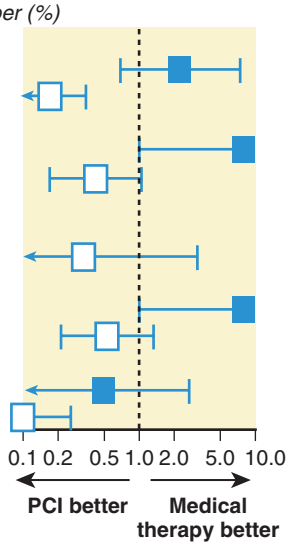


FIGURE 5-13 Landmark analysis of FAME 2 outcomes shows outcomes of lesions with fractional flow reserve (FFR) less than 0.80 over time. *CI,* Confidence interval; *PCI,* percutaneous coronary intervention. (From De Bruyne B, Pijls NH, Kalesan B, et al: Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 367[11]:991-1001, 2012.)

Fractional Flow Reserve in Daily Clinical Practice

FFR optimizes the benefit of PCI by providing objective evidence of coronary ischemia for individual coronary lesions that require revascularization irrespective of each operator's threshold to revascularization by visual assessment. It is best used when decisions regarding the need for PCI are ambiguous based on the angiogram and available noninvasive data (i.e., intermediate angiographic stenosis). FFR is especially useful when noninvasive testing is absent, equivocal, or does not provide objective evidence of ischemia in the myocardial segment subtended by the targeted lesion.

Studies have shown that routine use of FFR, even in those considered angiographically unambiguous, frequently leads to changes in the number and location of lesions that are functionally significant, and therefore it directs the clinician to what the appropriate treatment should be. In an analysis of the FAME trial, lesions with 50% to 70% diameter narrowing were hemodynamically significant based on FFR in only 35% of cases. In lesions with 71% to 90% narrowing, for which most operators would perform PCI, 20% were not hemodynamically significant by FFR. In two recently published studies of patients undergoing diagnostic angiography with routine FFR, clinicians were led to change their initial angiography-guided management decisions of medical therapy, PCI, or CABG in 26%[32] and 43%[33] of patients after taking the FFR data into consideration. Van Belle and coworkers[32] found that the 1-year rate of major adverse cardiac events (MACEs) for those whose final FFR-based treatment had differed from the a priori angiography-based decision was as good (11.2%) as in patients in whom the FFR concurred with the a priori decision (11.9%, $P = .78$). In the prospective study by Curzen and colleagues[33] in which *all* patent coronary arteries had FFR measured, not just those with angiographic lesions, the number and localization of functional stenoses changed in 32% of patients. Van Belle et al (Fig. 5-14) also show changes in strategy when FFR is used after angiography for decision making.

Multivessel Coronary Artery Disease and Coronary Artery Bypass Grafting Implications

Although the surgical practice of grafting all vessels with angiographic stenosis of greater than 50% has been a long-standing standard, CABG of vessels with hemodynamically insignificant stenosis have a higher rate of graft closure compared with those vessels with severe stenoses. This was shown by Botman and colleagues[34], who prospectively studied 525 lesions in 153 patients referred for bypass surgery on clinical grounds. FFR was performed on all lesions to be grafted, and the surgeon was blinded to the results. Repeat angiogram was performed 1 year after CABG, and at this early time, 21.4% of grafts on functionally insignificant lesions (FFR > 0.75) were occluded, compared with 8.9% of grafts on vessels with an FFR less than 0.75. As shown in Figure 5-15, the rate of graft closure correlated with functional severity of the lesion. Although the highest percentage of occluded grafts was found in the group placed on vessels with less than 50% stenosis, a high percentage of graft failure was still seen in the group with 50% to 70% stenosis. Thus FFR-guided bypass is a reasonable strategy to predict bypass graft patency and has superiority over the strategy of grafting all vessels with lesions with 50% or more stenosis.

In a prospective study of 150 patients with multivessel disease referred for CABG, FFR was performed on all vessels considered for bypass. If FFR proved functionally significant (FFR < 0.75) disease in three vessels or in two vessels with proximal LAD involvement, CABG was performed. Otherwise, patients underwent FFR-guided PCI. Ultimately, only 58% of patients underwent CABG and 42% received PCI. After a 2-year follow-up, no difference was found in event-free survival, including repeat revascularization, which shows that an individually tailored approach to patients with multivessel disease can be accomplished by determining the hemodynamic significance of each lesion.[35]

FFR-guided bypass was compared with angiography-guided bypass surgery in a retrospective review of 627 patients with stable CAD referred for CABG with at least one angiographically intermediate stenosis. In 31% of patients, FFR had been performed to determine whether an intermediate stenosis should be grafted or not.[36] In this group, the incidence of three-vessel disease was downgraded after FFR from 94% to 86%, and use of FFR was associated with a smaller number of anastomoses and rates of on-pump surgery. At 3 years, no difference in adverse events was found compared with those patients who underwent angiography-guided CABG, and the rate of angina was lower in the FFR group (31% vs. 47%, $P < .001$), possibly owing to a higher ratio of arterial-venous anastomosis (Fig. 5-16).

Whereas the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score has become incorporated into everyday practice as a useful tool to assist the

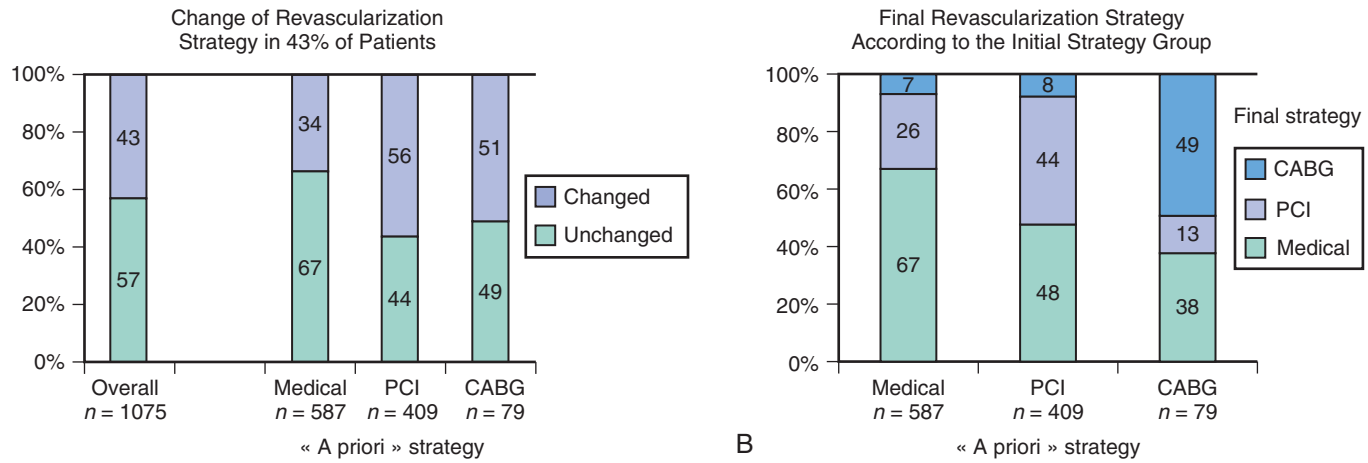


FIGURE 5-14 Outcome impact of coronary revascularization strategy reclassification with fractional flow reserve (FFR) at time of diagnostic angiography: insights from a large French multicenter FFR registry. **A,** Reclassification of the revascularization strategy according to the revascularization strategy a priori. Despite minor overall changes, a change in strategy has been observed in 43% of all patients (correlation statistic [κ], 0.22; 95% confidence interval, 0.17 to 0.27). **B,** Details of the final revascularization strategy applied in each group a priori. *CABG,* Coronary artery bypass surgery; *PCI,* percutaneous coronary intervention. (From Van Belle E, Rioufol G, Pouillot C, et al: Outcome impact of coronary revascularization strategy reclassification with fractional flow reserve at time of diagnostic angiography: insights from a large French multicenter fractional flow reserve registry. *Circulation* 129[2]:173-185, 2014.)

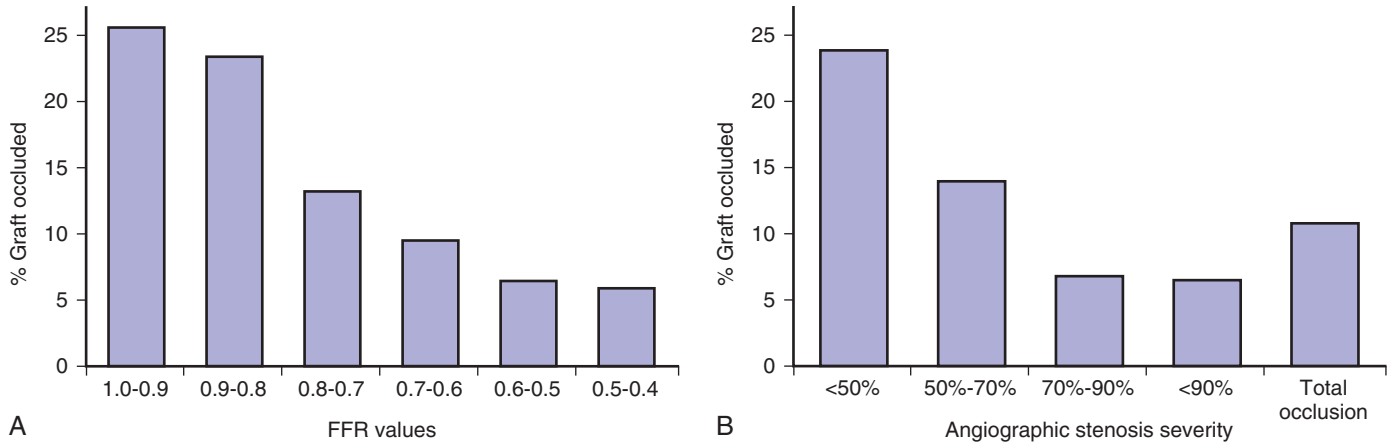


FIGURE 5-15 **A,** The relation between functional stenosis severity established by fractional flow reserve (FFR) measurements and graft failure at angiographic follow-up after 1 year. **B,** The relation between angiographic stenosis severity prior to bypass grafting and graft failure after angiographic follow-up at 1 year. (From Botman CJ, Schonberger J, Koolen S, et al: Does stenosis severity of native vessels influence bypass graft patency? A prospective fractional flow reserve-guided study. *Ann Thorac Surg* 83[6]:2093-2097, 2007.)

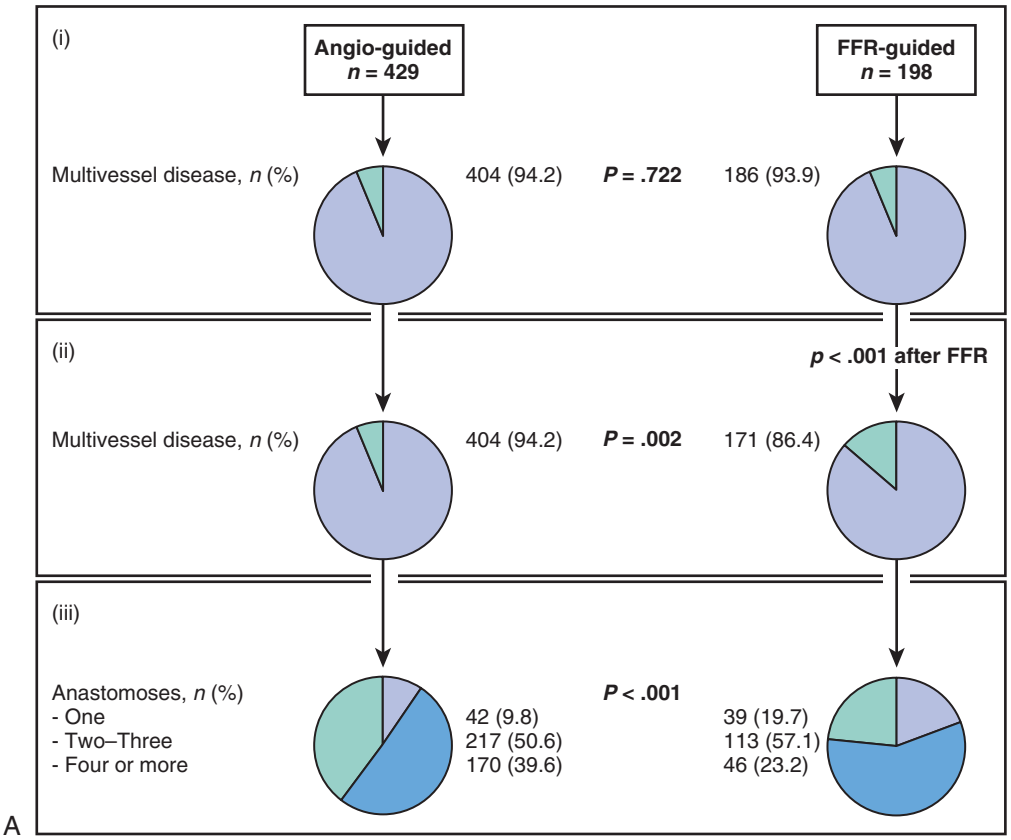
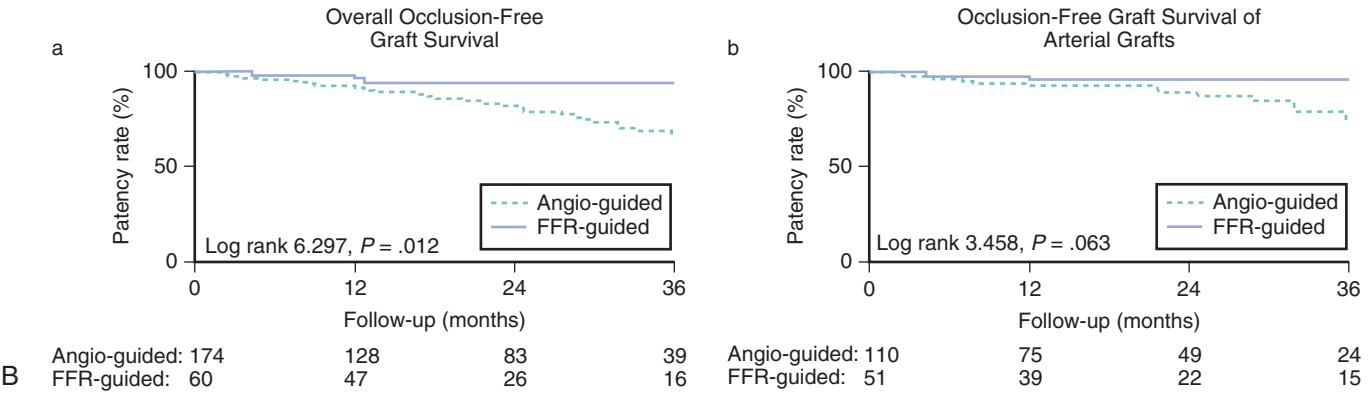


FIGURE 5-16 **A,** Fractional flow reserve (FFR)–guided versus angiography (Angio)-guided coronary artery bypass graft surgery. Rates of patients with multivessel disease before (i) and after (ii) FFR measurement and rates of patients with one, two to three, and four or more anastomoses (iii) are shown. **B,** Occlusion-free survival of grafts with angiographic follow-up: occlusion-free survival of *all* grafts are shown in panel *a* (log rank, 6.297; P = .012); arterial grafts *only* are shown in panel *b* (log rank, 3.45; *P* = .063). (Toth G, De Bruyne B, Casselman F, et al: Fractional flow reserve–guided versus angiography-guided coronary artery bypass graft surgery. *Circulation* 128[13]:1405-1411, 2013.)



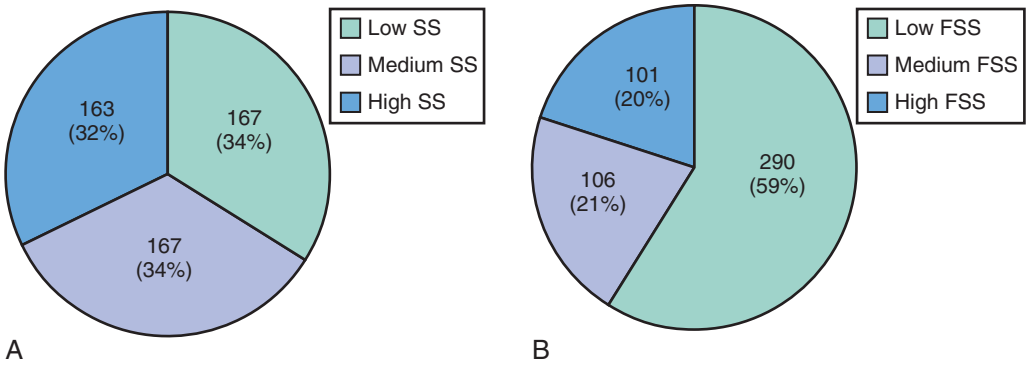


FIGURE 5-17 **A,** Percentage of patients from the FAME trial with corresponding SYNTAX scores based upon "traditional" angiographic SYNTAX score assessment. **B,** When those lesions with a fractional flow reserve (FFR) greater than 0.80 were excluded from the calculations, a marked change was noted in the distribution of SYNTAX scoring with a marked increase in the number of patients in the lowest tertile and a corresponding decrease in the number of patients in the medium and high tertiles. *FSS,* Functional syntax score; *SS,* syntax score. (Modified from Nam CW, Mangiacapra F, Entjes R, et al: Functional SYNTAX score for risk assessment in multivessel coronary artery disease. *J Am Coll Cardiol* 58(12):1211-1218, 2011.)

decision making of how best to revascularize patients with multivessel disease, it remains solely dependent on angiographic determinants of coronary lesions. When the SYNTAX score was applied to those patients in the FAME trial, 497 patients were divided into tertiles based on their angiographic SYNTAX score (34% in the low-risk SYNTAX score group, 34% in the intermediate-risk SYNTAX score group, and 32% in the high-risk SYNTAX score group). When the functional data were then added to the SYNTAX score, lesions that had an FFR greater than 0.80 were no longer considered. This allowed a significant reclassification of patients to the same risk tertiles, with 59% of them now falling into the lowest-risk SYNTAX score group, 21% in the intermediate-risk group, and only 20% in the highest-risk group (Fig. 5-17).[37]

Taken together, these studies strongly support the utilization of routine measurement of FFR in patients with multivessel disease to provide optimal outcomes, best revascularization strategies, and best decision making.

Cost-Effectiveness of a Routine Fractional Flow Reserve–Based Strategy

Measurement of FFR for any given coronary stenosis increases the utilization of materials within the lab. As costs for individual procedures becomes more important in the modern era, additive costs for a guide catheter, pressure wire/sensor, and pharmacologic stimuli for hyperemia may be a burden. Utilizing a computer modeling algorithm that compared evaluating intermediate coronary lesions with nuclear stress testing, stenting, or FFR assessment, Fearon and associates[38] found that FFR was less expensive than either of the other strategies ($1795 less than nuclear stress testing and $3830 less than stenting). Leesar and colleagues[39] evaluated the cost-effectiveness of utilizing FFR in patients with unstable angina compared with a nuclear stress-testing strategy and found that an FFR strategy for these patients resulted in overall lower costs. Finally, using the FAME trial, an extensive economic evaluation was performed in a prospective manner.[40] In the patients with multivessel coronary disease, the FFR-guided revascularization strategy not only improved patient outcomes but also resulted in a significant decrease in resource utilization (Fig. 5-18). Thus FFR has consistently been shown to be a cost-effective strategy despite its increase in up-front expenses within the lab.

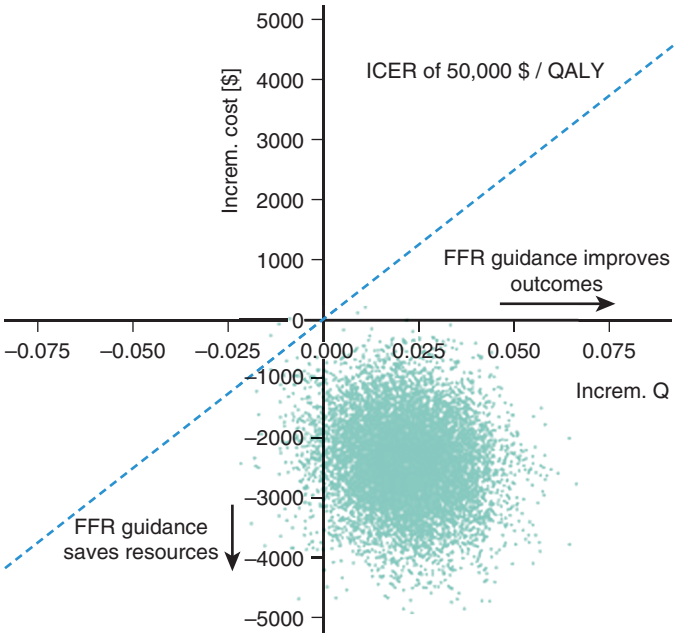


FIGURE 5-18 Cost-effectiveness of fractional flow reserve (FFR). The graph shows the improvement of patient-level outcomes on the x-axis and the costs on the y-axis. Each point represents a patient from the FAME trial; almost all points fall into the lower right quadrant, which reflects an improved outcome at a lower cost with FFR-guided multivessel revascularization as opposed to an angiographically guided strategy. *ICER,* Incremental cost-effectiveness ratio; *Increm.,* incremental; *Q,* quality; *QALY,* quality adjusted life years.

Left Main Coronary Artery Disease

LMCA stenosis maybe among the most difficult angiographic subsets to interpret and carries the most significant clinical impact on the patient's life. LMCA stenosis may involve the aortic-ostial junction, midbody, or distal LMCA, which may involve the LAD or circumflex (CFX) ostium. From a technical perspective, when assessing ostial LM narrowings, FFR can be used if the operator works to avoid guide catheter damping by disengaging the guide from the ostium, using IV rather than IC adenosine to achieve consistent hyperemia. Specifically, before the guiding catheter is seated, the guiding catheter and wire pressures should be matched (equalized) within the ascending aorta. Next, the guiding catheter is seated, and the pressure wire is advanced

TABLE 5-3 Left Main Coronary Artery Revascularization Outcomes and Fractional Flow Reserve

First Author	N			FFR Cutoff Value	FU Mean Duration (Months)	OVERALL SURVIVAL	
	Total	DEFER Group	Surgical Group			DEFER Group (%)	Surgical Group (%)
Bech[46]	54	24	30	0.75	29 ± 15	100	97
Jasti[47]	51	37	14	0.75	25 ± 11	100	100
Jimenez-Navarro[48]	27	20	7	0.75	26 ± 12	100	86
Legutko[49]	38	20	18	0.75	24 ± 12	100	89
Suemaru[50]	15	8	7	0.75	33 ± 10	100	100
Lindstaedt[51]	51	24	27	0.75	29 ± 16	100	81
Hamilos[41]	213	138	75	0.80	35 ± 12	90	86
Total (or mean)	449	271	178	–	28 ± 13	95*	89

From Puri R, Kapadia SR, Nicholls SJ, et al: Optimizing outcomes during left main percutaneous coronary intervention with intravascular ultrasound and fractional flow reserve the current state of evidence. *J Am Coll Cardiol Interv* 5:697-707, 2012.
**P* = nonsignificant compared with surgical group.
FFR, Fractional flow reserve; *FU,* duration of follow-up.

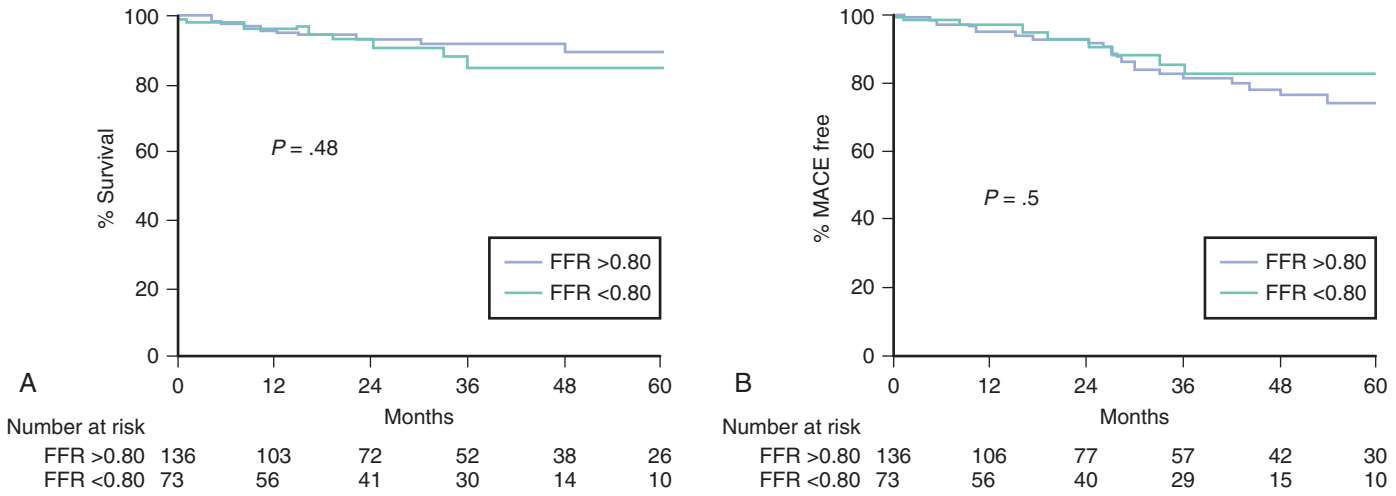


FIGURE 5-19 Outcomes in patients with intermediate left main coronary artery disease based on treatment guided by fractional flow reserve (FFR) assessment. **A,** Survival curves for patients who received medical therapy (FFR > 0.80) and coronary artery bypass grafting (CABG; FFR < 0.80) over 5 years. **B,** Major adverse cardiac event (MACE) rates in patients treated with medical therapy (FFR > 0.80) and CABG (FFR < 0.80) over 5 years. (From Hamilos M, Muller O, Cuisset T, et al: Long-term clinical outcome after fractional flow reserve–guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation* 120:1505-1512, 2009.)

into the LAD or the CFX artery. The guiding catheter is then disengaged, and IV adenosine infusion is initiated. After 1 to 2 minutes, the FFR is calculated, and thereafter the wire can be pulled back slowly to identify the exact location of the pressure drop. In case of a distal narrowing of the LMCA, this procedure may be performed twice, once with the pressure wire in the LAD artery and then again in the CFX artery.

Numerous studies support FFR use for assessment of LMCA stenoses (Table 5-3). In the largest of such studies, Hamilos and coworkers[41] examined 5-year outcomes in 213 patients with an angiographically equivocal LMCA stenosis in whom revascularization decisions were guided by FFR. When FFR was 0.80 or greater, patients were treated medically or another stenosis was treated by coronary angioplasty (nonsurgical group; $n = 138$). When FFR was less than 0.80, CABG surgery was performed (surgical group; $n = 75$). The 5-year survival and event-free survival rates were similar with 90% (74% in the nonsurgical [FFR ≥ 0.80]) group—and 85% (82% in the surgical [FFR < 0.80] group [$P = .48$; Fig. 5-19]). It is worth noting that only 23% of patients with greater than 50% diameter stenosis in the LMCA had a hemodynamically significant FFR.

Complex Left Main Coronary Artery Lesion Assessment (Left Main Coronary Artery Plus Downstream Lesions) With Fractional Flow Reserve

Whereas FFR of simple LMCA lesions has been shown to be predictive of clinical events, the measurement of FFR in complex LMCA lesions (LMCA plus downstream branch lesions) requires the operator to better understand the relationship between the multiple stenoses within the left coronary system and how they affect one another.

Basic tenets of FFR require maximal flow to be achieved across the target vessel. The LMCA transmits flow to the majority of the left ventricle through both the LAD and CFX branches and in proportion to the size of their associated viable myocardial beds. The myocardial bed for the LMCA is then the sum of both the LAD and LCX territories (Fig. 5-20). In the presence of a significant LAD stenosis, flow across the LAD may be reduced and could possibly limit maximal hyperemia, reducing total LMCA flow and hence LMCA FFR accuracy. This situation is the same as two lesions in series, which would be the LMCA and the LAD (or CFX) narrowing. The complex LMCA plus LAD stenosis could produce an "apparent" LMCA FFR (FFR_{app}) that is

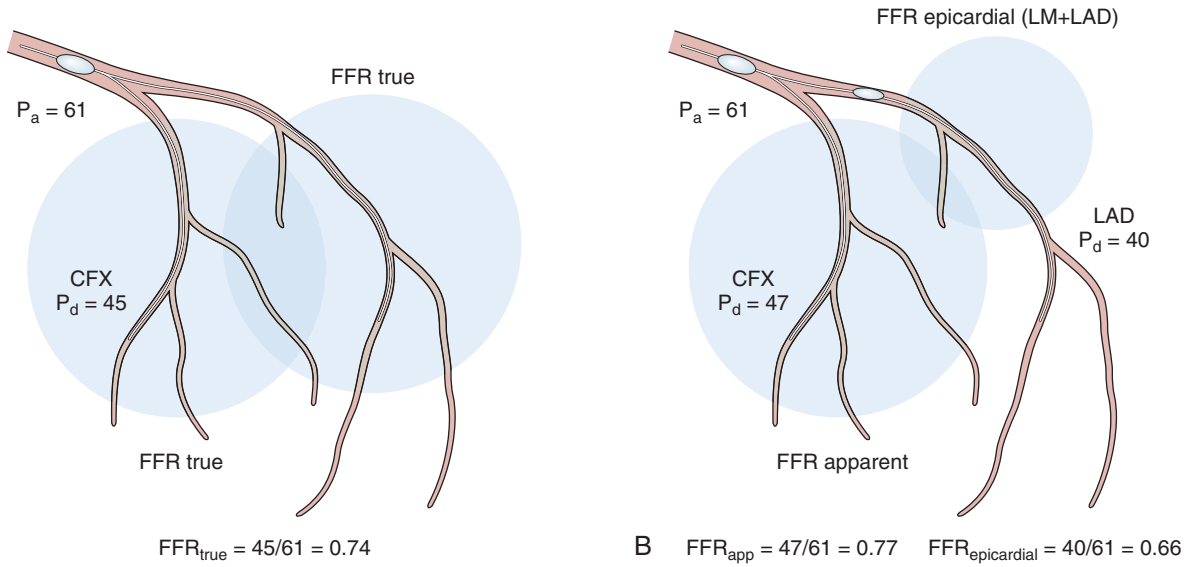


FIGURE 5-20 Schematic example of physiologic measurements from an animal model of the left main (LM) coronary artery with or without left anterior descending (LAD) coronary artery stenosis. **A,** True fractional flow reserve (FFR_{true}) of the left main coronary artery obtained during balloon inflation; no stenosis was evident in the LAD (FFR true = distal pressure [Pd]) in the circumflex (CFX) artery divided by proximal arterial pressure (Pa). **B,** FFR apparent (FFR_{app}) obtained during balloon inflation in the LAD (FFR_{app} = CFX Pd/Pa during downstream balloon inflation). $FFR_{epicardial}$ represents FFR of the LM plus the LAD ($FFR_{epicardial}$ = LAD Pd/Pa during LAD balloon inflation). (Modified from Yong AS, Daniels D, De Bruyne B, et al: Fractional flow reserve assessment of left main stenosis in the presence of downstream coronary stenoses, *Circ Cardiovasc Interv* 6[2]:161-165, 2013.)

higher than the true LMCA FFR (FFR_{true}) because the LMCA bed flow is decreased as a result of the LAD stenosis. The same consideration would apply in the setting of a CFX narrowing. The higher LMCA FFR_{app} is not a concern if either the LAD or CFX are not hemodynamically significant. As Yong and colleagues[42] have shown (discussed later in this section), the apparent and true LMCA FFR will be very close to one another.

When measuring simple FFR across lesions in the LMCA and subsequent major vessel, it is simplest to measure the effect of both lesions by placing the pressure transducer distal to the most distal lesion in question. If the FFR at that level is greater than 0.80, neither lesion is physiologically significant. If the FFR is less than 0.80, a pressure pullback during hyperemia is performed, noting the largest pressure gradient (ΔP) and then the lesion in the LAD or LMCA with the largest ΔP is treated, and FFR is repeated on the remaining lesion. The downside of this approach is that once a significant LAD lesion is removed (i.e., stented), the LMCA FFR may become significant, which mandates further revascularization by stenting or CABG. Thus performing a PCI of a downstream lesion solely to measure the LMCA FFR may not be the best option.

Yong and colleagues[42] used balloon angioplasty catheters in an animal model to create variable stenoses in the LMCA and then in the LAD. Pressure guidewires were positioned in the LAD and CFX arteries. With increasing LAD severity, the difference between FFR_{true} in the LMCA alone and the LMCA FFR_{app} was greater than 0.03 units only when the epicardial FFR ($FFR_{epicardial}$) was less than 0.60, meaning that for practical purposes, only a severe and proximal LAD stenosis is likely to influence the true LMCA FFR. Subsequently, these observations were confirmed in a series of patients. In 16 patients post elective coronary intervention of either the LAD or CFX artery, an intermediate left main stenosis was created with variable LAD stenoses using a balloon inflated within the newly placed stent. Sixty-seven pairs of LMCA FFR assessments were obtained before and after an LAD balloon stenosis was created with a pressure wire in the nonstenosed downstream vessel. The investigators found that the FFR_{app} was modestly higher than the FFR_{true} in the absence of downstream stenosis (FFR 0.82 vs. 0.80, $P < .001$). The difference between FFR_{true} and FFR_{app} correlated with the FFR ($r = 0.36$, $P < .001$). This difference was only

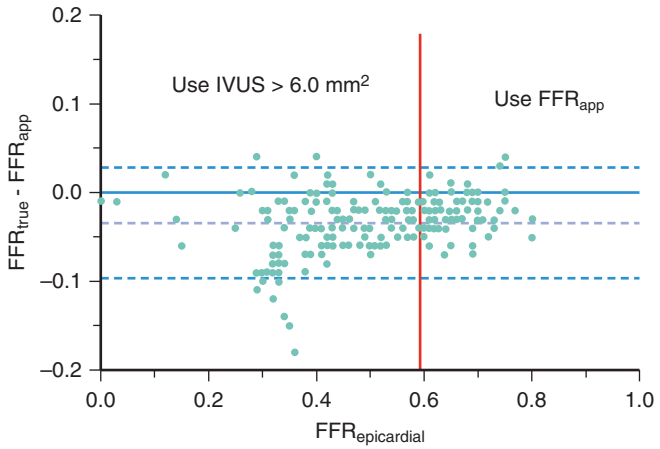
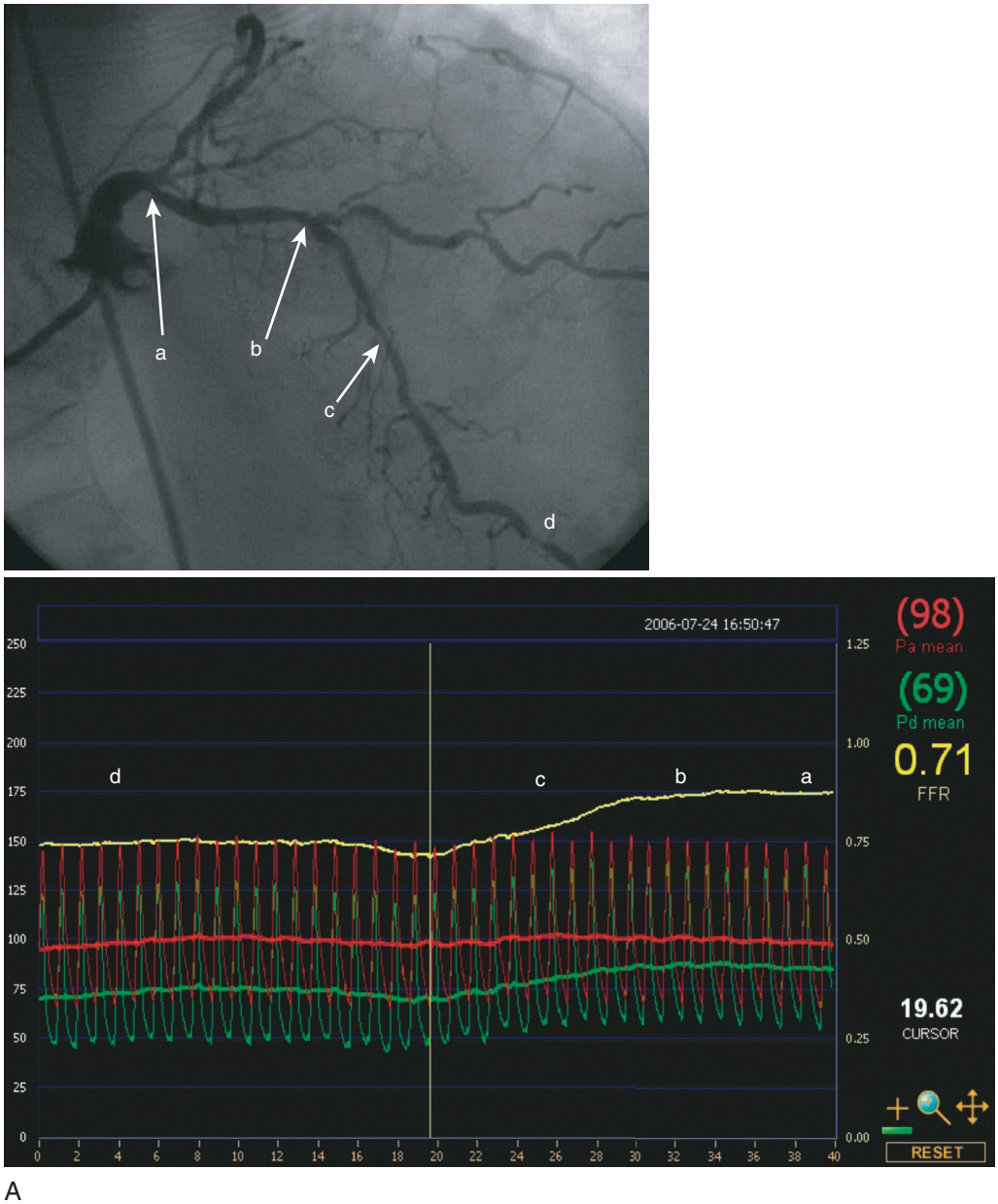


FIGURE 5-21 Impact of downstream left anterior descending (LAD) coronary artery on the left main coronary artery (LMCA) fractional flow reserve (FFR). A plot of the difference between true FFR (FFR_{true}) and apparent FFR (FFR_{app}) versus a composite FFR of the LMCA and stenosed downstream vessel ($FFR_{epicardial}$) is shown. *Dashed lines* and *dotted lines* indicate bias and 95% confidence interval of the agreement, respectively. IVUS, intravascular ultrasound. (From Yong AS, Daniels D, De Bruyne B, et al: Fractional flow reserve assessment of left main stenosis in the presence of downstream coronary stenoses. *Circ Cardiovasc Interv* 6[2]:161-165, 2013.)

significant when FFR was very severely low. Among the 67 measurements, only two (3%) had a difference between FFR_{true} and FFR_{app} of greater than 0.05, and the FFR was less than 0.2 in both cases. From the studies by Yong and colleagues[42] for a complex LMCA with downstream disease, when FFR less than 0.60, FFR_{app} may be questioned, and IVUS assessment with a threshold of less than 6.0 mm^2 is recommended (Fig. 5-21).



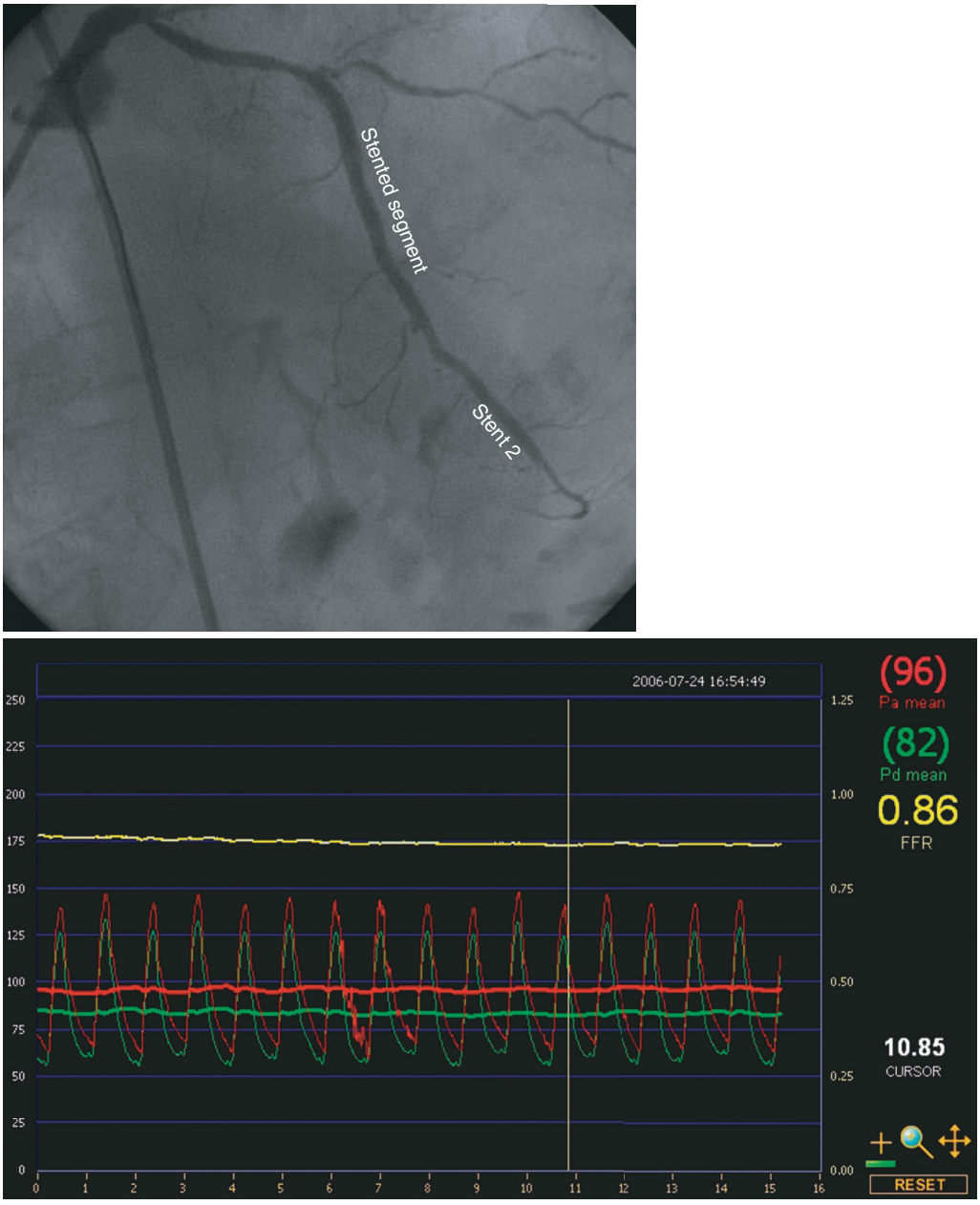
A

FIGURE 5-22 Case example of a patient who presented to the catheterization laboratory complaining of angina-like symptoms. **A,** *Top:* Right anterior oblique (RAO) cranial angiogram shows multiple lesions (*a* through *d*) within the left anterior descending (LAD) coronary artery. *Bottom:* A pull-back curve through the LAD during intravenous adenosine administration (points *a* through *d* represent the lesions identified in **A**).

Continued

Serial (Multiple) Lesions in a Single Vessel

If multiple stenoses are present in the same vessel, the hyperemic flow and pressure gradient through the first stenosis will be attenuated by the presence of the second one and vice versa. Each stenosis will mask the true effect of its serial counterpart by limiting the achievable maximum hyperemia. This fluid-dynamic interaction between two serial stenoses depends on the sequence, severity, and distance between the lesions, as well as the flow rate. If the distance between the two lesions is greater than six times the vessel diameter, the stenoses generally behave independently, and the overall pressure gradient is the sum of the individual pressure losses at any given flow rate. When addressing two stenoses in series, equations have been derived to mathematically predict the FFR (FFR_{pred}) of each stenosis separately (i.e., as if the other one were removed), using arterial pressure (Pa), pressure between the two stenoses (Pm), distal coronary pressure (Pd), and coronary occlusive pressure (Pw). FFR_{app}, the ratio of the pressure just distal to that just proximal to each stenosis, and FFR_{true}, the ratio of the pressures distal and proximal to each stenosis but after removal of the other one, have been compared in instrumented dogs and in humans.[43,44] FFR_{true} was more overestimated by FFR_{app} than by FFR_{pred}. It was clearly demonstrated that the interaction between two stenoses is such that the FFR of each lesion cannot be calculated by the equation for isolated stenoses applied to each separately; however, the FFR for each lesion can be predicted by more complete equations that take into account Pa, Pm, Pd, and Pw. Although calculation of the exact FFR for each lesion separately is possible, it remains largely academic. In clinical practice, the use of the pressure pull-back recording is particularly well suited to identify the various regions of a vessel with large pressure gradients that may benefit from treatment. The one stenosis with the largest gradient can be treated first, after which the FFR can be remeasured for the remaining stenoses to determine the need for further treatment (see case examples in Figs. 5-22 and 5-23).



B

FIGURE 5-22, cont'd **B,** *Top:* RAO cranial angiogram after treatment of lesions *d* and *c* with stents. *Bottom:* Fractional flow reserve (FFR) of the LAD after stenting, with the wire distal to the last stent. The FFR of 0.86 reflects the fact that the ostial and middle lesions (*a* and *b*) did not need to be treated.

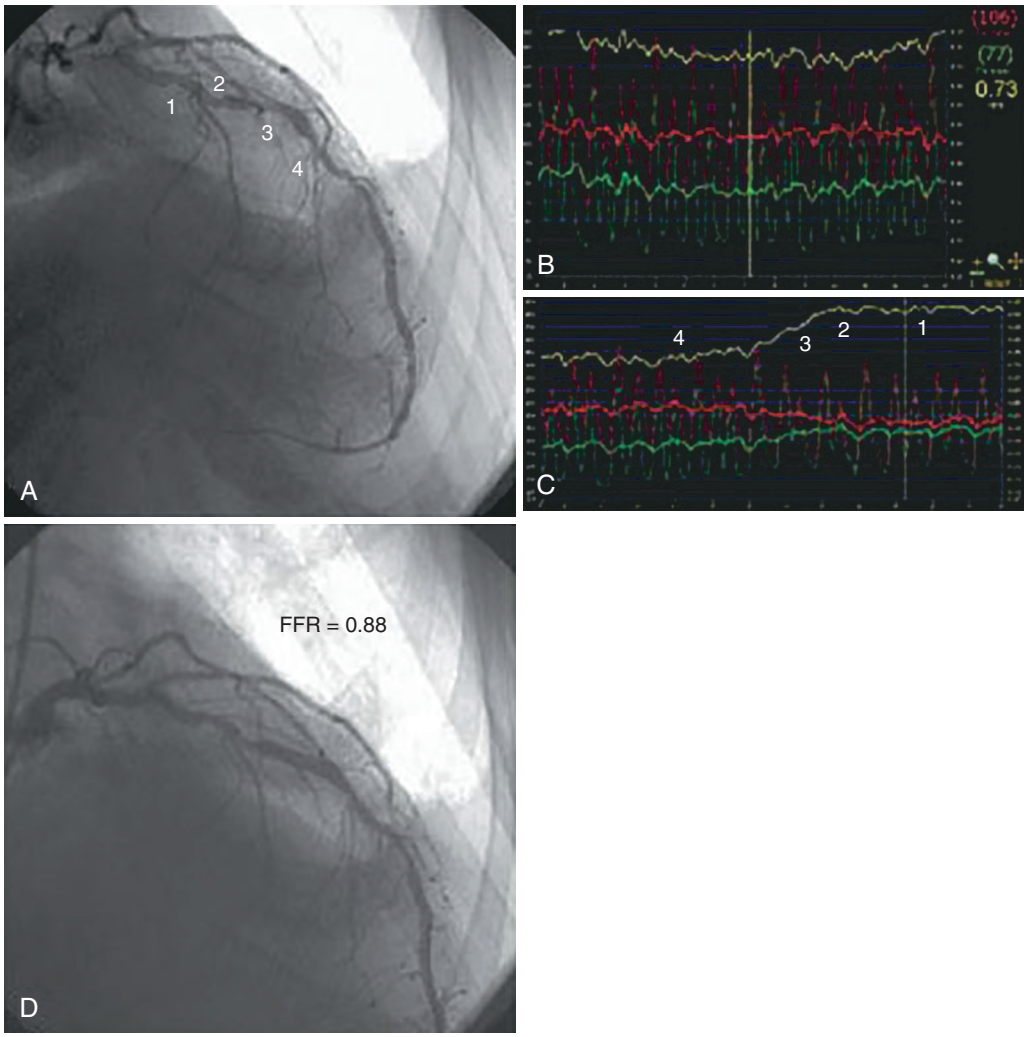


FIGURE 5-23 Example of a patient with serial lesions in the left anterior descending coronary artery (LAD). **A,** Multiple LAD artery lesions (one to four) were seen on angiography in a patient with a positive stress test for anterior ischemia. **B,** Fractional flow reserve (FFR) assessment of the LAD beyond all the lesions show a physiologically significant gradient in the vessel (FFR = 0.73). **C,** Pull-back recording during continuous hyperemia demonstrates the relative changes in FFR at lesions 1 to 4. The largest change in the pressure gradient is seen to occur at lesion 3 only. **D,** Right anterior oblique (RAO) angiogram of the LAD following stenting of lesion 3 with a final FFR across all lesions of 0.88.

Diffuse Coronary Disease

A diffusely diseased atherosclerotic coronary artery can be viewed as a series of branching units that divert and gradually distribute flow along the longitudinally narrowing conduit length. The perfusion pressure gradually diminishes along this artery. FFR is reduced but is unassociated with a focal stenotic pressure loss. Therefore in the diffusely diseased vessel, mechanical therapy directed at a presumed "culprit" stenosis to reverse such abnormal physiology would be ineffective in restoring normal coronary perfusion. A continuous-pressure pullback from a distal location to a proximal location will identify any specific area of focal angiographic narrowing and will confirm the presence of diffuse atherosclerosis. Diffuse atherosclerosis, as opposed to a focal narrowing, is characterized by a continuous and gradual pressure recovery without localized abrupt increase in pressure related to an isolated region. De Bruyne and coworkers[45] demonstrated the influence of diffuse atherosclerosis that often remains invisible at angiography. FFR measurements were obtained from 37 arteries in 10 individuals without atherosclerosis (group I) and from 106 nonstenotic arteries in 62 patients with arteriographic stenoses in another coronary artery (group II). In group I, the pressure gradient between the aorta and the distal coronary artery was minimal at rest (1 ± 1 mm Hg) and during maximal hyperemia (3 ± 3 mm Hg). Corresponding values were significantly larger in group II (5 ± 4 and 10 ± 8 mm Hg, respectively; both $P < .001$). The FFR was near unity (0.97 ± 0.02; range, 0.92 to 1) in group I, indicating no resistance to flow in truly normal coronary arteries; but it was significantly lower (0.89 ± 0.08; range, 0.69 to 1) in group II, indicating a higher resistance to flow. This resistance to flow contributes to myocardial ischemia and has consequences for decision making during PCI. As for patients with several discrete stenoses within one coronary artery, similar considerations can be applied for patients with diffuse CAD or long lesions. The pressure pull-back recording at maximum hyperemia provides the necessary information to decide whether and where stent implantation may be useful. The location of a focal pressure drop superimposed on the diffuse disease can be identified as an appropriate location for treatment. In some cases, the gradual decline of pressure along the vessel occurs over a very long segment, such that interventional treatment is not possible (Fig. 5-24). Medical treatment (or CABG) can then be elected.

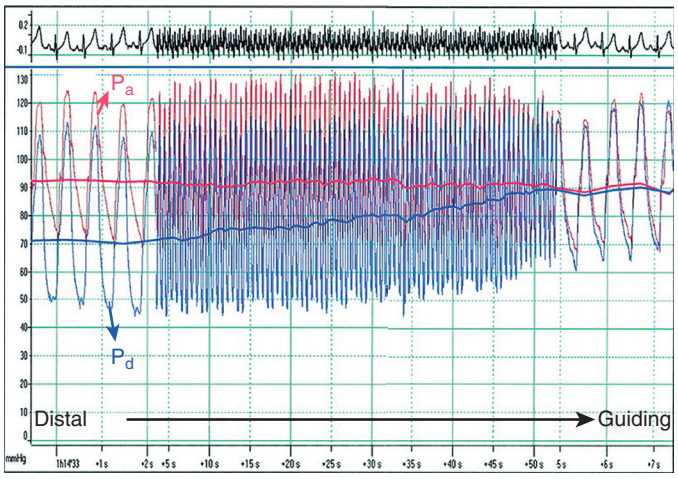


FIGURE 5-24 A pull-back curve created in a patient with diffuse disease throughout the left anterior descending coronary artery. The fractional flow reserve for this vessel is 0.67, which reflects ischemia-producing lesions. However, the gradual decrease in gradient from pressure distal to the stenosis (Pd) to arterial pressure (Pa) is reflective of severe, diffuse narrowing in the major portion of the vessel. This gradual change in the pressure curve shows that an extremely long segment is responsible for the ischemia and is most likely *not* best treated with multiple stents (i.e., "full metal jacket"). (Courtesy B. De Bruyne, Aalst, Belgium.)

Ostial Lesions and Jailed Side Branches

The assessment of ostial narrowings, particularly in side branches "jailed" within stents, remains difficult with current angiographic techniques because of image foreshortening, the overlap orientation relative to the parent branch, and, in the case of jailed vessels, stent struts across the branch.

Koo and colleagues[52] compared FFR with the stenosis severity as measured by QCA for 94 jailed side-branch lesions. Only 20 (27%) of 73 lesions with 75% or greater stenosis were functionally significant by FFR. Reassuringly, no lesion with less than 75% angiographic stenosis had an FFR less than 0.75. These results suggest that most of these lesions do not have functional significance and thus may not need intervention. Similar findings have been reported for native ostial and branch stenoses found during routine coronary angiography.[53,54]

Fractional Flow Reserve in Acute Coronary Syndromes

After an acute MI, the predictive ability of FFR has some theoretic limitations because the microvascular bed in the infarct zone may not necessarily have a uniform and constant response to a pharmacologic hyperemic stimulus. Transient microvascular dysfunction impairs maximal coronary hyperemia to varying degrees, reducing the flow across a stenosis and elevating the measured FFR across lesions. It has been questioned to what extent this might affect the accuracy of FFR for both culprit and nonculprit lesions around the time of an ACS.

In an acute STEMI, FFR of most nonculprit lesions has been shown to be accurate, with the caveat that diffuse microvascular impairment may falsely elevate the apparent FFR. Therefore in this setting, a low FFR indicates hemodynamic significance of the nonculprit lesion, but a normal FFR may not be definitive. Ntalianis and associates[55] measured the FFR of 112 nonculprit lesions during an acute MI (75 patients with STEMI, 26 with non-STEMI [NSTEMI]) and again 35 (SD ± 24) days later. Only two lesions had a clinically meaningful change in which the FFR was greater than 0.80 during the acute episode and less than 0.75 at follow-up.

De Bruyne and associates[56] and Samady and colleagues[57] obtained FFR measurements of culprit vessels three or more days after acute MI and compared them with subsequent single photon emission computed tomography (SPECT) imaging to identify true positives and negatives. Both studies showed that an FFR below 0.75 had high sensitivity, specificity, and overall accuracy for detecting reversible ischemia on truly positive or negative SPECT imaging results, and they both reached the same BCV for FFR of 0.78. Furthermore, data from the FAME trial showed that among the 173 patients who had ACS prior to enrollment, an impressive 30% overall reduction in MACE was reported when FFR was applied to the revascularization decision making.[58] Trials that have evaluated the use of FFR in ACS are summarized in Table 5-4. Taken together, these studies strongly show that when used appropriately, FFR can be a useful tool in assessing patients after an acute MI.

FUTURE APPLICATIONS AND RESEARCH: INTRACORONARY PHYSIOLOGIC MEASUREMENTS

Simultaneous Measurement of Flow Velocity and Transstenotic Pressure Gradient

Although the maximal flow and, consequently, the maximal transstenotic gradient are determined also by factors independent of the stenosis resistance, the pressure gradient–flow velocity relationship is intimately correlated with the stenosis hemodynamics. A method to assess the coronary vasculature that is easy to perform and currently poses the greatest clinical usefulness is the index of microcirculatory resistance (IMR). This index relies on using distal pressure and thermodilution flow, as assessed by the inverse of the arrival (transit) time of a room-temperature saline bolus to the distal coronary artery segment. By measuring the mean transit time at rest and comparing it with the mean transit time at peak hyperemia, a thermodilution CFR can be calculated. The ability to measure distal pressure and estimate flow using the thermodilution technique (example shown in Fig. 5-25) with a single wire also allows independent assessment of the microvasculature by calculating the IMR. Although principally a research tool, assessment of IMR permits a unique characterization of the microcirculation, and this has been shown to be prognostic in patients after STEMI.[59,60]

Hyperemic microvascular resistance (HMR) is defined as the ratio of mean distal coronary pressure to flow velocity. Hyperemia is underestimated in the presence of coronary stenosis, compared with actual microvascular resistance, because of the lack of collateral flow contribution. To test whether HMR can accurately identify microvascular function abnormalities, the association between HMR and noninvasive testing was examined in 228 patients with 299 lesions.[61] Intracoronary distal pressure flow velocity assessed during intracoronary adenosine hyperemia (20 to 40 μg) determined hyperemic stenosis resistance (HSR) and HMR. HMR values greater than 1.9 mm Hg/cm/second were defined as "high." The odds ratio (OR) for myocardial ischemia with high IMR compared with low IMR was 2.6 ($P < .001$). The authors concluded that increased risk of myocardial ischemia in the presence of high HMR is reflective of an increase in actual myocardial resistance, identifying pertinent pathophysiologic alteration in the microvasculature.

Periprocedural MI (PMI) may involve a significant number of patients after PCI and is associated with poor outcome. In the prediction of periprocedural events, no single laboratory test can be useful. Ng and colleagues[62] hypothesized that impaired baseline coronary microvascular reserve (IMR) results in the inability to tolerate ischemic insults—that is, the IMR may predict the occurrence of PMI. The investigators used the pressure-temperature sensor wire to measure IMR before PCI in 50 patients, 10 of whom had PMIs. Univariate predictors of PMI included the pre-PCI IMR ($P = .003$) and the number of stents. A pre-PCI IMR of 27 units or more had 80% sensitivity and 85% specificity for PMI ("C" is the statistical notation used as a correlative statistic. not see statistic 0.80). The pre-PCI IMR was

TABLE 5-4 Fractional Flow Reserve and Acute Coronary Syndrome Trials

First Author	*N*		Vessel Assessed	Usefullness of FFR	Summary
Tamita[64]	33 STEMI	AMI	Culprit vessel	Unreliable	Mean FFR after successful PCI was higher (0.95 ± 0.04) than in the reference group of stable angina patients (0.90 ± 0.04, $P = .002$) despite identical IVUS parameters, likely reflecting microvascular stunning and dysfunction.
Ntalianis[55]	75 STEMI, 26 NSTEMI	AMI	Nonculprit vessel	Reliable	Nonculprit lesions ($n = 112$) were measured acutely and 35 ± 24 days later. Only two had clinically meaningful change (FFR > 0.80 during the acute episode and FFR < 0.75 at follow-up).
De Bruyne[56]	57 AMI with viable myocardium on left venogram	Recent MI	Culprit vessel	Reliable	FFR after acute MI (≥6 days, mean 20 days) was compared with SPECT before and after PCI. FFR < 0.75 had high sensitivity (87%) and specificity (100%) for detecting ischemia on true positive/negative SPECT (BCV for FFR, 0.78). An inverse correlation was found between FFR and LVEF; for a similar degree of stenosis, FFR depends on mass of viable myocardium.
Samady[57]	36 STEMI, 12 NSTEMI	Recent MI	Culprit vessel	Reliable	FFR after acute MI (STEMI ≥3 days, NSTEMI ≥2 days, mean 3.7 days) was compared with SPECT at 11 weeks. FFR ≤0.75 had high sensitivity (88%), specificity (93%), and overall accuracy (91%) for detecting reversibility on true positive/negative SPECT. BCV for FFR was 0.78.
Potvin[65]	125 ACS, 60 SIHD, 16 Atypical CP	Recent MI	Nonculprit vessel	FFR-guided PCI = good clinical outcomes	Patients ($n = 201$ consecutive, 62% UA, NSTEMI, or >24 hr after STEMI) had ~50% stenosis in which PCI was deferred based on FFR ≥ 0.75; no differences were found in clinical outcomes between those with ACS and stable angina patients.
Fischer[66]	35 ACS	Recent MI		FFR-guided PCI = good clinical outcomes	FFR-guided PCI of intermediate lesions (50%-70%) was studied, deferring PCI for FFR ≥0.75 in patients with recent ACS; MACE rates were similar at 12 mo compared with patients without ACS.
Leesar[39]	70 UA/NSTEMI	UA/NSTEMI	Culprit vessel	FFR-guided PCI = good clinical outcomes	Recent NSTE-ACS with intermediate single-vessel lesion was randomized to immediate FFR-guided PCI versus postangio SPECT. FFR-guided treatment reduced hospital stay and cost with no increase in procedure time, radiation exposure, or clinical event rates at 1 year.
Sels[58]	326 UA/NSTEMI	UA/NSTEMI	Culprit + nonculprit vessel	FFR-guided PCI = good clinical outcomes	FAME studied FFR-guided PCI versus angiography-guided PCI for multivessel disease; in a subset of patients with recent NSTE-ACS, the MACE rate was significantly lower with FFR-guided PCI.

ACS, Acute coronary syndrome; *AMI,* acute MI; *BCV,* best cut-off value; *CP,* chest pain; *FFR,* fractional flow reserve; *IVUS,* intravascular ultrasound; *LVEF,* left ventricle ejection fraction; *MACE,* major adverse cardiac event; *MI,* myocardial infarction; *NSTE,* non-ST elevation; *PCI,* percutaneous coronary intervention; *SIHD,* stable ischemic heart disease; *SPECT,* single photon emission computed tomography; *STEMI,* ST-elevation myocardial infarction; *UA,* unstable angina.

FIGURE 5-25 Simultaneous measurement of pressure and flow (by thermodilution). The upper portion of the figure shows pressures proximal (Pa) and distal (Pd) at rest (*left*) and during hyperemia (*right*). The lower portion of the figure depicts the thermodilution curves at rest and during hyperemia (Hyp) with the associated average transit times at baseline and at hyperemia circled. These values are used to calculate the coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR), as seen on the right side of the panel. *FFR,* Fractional flow reserve. (From Martin KC, Yeung AC, Fearon WF: Invasive assessment of the coronary microcirculation. *Circulation* 113[17]:2054-2061, 2006.)

independently associated with a 23-fold risk of developing PMI. The authors indicated that the status of coronary microcirculation does play a role in determining susceptibility to PMI during elective PCI and may guide adjunctive preventive therapies.

Nonhyperemic Indices of Coronary Stenosis Significance

Utilization of an adenosine-free or adenosine-independent pressure-derived index of coronary stenosis severity is a desirable feature among those working in the cardiac catheterization lab. The assessment of stenosis severity by FFR requires that coronary resistance be stable and minimal, which is usually achieved by the administration of adenosine. Through the use of wave-intensity analysis, Sen and coworkers[63] found a period of diastole in which equilibration or balance is reached between pressure waves from the aorta and distal microcirculatory reflection; hence it is wave free. This wave-free period (WFP) occurs 75% of the way through diastole to just before systole and is a period during which the resistance is fixed and potentially minimal. The use of the WFP resistance, as compared with the FFR, provided a measure of instantaneous wave-free pressure ratio (iFR). In the Adenosine Vasodilator Independent Stenosis Evaluation (ADVISE) study, 157 stenoses were assessed with pressure and flow distal to the stenosis with 118 stenoses assessed as a second segment of the research using pressure alone. The intracoronary resistance at rest during the WFP was similar in variability and magnitude to that during FFR, and the iFR correlated closely with FFR ($r = 0.90$). However, there were limitations to this analysis despite having high sensitivity, specificity, NPV, and PPV, including the fact that the iFR at rest was different than the iFR during hyperemia. Subsequently, Petraco and associates[67] demonstrated that at iFR cutpoints of greater than 0.93 or less than 0.86, the correlation was strong with normal and abnormal FFR values (using 0.80 as an FFR cutpoint). Thus potentially one third of the patients with intermediate stenosis could be assessed without the need for hyperemic stimulus.

The RESOLVE study[68] compared the diagnostic accuracy of the iFR and resting coronary artery pressure with the aortic pressure ratio Pd/Pa with respect to the FFR in a core laboratory. The iFR, Pd/Pa, and FFR were measured in 1768 patients from 15 clinical sites. The core lab was used to analyze the data, and thresholds corresponding to 90% accuracy in predicting ischemic versus nonischemic FFR were then identified. In 1974 lesions, the optimal iFR to predict an FFR less than 0.8 was 0.92 with an accuracy of 80%. For the resting Pd/Pa ratio, the cutpoint was 0.92 with an overall accuracy of 92% with no significant differences between iFR and Pd/Pa. Both measures have 90% accuracy to predict positive or negative FFR in 65% and 48% of lesions, respectively. These data suggest that resting indices of lesion severity demonstrated an overall accuracy with FFR of about 80%, which can be improved to 90% in a subset of lesions. Clinical outcome studies are required to determine whether the use of iFR or Pd/Pa might obviate the need for hyperemia in selected patients and are currently underway (Fig. 5-26).

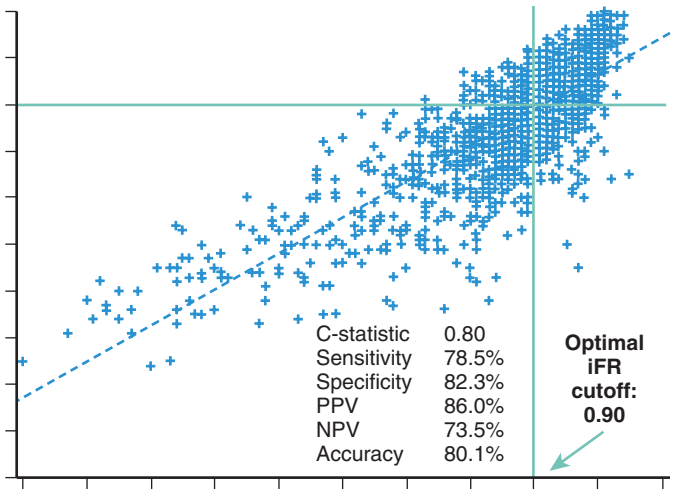


FIGURE 5-26 Plot comparing fractional flow reserve (FFR) with instantaneous wave-free ratio (iFR) values in the RESOLVE study, showing an optimal cut-off value of 0.90 for an iFR to correlate best with an FFR of 0.80. *NPV,* Negative predictive value; *PPV,* positive predictive value. (Jeremias A, Maehara A, Généreux P, et al: Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. *J Am Coll Cardiol* 63[13]: 1253-1261, 2014.)

CONCLUSION

The technological advances in the field of interventional cardiology and the use of coronary physiology continue to provide valuable critical diagnostic assistance to the catheterization lab operator to make meaningful patient care decisions. Invasive assessment of FFR is increasingly being integrated into some laboratories for routine assessment of angiographically intermediate lesions with strong outcome data to support this practice. The physiologic assessment of intermediate stenoses in patients with complex CAD, including left main CAD and multivessel disease, has improved the outcomes of patients with these complex anatomic subsets. FFR has been especially useful with the replacement of surgical revascularization by percutaneous revascularization in recent years, and it can help operators achieve complete resolution of coronary ischemia, similar to complete surgical revascularization. Future advances in coronary physiology will give practitioners the ability to (1) evaluate the contribution of microvascular disease to a patient's symptoms, (2) target therapies that can improve microvascular dysfunction, and (3) evaluate endothelial dysfunction as a precursor to the atherosclerotic process. Conscientious operators use FFR and IVUS for appropriate decision making and best outcomes in patients undergoing modern, complex PCI.

REFERENCES

1. Topol EJ, Nissen SE: Our preoccupation with coronary luminology: the dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation* 92(8):2333–2342, 1995.
2. Meijboom WB, Van Mieghem CA, van Pelt N, et al: Comprehensive assessment of coronary artery stenoses: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. *J Am Coll Cardiol* 52(8):636–643, 2008.
3. Duncker DJ, Bache RJ: Regulation of coronary vasomotor tone under normal conditions and during acute myocardial hypoperfusion. *Pharmacol Ther* 86(1):87–110, 2000.
4. Gould KL, Kirkeeide RL, Buchi M: Coronary flow reserve as a physiologic measure of stenosis severity. *J Am Coll Cardiol* 15(2):459–474, 1990.
5. Pijls NH, van Son JA, Kirkeeide RL, et al: Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation* 87(4):1354–1367, 1993.
6. Pijls NH, Van Gelder B, Van der Voort P, et al: Fractional flow reserve: a useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation* 92(11): 3183–3193, 1995.
7. De Bruyne B, Baudhuin T, Melin JA, et al: Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. *Circulation* 89(3):1013–1022, 1994.
8. De Bruyne B, Bartunek J, Sys SU, et al: Simultaneous coronary pressure and flow velocity measurements in humans. Feasibility, reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve. *Circulation* 94(8):1842–1849, 1996.
9. Pijls NH, Kern MJ, Yock PG, De Bruyne B: Practice and potential pitfalls of coronary pressure measurement. *Catheter Cardiovasc Interv* 49(1):1–16, 2000.
10. Qian J, Ge J, Baumgart D, et al: Safety of intracoronary Doppler flow measurement. *Am Heart J* 140(3):502–510, 2000.
11. Jeremias A, Filardo SD, Whitbourn RJ, et al: Effects of intravenous and intracoronary adenosine 5′-triphosphate as compared with adenosine on coronary flow and pressure dynamics. *Circulation* 101(3):318–323, 2000.
12. Prasad A, Zareh M, Doherty R, et al: Use of regadenoson for measurement of fractional flow reserve. *Catheter Cardiovasc Interv* 83(3):369–374, 2014.
13. Arumugham P, Figueredo VM, Patel PB, Morris DL: Comparison of intravenous adenosine and intravenous regadenoson for the measurement of pressure-derived coronary fractional flow reserve. *EuroIntervention* 8(10):1166–1171, 2013.
14. Nair PK, Marroquin OC, Mulukutla SR, et al: Clinical utility of regadenoson for assessing fractional flow reserve. *JACC Cardiovasc Interv* 4(10):1085–1092, 2011.
15. Bartunek J, Marwick TH, Rodrigues AC, et al: Dobutamine-induced wall motion abnormalities: correlations with myocardial

fractional flow reserve and quantitative coronary angiography. *J Am Coll Cardiol* 27(6):1429–1436, 1996.
16. Parham WA, Bouhasin A, Ciaramita JP, et al: Coronary hyperemic dose responses of intracoronary sodium nitroprusside. *Circulation* 109(10):1236–1243, 2004.
17. De Bruyne B, Bartunek J, Sys SU, Heyndrickx GR: Relation between myocardial fractional flow reserve calculated from coronary pressure measurements and exercise-induced myocardial ischemia. *Circulation* 92(1):39–46, 1995.
18. Pijls NH, De Bruyne B, Peels K, et al: Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med* 334(26):1703–1708, 1996.
19. Watkins S, McGeoch R, Lyne J, et al: Validation of magnetic resonance myocardial perfusion imaging with fractional flow reserve for the detection of significant coronary heart disease. *Circulation* 120(22):2207–2213, 2009.
20. Melikian N, De Bondt P, Tonino P, et al: Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. *JACC Cardiovasc Interv* 3(3): 307–314, 2010.
21. Toth G, Hamilos M, Pyxaras S, et al: Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. *Eur Heart J* 35(40):2831–2838, 2014.
22. Abizaid A, Mintz GS, Pichard AD, et al: Clinical, intravascular ultrasound, and quantitative angiographic determinants of the coronary flow reserve before and after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 82(4):423–428, 1998.
23. Takagi A, Tsurumi Y, Ishii Y, et al: Clinical potential of intravascular ultrasound for physiological assessment of coronary stenosis: relationship between quantitative ultrasound tomography and pressure-derived fractional flow reserve. *Circulation* 100(3):250–255, 1999.
24. Briguori C, Anzuini A, Airoldi F, et al: Intravascular ultrasound criteria for the assessment of the functional significance of intermediate coronary artery stenoses and comparison with fractional flow reserve. *Am J Cardiol* 87(2):136–141, 2001.
25. Waksman R, Legutko J, Singh J, et al: FIRST: Fractional Flow Reserve and Intravascular Ultrasound Relationship Study. *J Am Coll Cardiol* 61(9):917–923, 2013.
26. Levine GN, Bates ER, Blankenship JC, et al: 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 58(24):e44–e122, 2011.
27. Johnson NP, Kirkeeide RL, Gould KL: Coronary anatomy to predict physiology: fundamental limits. *Circ Cardiovasc Imaging* 6(5):817–932, 2013.
28. Gonzalo N, Escaned J, Alfonso F, et al: Morphometric assessment of coronary stenosis relevance with optical coherence tomography: a comparison with fractional flow reserve and intravascular ultrasound. *J Am Coll Cardiol* 59(12):1080–1089, 2012.
29. Pijls NH, van Schaardenburgh P, Manoharan G, et al: Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol* 49(21): 2105–2111, 2007.
30. Tonino PA, Fearon WF, De Bruyne B, et al: Angiographic versus functional severity of coronary artery stenoses in the FAME study: fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol* 55(25):2816–2821, 2010.
31. De Bruyne B, Pijls NH, Kalesan B, et al: Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 367(11):991–1001, 2012.
32. Van Belle E, Rioufol G, Pouillot C, et al: Outcome impact of coronary revascularization strategy reclassification with fractional flow reserve at time of diagnostic angiography: insights from a large French multicenter fractional flow reserve registry. *Circulation* 129(2):173–185, 2014.
33. Curzen N, Rana O, Nicholas Z, et al: Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain? the RIPCORD study. *Circ Cardiovasc Interv* 7(2):248–255, 2014.
34. Botman CJ, Schonberger J, Koolen S, et al: Does stenosis severity of native vessels influence bypass graft patency? A prospective fractional flow reserve-guided study. *Ann Thorac Surg* 83(6):2093–2097, 2007.
35. Botman KJ, Pijls NH, Bech JW, et al: Percutaneous coronary intervention or bypass surgery in multivessel disease? A tailored approach based on coronary pressure measurement. *Catheter Cardiovasc Interv* 63(2):184–191, 2004.
36. Toth G, De Bruyne B, Casselman F, et al: Fractional flow reserve-guided versus angiography-guided coronary artery bypass graft surgery. *Circulation* 128(13):1405–1411, 2013.
37. Nam CW, Mangiacapra F, Entjes R, et al: Functional SYNTAX score for risk assessment in multivessel coronary artery disease. *J Am Coll Cardiol* 58(12):1211–1218, 2011.
38. Fearon WF, Yeung AC, Lee DP, et al: Cost-effectiveness of measuring fractional flow reserve to guide coronary interventions. *Am Heart J* 145(5):882–887, 2003.
39. Leesar MA, Abdul-Baki T, Akkus NI, et al: Use of fractional flow reserve versus stress perfusion scintigraphy after unstable angina: effect on duration of hospitalization, cost, procedural characteristics, and clinical outcome. *J Am Coll Cardiol* 41(7):1115–1121, 2003.
40. Fearon WF, Shilane D, Pijls NH, et al: Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary artery disease and abnormal fractional flow reserve. *Circulation* 128(12):1335–1340, 2013.
41. Hamilos M, Muller O, Cuisset T, et al: Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation* 120(15):1505–1512, 2009.
42. Yong AS, Daniels D, De Bruyne B, et al: Fractional flow reserve assessment of left main stenosis in the presence of downstream coronary stenoses. *Circ Cardiovasc Interv* 6(2):161–165, 2013.
43. De Bruyne B, Pijls NH, Heyndrickx GR, et al: Pressure-derived fractional flow reserve to assess serial epicardial stenoses: theoretical basis and animal validation. *Circulation* 101(15):1840–1847, 2000.
44. Pijls NH, De Bruyne B, Bech GJ, et al: Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: validation in humans. *Circulation* 102(19):2371–2377, 2000.
45. De Bruyne B, Hersbach F, Pijls NH, et al: Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but "Normal" coronary angiography. *Circulation* 104(20):2401–2406, 2001.
46. Bech GJ, Droste H, Pijls NH, et al: Value of fractional flow reserve in making decisions about bypass surgery for equivocal left main coronary artery disease. *Heart* 86(5):547–552, 2001.
47. Jasti V, Ivan E, Yalamanchili V, et al: Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. *Circulation* 110(18):2831–2836, 2004.
48. Jiménez-Navarro M, Hernández-García JM, Alonso-Briales JH, et al: Should we treat patients with moderately severe stenosis of the left main coronary artery and negative FFR results? *J Invasive Cardiol* 16(8):398–400, 2004.
49. Legutko J, Dudek D, Rzeszutko L, et al: Fractional flow reserve assessment to determine the indications for myocardial revascularisation in patients with borderline stenosis of the left main coronary artery. *Kardiol Pol* 63(5):499–506, 2005.
50. Suemaru S, Iwasaki K, Yamamoto K, et al: Coronary pressure measurement to determine treatment strategy for equivocal left main coronary artery lesions. *Heart Vessels* 20(6):271–277, 2005.
51. Lindstaedt M, Yazar A, Germing A, et al: Clinical outcome in patients with intermediate or equivocal left main coronary artery disease after deferral of surgical revascularization on the basis of fractional flow reserve measurements. *Am Heart J* 152(1):156, 2006.
52. Koo BK, Kang HJ, Youn TJ, et al: Physiologic assessment of jailed side branch lesions using fractional flow reserve. *J Am Coll Cardiol* 46(4):633–637, 2005.
53. Lim MJ, Kern MJ: Utility of coronary physiologic hemodynamics for bifurcation, aorto-ostial, and ostial branch stenoses to guide treatment decisions. *Catheter Cardiovasc Interv* 65(4):461–468, 2005.
54. Ziaee A, Parham WA, Herrmann SC, et al: Lack of relation between imaging and physiology in ostial coronary artery narrowings. *Am J Cardiol* 93(11):1404–1407, A9, 2004.
55. Ntalianis A, Sels JW, Davidavicius G, et al: Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv* 3(12):1274–1281, 2010.
56. De Bruyne B, Pijls NH, Bartunek J, et al: Fractional flow reserve in patients with prior myocardial infarction. *Circulation* 104(2): 157–162, 2001.
57. Samady H, Lepper W, Powers ER, et al: Fractional flow reserve of infarct-related arteries identifies reversible defects on noninvasive myocardial perfusion imaging early after myocardial infarction. *J Am Coll Cardiol* 47(11):2187–2193, 2006.
58. Sels JW, Tonino PA, Siebert U, et al: Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) study. *JACC Cardiovasc Interv* 4(11):1183–1189, 2011.
59. Fearon WF, Balsam LB, Farouque HM, et al: Novel index for invasively assessing the coronary microcirculation. *Circulation* 107(25):3129–3132, 2003.
60. Fearon WF, Shah M, Ng M, et al: Predictive value of the index of microcirculatory resistance in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 51(5):560–565, 2008.
61. Nolte F, van de Hoef TP, Meuwissen M, et al: Increased hyperaemic coronary microvascular resistance adds to the presence of myocardial ischaemia. *EuroIntervention* 9(12):1423–1431, 2014.
62. Ng MK, Yong AS, Ho M, et al: The index of microcirculatory resistance predicts myocardial infarction related to percutaneous coronary intervention. *Circ Cardiovasc Interv* 5(4):515–522, 2012.
63. Sen S, Escaned J, Malik IS, et al: Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *J Am Coll Cardiol* 59(15):1392–1402, 2012.
64. Tamita K, Akasaka T, Takagi T, et al: Effects of microvascular dysfunction on myocardial fractional flow reserve after percutaneous coronary intervention in patients with acute myocardial infarction. *Catheter Cardiovasc Interv* 57(4):452–459, 2002.
65. Potvin JM, Rodés-Cabau J, Bertrand OF, et al: Usefulness of fractional flow reserve measurements to defer revascularization in patients with stable or unstable angina pectoris, non-ST-elevation and ST-elevation acute myocardial infarction, or atypical chest pain. *Am J Cardiol* 98(3):289–297, 2006.
66. Fischer JJ, Wang XQ, Samady H, et al: Outcome of patients with acute coronary syndromes and moderate coronary lesions undergoing deferral of revascularization based on fractional flow reserve assessment. *Catheter Cardiovasc Interv* 68(4):544–548, 2006.
67. Petraco R, Park JJ, Sen S, et al: Hybrid iFR-FFR decision-making strategy: implications for enhancing universal adoption of physiology-guided coronary revascularisation. *EuroIntervention* 8(10):1157–1165, 2013.
68. Jeremias A, Maehara A, Généreux P, et al: Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. *J Am Coll Cardiol* 63(13):1253–1261, 2014.

6 Contrast-Induced Acute Kidney Injury and the Role of Chronic Kidney Disease in Percutaneous Coronary Intervention

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KEY POINTS

- Acute kidney injury (AKI) after cardiac catheterization and percutaneous coronary intervention (PCI) is common, primarily because of exposure to contrast agents, and it is associated with worse clinical outcomes.
- The prevalence of chronic kidney disease (CKD) and diabetes mellitus is rising. Both are key risk factors for AKI after cardiac catheterization and PCI.
- The presence of CKD and end-stage renal disease (ESRD) are associated with worse short- and long-term outcomes even after successful PCI, including higher rates of restenosis and repeat revascularization. The use of coronary stenting with drug-eluting stents may diminish these risks.
- Beyond the use of serum creatinine level, calculation of the glomerular filtration rate and a simple risk score can help to identify high-risk patients prior to their procedures.
- Established keys to preventing AKI after cardiac catheterization and PCI include periprocedural hydration and the use of low-osmolar or isoosmolar contrast agents.
- Intraprocedural strategies should consistently be used to minimize the volume of contrast agent exposure as much as possible.

Alterations of kidney function are commonly encountered in the interventional cardiology setting. Sudden changes in kidney function are a common complication of cardiac catheterization and PCI, primarily because of contrast-induced acute kidney injury (CI-AKI), also known as *contrast-induced nephropathy*. Chronically decreased kidney function is also prevalent in patients with cardiovascular disease and is a strong predisposing risk factor for AKI. Transient rises in serum creatinine levels, a common marker for the development of mild kidney dysfunction, occur in more than 15% of patients who undergo these procedures. Although many of these rises are unlikely to be clinically significant, even mild AKI after cardiac catheterization and PCI is associated with longer hospital stays, greater inpatient costs, and worse short- and long-term mortality.

Significantly, recent diagnostic and therapeutic advances have improved our ability to identify those patients who are at highest risk for developing CI-AKI and to minimize its occurrence. In this chapter we provide a summary of these data with an additional focus on patients with CKD who undergo PCI, given its strong association with CI-AKI and subsequent cardiovascular complications. We discuss the role of nonpharmacologic and pharmacologic strategies for reducing the likelihood that AKI will develop in high-risk patients. Finally, we briefly comment on three groups of patients who represent growing segments of the population commonly encountered in the catheterization laboratory: patients with ESRD, recipients of transplanted kidneys, and patients with heart failure.

PATHOPHYSIOLOGY OF CONTRAST-INDUCED ACUTE KIDNEY INJURY

The most common reason for CI-AKI after cardiac catheterization and PCI is related to the use of intravascular contrast agents. However, despite their widespread use in imaging studies, the mechanism of kidney injury caused by contrast agents has not been fully elucidated.[1] Most studies suggest that both direct toxic injury to the renal tubules and ischemic injury to the renal medulla from vasomotor changes and decreased perfusion are responsible. The latter appears to be mediated partly by the development of reactive oxygen species, such as superoxide, and has important implications for treatment with scavenging agents.[2] Diabetes mellitus and hemodynamic instability may also exacerbate contrast-induced nephropathy, specifically by impeding vasodilatory responses in the renal vasculature.[3] However, these mechanisms are often insufficient in the absence of reduced baseline renal function.

Medications and hemodynamic alterations are two of the many factors that can exacerbate the development of AKI after cardiac catheterization and PCI (Table 6-1). Many medications can contribute to kidney toxicity directly or indirectly, by decreasing microvascular perfusion in the renal medulla, potentially extending areas of ischemic injury. These agents (Table 6-2) should be monitored closely, because they can exacerbate CI-AKI. Toxicities of other medications may be enhanced by CI-AKI.[4] For example, metformin can cause lactic acidosis in the setting of kidney dysfunction and AKI; this has led the Food and Drug Administration (FDA) to recommend withholding it on the day of exposure to contrast agents and for 48 to 72 hours after. Additionally, volume depletion and hemodynamic changes from heart failure or cardiogenic shock may aggravate CI-AKI by decreasing renal perfusion and predisposing the renal medulla to ischemic injury.

A much less common but well-recognized cause of AKI after cardiac catheterization and PCI is renal atheroembolic disease. This disease process is part of the larger cholesterol embolization syndrome, which can result from the embolism of minor atheromatous debris from the aorta or other large vessels and its movement into small arteries in different vascular beds. Traumatic injury from catheter manipulation is thought to be the most common cause of atheroembolic disease. Notably, however, anticoagulants such as warfarin and heparin, given their potential to prevent proper healing of atheromas in the aorta after instrumentation, have been implicated in case reports as causative agents in renal atheroembolic disease.[5,6] The clinical spectrum of renal atheroembolic disease includes blue toe syndrome, livedo reticularis, visual deficits, and abdominal pain from mesenteric ischemia.[7] Laboratory abnormalities include elevated eosinophil counts in the blood and eosinophiluria. AKI is believed to be caused by distal and partial occlusion of the small arteries that leads to ischemic atrophy, as opposed to large areas of infarction.[5] Treatment for renal atheroembolic disease is largely supportive.

EPIDEMIOLOGY OF ACUTE KIDNEY INJURY

Definitions of Acute Kidney Injury

Several definitions have been used to identify AKI, which has resulted in wide variation in estimates of its incidence. The interventional

cardiology and radiology literature has traditionally defined *contrast-induced acute kidney injury* as a rise in serum creatinine of at least 0.5 mg/dL or a 25% increase from baseline within 48 to 72 hours after contrast administration.[8,9] However, these definitions differ from those in the cardiothoracic and nephrology literature, which seek to evaluate AKI in a variety of settings not limited to contrast exposure.[10] For example, the Society of Thoracic Surgeons defines *postoperative renal insufficiency* as a twofold or greater elevation of creatinine that must exceed 2.0 mg/dL, whereas *kidney failure* is defined as AKI that requires dialysis.[11]

In an attempt to standardize the definition across disciplines, the nephrology community has adopted graded criteria for AKI that are similar in principle to the staging system applied to CKD. The most recent practice guidelines from the Kidney Disease Improving Global Outcomes (KDIGO) working group synthesized elements of the previous Acute Kidney Injury Network (AKIN) group criteria and Acute Dialysis Quality Initiative (ADQI) group (risk, injury, failure, loss, and end-stage renal failure [RIFLE]) criteria to grade AKI based on urine output or change in creatinine (Table 6-3).[12-14] The mildest stage of AKI, stage 1, was defined as the rapid development of kidney dysfunction, including either a rise in serum creatinine (absolute rise ≥0.3 mg/dL [≥26.4 μmol/L] within 48 hours or a relative rise of 50% or more from baseline in 7 days or less) or a reduction in urine output to less than 0.5 mL/kg/hour for 6 to 12 hours. The severity of AKI can be further staged by the magnitude of increase in serum creatinine or reduction in urine output and the need for renal replacement therapy (i.e., stages 2 or 3).[12] The time frame for alteration in serum creatinine or urine output after contrast exposure was not specified because the authors acknowledged that changes can often be detected within 12 hours but may not manifest fully for up to 5 days.

An important acknowledgement in the KDIGO guidelines was that some cases of AKI after contrast exposure may be due to unrelated factors, such as drug toxicity or hemodynamic instability. Accordingly, the KDIGO guidelines recommended that other causes of AKI should be evaluated before assuming it is due to contrast-induced injury. This caveat is an important difference from the definition of CI-AKI traditionally used in the interventional cardiology and radiology literature that includes all cases of AKI after contrast exposure, regardless of etiology. The criteria proposed in the KDIGO guidelines have been embraced in the cardiology community and are used in most current studies of AKI in the cardiology literature.[15,16]

Incidence and Prognosis of Acute Kidney Injury

The incidence of AKI depends on both the population studied and the definition used. Using the KDIGO definition (a rise in serum creatinine levels of 0.3 mg/dL or at least a 50% increase from baseline), the

TABLE 6-1 Risk Factors for the Development of Contrast-Induced Nephropathy

Clinical Factors
Chronic kidney disease
Diabetes mellitus
Advanced age
Female gender
Peripheral vascular disease
Hypertension
Ejection fraction less than 40%
Presenting Factors
Acute coronary syndrome
Hypotension
Heart failure
Volume depletion
Concomitant nephrotoxic medications
Anemia
Procedural factors
Intraaortic balloon pump placement
Multivessel disease
Contrast amount
Contrast type

TABLE 6-2 Concomitant Drugs to Monitor With Exposure to Contrast Agents

Drugs That Influence Renal Hemodynamics
Nonsteroidal antiinflammatory drugs (NSAIDs)
Cyclooxygenase 2 (COX-2) inhibitors
Nesiritide
Angiotensin-converting enzyme (ACE) inhibitors
Angiotensin receptor blockers
Dipyrimadole
Drugs That Cause Tubular Toxicity
Diuretics, including mannitol
Antibiotics, including aminoglycosides, vancomycin, amphotericin B
Immunosuppressants, including tacrolimus and cyclosporine A
Drugs With Potentially Enhanced Toxicity After Contrast-Induced Nephropathy
Metformin
Statins

Adapted from Erley C: Concomitant drugs with exposure to contrast media, *Kidney Int Suppl* (100):S20-S24, 2006.

TABLE 6-3 Comparison of RIFLE and AKIN Criteria for Diagnosis and Classification of Acute Kidney Injury

AKIN		RIFLE	
Serum creatinine (Cr)	**Urine output (common to both)**	**Class**	**Serum creatinine or glomerular filtration rate (GFR)**
Stage 1: increase of ≥0.3 mg/dL or increase to 1.5× to 2× baseline Cr	<0.5 mL/kg/hr for at least 6 hours	**R**isk	Increase to 1.5× baseline Cr or decrease in GFR by >25%
Stage 2: increased to 2× to 3× baseline Cr	<0.5 mL/kg/hr for >12 hours	**I**njury	Increase to 2× baseline Cr or decrease in GFR by >50%
Stage 3: increased to >3× baseline Cr or ≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL or on RRT	<0.3 mL/kg/hr for 24 hours or anuria for 12 hours	**F**ailure	Increase to 3× baseline or Cr >4 mg/dL with an acute increase of >0.5 mg/dL or decrease in GFR by >75%
		Loss	Persistent acute renal failure or complete loss of kidney function for >4 weeks
		ESRD	ESRD for >3 months

Adapted from Kidney Disease Improving Global Outcomes (KDIGO): Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl* 2(1):21, 2012.
AKIN, Acute Kidney Injury Network; *ESRD,* end-stage renal disease; *RIFLE,* risk, injury, failure, loss, and end-stage renal failure; *RRT,* renal replacement therapy.

reported incidence from the National Cardiovascular Data Registry (NCDR) was 7% in the general population[15] and 16% in those presenting with acute myocardial infarction (MI).[16] In most cases, AKI after cardiac catheterization and PCI is completely reversible, with a typical clinical course consistent with acute tubular necrosis and nonoliguric AKI. Abnormalities in serum creatinine levels start within 24 to 48 hours after the procedure, peak at 5 days, and then completely recover within 2 to 4 weeks.[17] The need for renal replacement therapy with hemodialysis or peritoneal dialysis is rare (1% to 4%).[18] Among those who do require renal replacement therapy, less than 50% require it long term.[19] The requirement for renal replacement therapy appears to be more likely in the setting of renal atheroembolic disease, which has a more progressive course than CI-AKI and a lower likelihood of recovery. Notably, the development of AKI after cardiac catheterization and PCI has been associated with several clinical outcomes unrelated to kidney disease, including longer hospital stays and greater inpatient costs.[20] Recent reports also suggest that the development of CI-AKI predicts short- and long-term mortality.[21-24] What remains unclear from this literature, however, is whether the development of AKI after PCI is simply a marker of greater disease acuity or additional comorbidities such as diabetes mellitus.

RISK FACTORS FOR CONTRAST-INDUCED ACUTE KIDNEY INJURY

The most powerful predictor of AKI following cardiac catheterization is the presence of preexisting CKD. Most cases of CI-AKI with long-term complications occur in patients who have preexisting evidence of advanced CKD, and the risk of developing AKI following PCI increases with increasing severity of CKD: 8% for patients with an estimated glomerular filtration rate (eGFR) between 45 and 60 mL/min/1.73 m^2, 12.9% for patients with an eGFR between 30 and 45 mL/min/1.73 m^2, and 26.6% for patients with an eGFR less than 30 mL/min/1.73 m^2.[15] In addition to CKD, certain key risk factors for CI-AKI must be recognized on preprocedural evaluation; this includes advanced age, diabetes mellitus, and heart failure. Several bedside tools have been created to predict a patient's risk of developing CI-AKI after cardiac catheterization and PCI.[25-28] Historically, the most commonly used risk models have been heavily influenced by total contrast exposure, a variable that can only be determined after the completion of the procedure.[25] An ideal risk model, however, would allow clinicians to prospectively identify patients at high risk for CI-AKI before cardiac catheterization. Recently, Gurm and colleagues[26] used a cohort of 68,573 PCI procedures in Michigan to develop an easy-to-use online calculator (https://bmc2.org/calculators/cin) that utilizes only preprocedural variables to accurately estimate a patient's risk of CI-AKI and a new requirement for dialysis (Table 6-4). Risk models allow clinicians to discuss the potential benefits and risks of cardiac catheterization more precisely and can help focus the use of certain preventive strategies on patients at highest risk.

TABLE 6-4 BMC2 Contrast-Induced Acute Kidney Injury Risk-Prediction Model, Reduced Version

Patient Presentation
Percutaneous coronary intervention (PCI) indication
PCI status
Coronary artery disease presentation
Cardiogenic shock
Heart failure within 2 weeks
Pre-PCI left ventricular ejection fraction
Clinical History
Diabetes mellitus and type of therapy
Patient Characteristics
Age
Weight
Height
Preprocedural Laboratory Assessment
Serum creatinine
Hemoglobin
Troponin I
Troponin T
Creatine kinase MB

Adapted from Gurm HS, Seth M, Kooiman J, Share D: A novel tool for reliable and accurate prediction of renal complications in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 61(22):2242-2248, 2013, doi:10.1016/j.jacc.2013.03.026.
BMC2, Blue Cross Blue Shield of Michigan Cardiovascular Consortium.

CHRONIC KIDNEY DISEASE

Epidemiology and Classification

The population of patients with CKD worldwide is growing at a tremendous rate. Recent studies estimate the prevalence of CKD in the general adult population of the United States to be 14%, and the rate is 35% in patients 60 years of age or older.[29] Consequently, these high-risk patients are now encountered much more frequently in the cardiac catheterization laboratory. In one recent registry, for example, 29% of patients who underwent PCI had at least mild CKD.[15] For the interventional cardiologist, identifying these patients is important for two reasons: First, this group represents those patients at highest risk for developing kidney dysfunction following PCI, and they require specific preventive therapies prior to their procedures. Second, patients with CKD at baseline are also more likely to have worse cardiovascular outcomes after their procedures. This latter finding is due in part to the well-established relationship between CKD and cardiovascular disease. Until recently, defining patients with CKD was problematic owing to a multitude of nonstandardized definitions and inaccurate assessments of eGFR.

The National Kidney Foundation now specifically defines *chronic kidney disease* as the presence of sustained abnormalities of kidney function manifest by either a reduced GFR or the presence of kidney damage.[30] Kidney damage is defined by structural or functional abnormalities of the kidney in the presence or absence of decreased GFR manifest by either pathologic abnormalities (assessed by kidney biopsy) or markers of kidney damage that include laboratory abnormalities (in the composition of blood or urine) and radiographic abnormalities (on imaging tests).[30] Once GFR has been assessed, patients with CKD can be stratified into one of five stages (Table 6-5) in order of increasing impairment (in mL/min/1.73 m^2): stage 1 (eGFR ≥90), stage 2 (eGFR 60 to 89), stage 3a (eGFR 30 to 44), stage 3b (eGFR 45 to 59), stage 4 (eGFR 15 to 29), and stage 5 (eGFR <15). Patients with eGFRs of 60 mL/min/1.73 m^2 or more are considered to have CKD if they meet additional criteria that demonstrate evidence of kidney damage based on pathologic, laboratory, or imaging tests. Such markers of kidney damage include microalbuminuria, proteinuria, abnormalities of the urinary sediment, pathologic findings, or abnormal radiologic findings. In all cases, the definition of CKD requires that kidney disease has persisted for 3 months or longer.

Estimation of Glomerular Filtration Rate

It is important to note that a normal serum creatinine level does not necessarily reflect normal kidney function, and standard reference ranges for "normal" often misclassify patients with early disease (Fig. 6-1).[31] Such errors result from the fact that serum creatinine level alone does not accurately reflect the level of GFR because of nonlinear relationships that vary according to age, gender, race, and lean body mass. Both direct and indirect measures of GFR are available: Direct measurements of GFR may be more accurate, but they are impractical in routine clinical practice. Indirect measurements of GFR are obtained by incorporating serum creatinine values into formulas such as the Cockcroft-Gault equation or Modification of Diet in Renal Disease (MDRD) study equation.[30] Although the MDRD study equation has

TABLE 6-5 Stages of Chronic Kidney Disease, Action Recommendations, and Prevalence

CKD Stages	Description	GFR mL/min per 1.73 m2	Action Recommendation	Prevalence (%)
1	Kidney damage with normal or increased GFR	≥90	Diagnosis and treatment Treatment of coexisting conditions Slowing progression CVD risk reduction	2.3
2	Kidney damage with mild decrease in GFR	60-89	Estimation of progression	2.5
3A	Kidney damage with mild to moderate decrease in GFR	45-59	Evaluation and treatment of complications	4.6
3B	Kidney damage with moderate to severe decrease in GFR	30-44	Evaluation and treatment of complications Referral to nephrologist	1.6
4	Kidney damage with severe decrease in GFR	15-29	Referral to nephrologist Consideration for renal replacement therapy	0.4
5	Kidney failure	<15	Replacement (if uremia present)	0.1

Adapted from National Kidney Foundation Kidney Disease Outcome Quality Initiative Advisory B: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. *Am J Kidney Dis* 39:S1-S246, 2002; Kidney Disease Improving Global Outcomes (KDIGO): Clinical Practice Guideline for Chronic Kidney Disease. *Kidney Int Suppl* 3(1):14, 31, 2013.
CKD, Chronic kidney disease; *CVD,* cardiovascular disease; *GFR,* glomerular filtration rate.

generally been purported to have less bias, both formulas have limitations in accuracy, especially for patients with normal kidney function.[32] In addition, these formulas do not perform well for many other individuals who were not well represented in the cohorts from which these equations were developed, including those who (1) have very high or low muscle mass, weight, or age; (2) are severely ill or hospitalized; (3) ingest no meat or large amounts of meat; or (4) are from minority racial and ethnic groups, such as Asians or Hispanics.[32]

Serum cystatin C level has been suggested as a superior alternative to serum creatinine level in estimating GFR in patients with CKD because cystatin C has a more constant rate of production.[32,33] However, serum levels of cystatin C may also be influenced by age, gender, and muscle mass.[34] Although cystatin C has been used in research studies for many years, it has not been widely adopted in clinical practice because it provides only a marginal improvement in the accuracy and staging of CKD over current methods that use serum creatinine levels. Additionally, many clinical laboratories are not yet equipped to perform this test. In the setting of acute coronary syndrome (ACS), conservative estimation of kidney function using serum creatinine level with the Cockcroft-Gault equation is critically important for drug dosage adjustments. Appropriate dosing of anticoagulants and antiplatelet medications during PCI is crucial to prevent bleeding complications, particularly in women and older adult patients who are at higher risk.[35]

Cardiovascular Risk

Patients with CKD are at particularly high risk for death and adverse cardiovascular events following interventional procedures.[36-39] The risk of adverse outcomes is progressive, with an independent, graded association between reduced eGFR and risk of hospitalizations, cardiovascular events, and death.[36,38,39] Consequently, the National Kidney Foundation, American Heart Association, and the Eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure have classified the presence of CKD as a cardiovascular risk factor.[30,37,40] Mechanisms by which CKD increases cardiovascular risk are unclear and are under investigation. The progressive increase in cardiovascular risk associated with declining kidney function is largely explained by a larger burden of traditional risk factors.[41] However, CKD is also associated with many nontraditional risk factors that include albuminuria, proteinuria, homocysteinemia, elevated uric acid levels, anemia, dysregulation of mineral metabolism and arterial calcification, oxidative stress, inflammation, malnutrition, endothelial dysfunction, insulin resistance, and conditions that promote coagulation, all of which are associated with accelerated atherosclerosis.[30,37,42] Finally, another contributing factor may be the paradox of lower rates of appropriate therapy with risk-factor modification and intervention among CKD patients than in the general population despite established awareness of their high cardiovascular risk, a concept referred to as *therapeutic nihilism*.[43]

Planning for Hemodialysis

Because many patients with advanced CKD ultimately require hemodialysis, particular care should be taken to preserve arterial and venous targets that may be used to create a vascular access site for hemodialysis in the future. Although little evidence is available on the long-term implications of radial access and instrumentation of the arterial system of the upper extremity for coronary angiography using contemporary equipment, some concern exists in the nephrology community that this may compromise success rates of future arteriovenous fistulas and grafts, whose function is essential for patients who progress to ESRD. Although this topic needs to be investigated, it would be reasonable to preferentially choose a femoral approach in patients with advanced CKD when no contraindications are present and patients are otherwise not at high risk for bleeding.

MINIMIZING THE RISK OF ACUTE KIDNEY INJURY

Patients with CKD often have existing comorbidities that may complicate their procedure and postprocedure management. As always, developing a systematic approach that reviews the patient's history, physical examination, and laboratory studies is critical (Fig. 6-2). As described earlier, the clinician must pay particular attention to accurate assessment of the degree of CKD at baseline in addition to several clinical risk factors that have been consistently associated with poor outcomes in patients with CKD such as diabetes mellitus, concomitant medication use, and volume depletion or hemodynamic instability. The approaches below are designed to minimize the risk of CI-AKI after cardiac catheterization and PCI.

Periprocedural Strategies

Most strategies to reduce the risk of procedural complications in patients with CKD must be considered even before cardiac catheterization and PCI begin. These include measures to carefully prepare the patient with adequate hydration and the use of specific drug therapies.

Periprocedural Hydration

The most important preventative strategy to lower the risk of CI-AKI is to ensure adequate hydration at the time of contrast administration. Patients are at risk for dehydration given that they have traditionally been asked to avoid oral intake starting at midnight on the night before

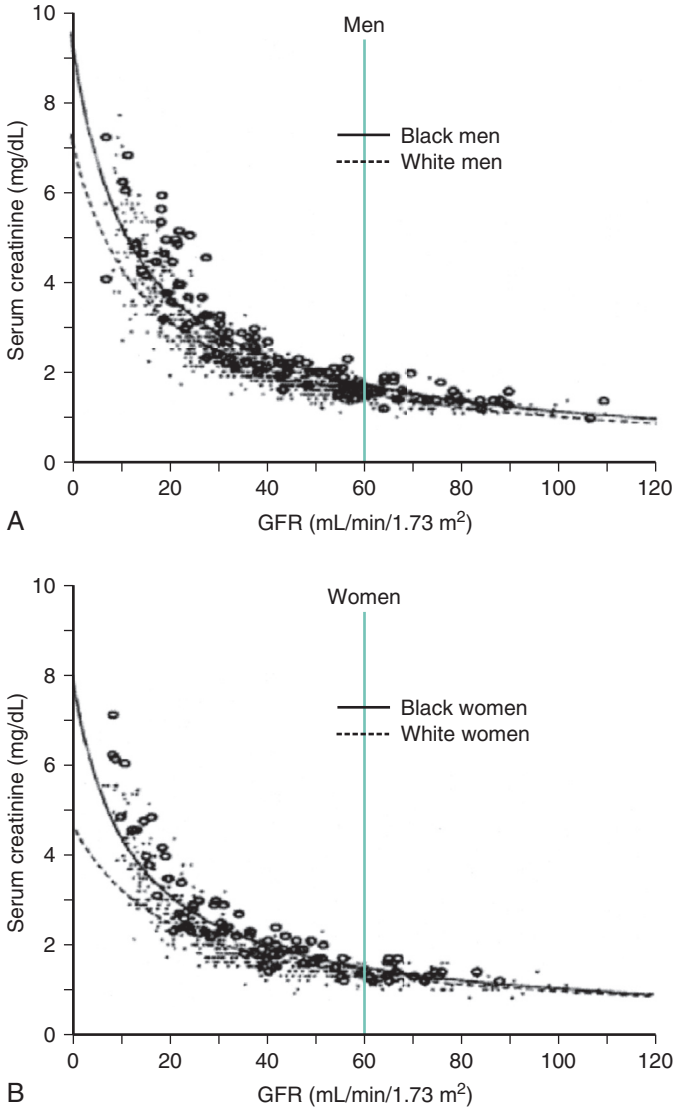

FIGURE 6-1 Relationship of measured serum creatinine levels to measured glomerular filtration rates in the Modification of Diet in Renal Disease Study, by men (**A**) and women (**B**). (Adapted from Levey AS, Bosch JP, Lewis JB, et al: A more accurate method to estimate glomerular filtration rate from serum creatintine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130: 464, 1999.)

their procedure. However, this paradigm has been challenged recently as evidence supporting preprocedural oral hydration has emerged. A recent meta-analysis of six small clinical trials that compared preprocedural oral and intravenous (IV) volume expansion strategies showed no difference in the incidence of CI-AKI.[44] Despite clear practical advantages, oral hydration regimens have not been widely accepted into clinical practice, likely because of the theoretic increased risk for aspiration with moderate sedation and the lack of evidence from large clinical trials.

For those patients suspected to be dehydrated or at greater risk of CI-AKI because of CKD, it is important to initiate IV fluid early while carefully monitoring for heart failure in those sensitive to rapid volume changes. The best-studied fluid regimen in clinical trials has been 0.9% normal saline infusions at a rate of 1 mL/kg/hr for 6 to 12 hours prior to the procedure and continuing after the procedure.[45] Data from a large trial suggest that administration of isotonic 0.9% normal saline may modestly reduce the incidence of CI-AKI, particularly among patients with diabetes mellitus and those receiving large doses of contrast agents, when compared with 0.45% saline.[46]

From a practical standpoint, a quick assessment of the adequacy of hydration is possible prior to contrast injection by assessing the left ventricular end-diastolic pressure (LVEDP) with a pigtail or multipurpose catheter. If the patient appears to be dehydrated based on his or her hemodynamic parameters, fluid boluses may be given prior to contrast agent exposure, and a continuous saline infusion can be considered. In the Prevention of Contrast Renal Injury with Different Hydration Strategies (POSEIDON) trial, Brar and colleagues[47] showed that a sliding-scale IV saline infusion protocol based on LVEDP (5 mL/kg/hr for a LVEDP <13 mm Hg, 3 mL/kg/hr for a LVEDP of 13 to 18, and 1.5 mL/kg/hr for a LVEDP >18 mm Hg) during and for 4 hours after cardiac catheterization significantly decreased the incidence of CI-AKI compared with a standard hydration strategy (1.5 mL/kg/hr regardless of LVEDP) in high-risk patients. This simple and intuitive hydration strategy would be reasonable to consider for all patients with CKD or other risk factors for CI-AKI (see Fig. 6-2).

Recently, great interest has been shown in the use of sodium bicarbonate infusions to hydrate patients with CKD during the periprocedural period. Sodium bicarbonate may relieve oxidative stress, which is thought to be a potential mechanism of action by which CI-AKI occurs. Although some early clinical trials suggested a benefit of sodium bicarbonate over sodium chloride infusion, most recent studies have not demonstrated any significant difference in the incidence of CI-AKI between these hydration strategies.[45,48-52] Also, in contrast to readily available sodium chloride solutions at most medical facilities, commercially manufactured sodium bicarbonate solutions may not be readily available. Relying on pharmacists to make a volume of sodium bicarbonate solution for each patient with CKD who will undergo a cardiac catheterization is more time consuming, labor intensive, and prone to error than administering manufactured solutions of sodium chloride. Thus without a consistent benefit observed in clinical trials, it is difficult to justify the routine administration of sodium bicarbonate in patients with CKD undergoing cardiac catheterization.

Medications

Several medications have been investigated as potential preventative therapies for CI-AKI. The most extensively studied agent is *N*-acetylcysteine, which has been evaluated in more than 20 randomized clinical trials.[53] The premise behind the use of *N*-acetylcysteine is that it acts as a scavenger of reactive oxygen species and promotes vasodilatory effects in the renal medulla. The first major trial, reported by Tepel and colleagues,[54] evaluated its use in 83 patients who received IV contrast agents for computed tomography (CT). This study found an approximately 90% relative risk reduction in CI-AKI with the use of *N*-acetylcysteine. However, a recent large, multicenter, randomized trial by the Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT) investigators studied 2308 patients with a least one risk factor for CI-AKI undergoing elective coronary or peripheral vascular angiography and found no difference in the incidence of CI-AKI or the need for dialysis at 30 days in patients treated with *N*-acetylcysteine versus placebo.[55] These findings were consistent across high-risk subgroups of patients with diabetes and moderate to severe CKD who had previously been thought to derive the most benefit from this preventative strategy.[56] Additional studies of periprocedural *N*-acetylcysteine in patients with acute coronary syndromes, another high-risk subset of patients, have shown no consistent benefit.[57,58] Though *N*-acetylcysteine is a relatively benign intervention, the balance of evidence does not favor its routine use to prevent CI-AKI.[59] Some continue to recommend its use, largely given a benefit seen in some limited trials and the low cost and safety of the intervention.[12] Further studies, such as the ongoing Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial, may provide some additional clarity about the potential benefits of *N*-acetylcysteine in certain subsets of patients.[60]

Statins have antioxidant, antiinflammatory, and antithrombotic effects that are thought to be nephroprotective. Several recent trials

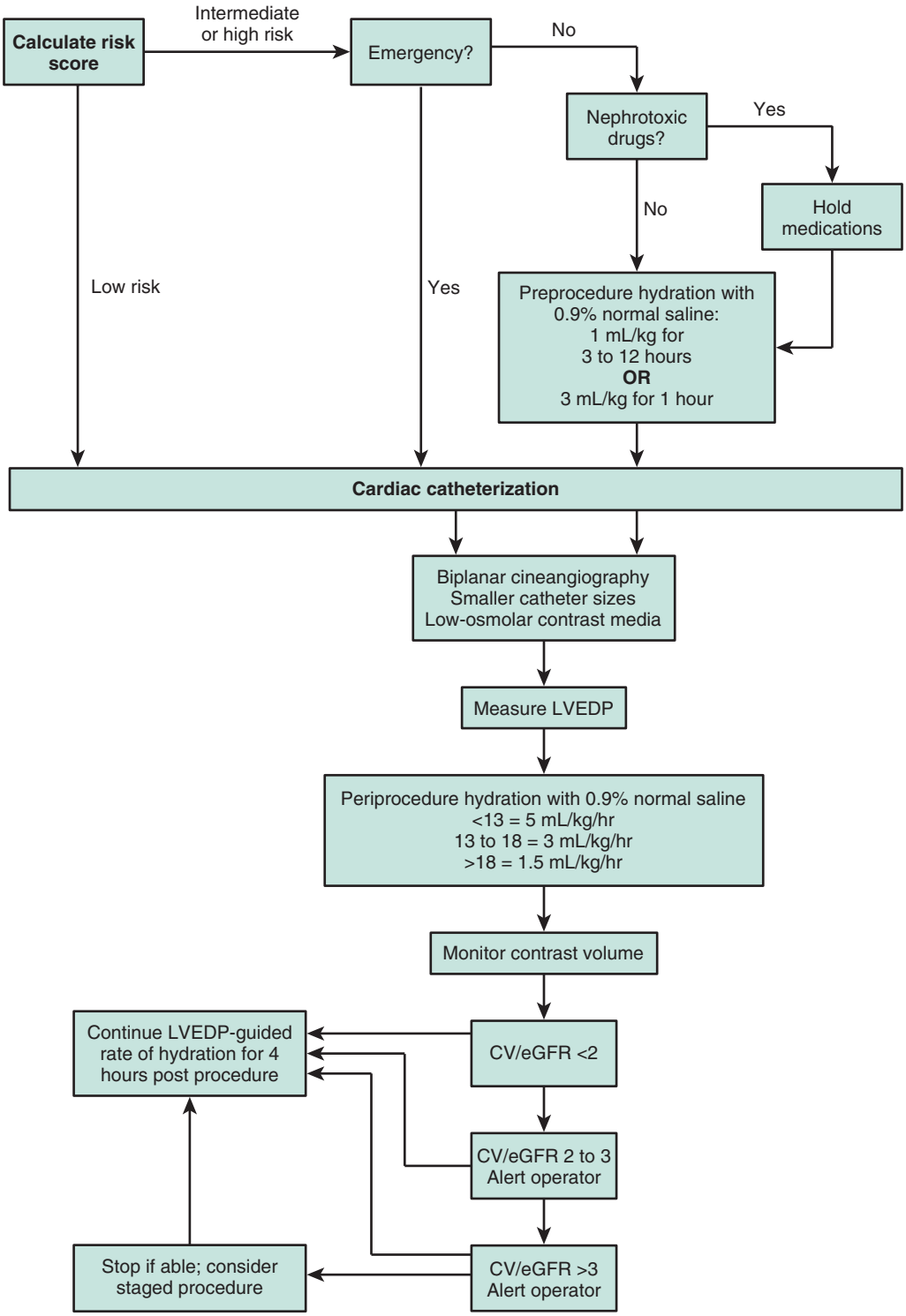

FIGURE 6-2 Strategies to reduce the risk of contrast-induced acute kidney injury in patients undergoing cardiac catheterization. *CV,* Cardiovascular; *eGFR,* estimated glomerular filtration rate; *LVEDP,* left ventricular end-diastolic pressure. (Adapted from Howe M, Gurm HS: A practical approach to preventing renal complications in the catheterization laboratory. *Intervent Cardiol Clin* 3:429-439, 2014.)

have shown lower rates of CI-AKI in statin-naïve patients when they are treated with high-dose statins before coronary angiography.[61-64] The largest trial was the Rosuvastatin to Prevent Contrast-Induced Acute Kidney Injury in Patients With Diabetes (TRACK-D) trial, which studied 2998 statin-naïve patients with diabetes mellitus and CKD undergoing coronary angiography or PCI and found that patients who were randomized to pretreatment with 10 mg of rosuvastatin 2 days before and 3 days after contrast administration had a significantly lower incidence of CI-AKI than patients who did not receive a statin until 3 days after contrast administration (2.3% vs. 3.9%).[64] Currently, most patients who undergo coronary angiography will already have some indication for statin therapy, so it may be reasonable to pretreat

patients who have risk factors for CI-AKI (i.e., CKD, ACS, and congestive heart failure [CHF]) with a high-potency statin unless a clear contraindication is present.

Another important medication that has been studied extensively in randomized clinical trials is fenoldopam, which works as a dopamine-receptor agonist and is believed to preserve renal blood flow despite insults from contrast agent exposure. A series of small clinical studies had suggested significant benefit in terms of the reduction of CI-AKI, particularly in high-risk patients.[65,66] However, enthusiasm for the use of fenoldopam has fallen since publication of a large, multicenter trial by Stone and colleagues in 2003.[67] In this study, no benefit was seen with fenoldopam in 315 patients who had eGFRs below 60 mL/min and underwent cardiac catheterization.

Ascorbic acid has antioxidant properties that have led to investigation into its use for preventing CI-AKI. A recent meta-analysis of nine small, randomized controlled trials of 1536 patients treated with ascorbic acid (usually 1 to 3 g the night before, the day of, and daily for 1 to 2 days after cardiac catheterization) showed a 33% relative risk reduction of CI-AKI compared with that of patients given placebo or an alternative therapy.[68] This finding should be confirmed with larger clinical trials, but ascorbic acid is a well-tolerated, low-risk, inexpensive therapy that may be worth considering for selected patients. Additional agents that have been studied include iloprost, theophylline (or aminophylline), probucol, captopril, dopamine, atrial and brain natriuretic peptides, calcium channel blockers, and prostaglandin E1. Most of these agents have either been studied only in small trials (iloprost[69]) or have yielded largely conflicting results (theophylline[70,71]); thus their routine use cannot be recommended. Medications that should be avoided unless otherwise indicated include mannitol or furosemide for forced diuresis (without matched hydration or hemodynamic monitoring), given their potential to result in volume depletion and to exacerbate AKI.[72]

Other Strategies

Several other nonpharmacologic strategies have been suggested as approaches for minimizing AKI after cardiac catheterization and PCI. However, many of these require intense resources, and their use is limited to the highest-risk patients. The use of furosemide-induced high-volume diuresis with automated matched hydration using the RenalGuard System (PLC Medical Systems, Franklin, MA) has shown promise in reducing CI-AKI in high-risk patients with CKD. The system directly measures urine output in real time using a standard Foley catheter, and it simultaneously infuses an equivalent volume of IV normal saline. Patients are given a priming bolus of 250 mL of 0.9% normal saline 90 minutes prior to contrast administration, followed by 0.25 to 0.5 mg/kg of IV furosemide (50 mg maximum). They are continued on an IV saline infusion at a rate that is automatically adjusted to maintain a urine output rate greater than 300 mL/hour throughout the procedure and for 4 hours after final contrast administration. In the randomized, multicenter Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II; $N = 292$), Briguori and colleagues[73] reported a significant reduction in CI-AKI (11% vs. 20.5%) and in-hospital dialysis (0.7% vs. 4.1%) in high-risk patients with CKD who were treated with the RenalGuard System compared with sodium bicarbonate and *N*-acetylcysteine. In the smaller Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast-Induced Nephropathy Prevention (MYTHOS) trial ($N = 170$), Marenzi and colleagues[74] reported a similarly impressive reduction in CI-AKI (4.6% vs. 18%) as well as fewer in-hospital clinical complications.

Another preventative approach that has been suggested for high-risk patients is the use of hemodialysis or hemofiltration after or during contrast agent exposure. Although contrast agents can be effectively removed from the blood by hemodialysis, clinical studies have not consistently demonstrated a benefit.[75,76] One explanation for this has been that it may result in hemodynamic or inflammatory changes that are in turn nephrotoxic and thus offset the removal of contrast agents. To better address this issue, Marenzi and colleagues[77] studied the use of hemofiltration in 114 patients with severe CKD who underwent PCI. Hemofiltration has the advantage of avoiding hypovolemia and can provide high-volume hydration without concerns of intravascular congestion. In this extremely high-risk group, the use of hemofiltration starting at least 4 to 6 hours prior to PCI was associated with improved clinical outcomes that included lower rates of renal replacement therapy, as well as reduced in-hospital and 1-year mortality. However, these findings have not been consistently replicated, and a recent meta-analysis by Cruz and colleagues[78] showed no benefit of hemofiltration compared with standard medical therapy. Nonetheless, some tertiary care centers continue to utilize this intervention in their highest-risk patients.

Finally, remote ischemic conditioning, either with sequential blood pressure cuff inflations or repeated intracoronary balloon inflations, is another nonpharmacologic strategy that has been studied for protective effects. The results of exploratory trials have been favorable, although the results need to be validated in larger trials.[79,80] Also, the underlying mechanism of the effects on the kidney of transient ischemia in a remote organ are not clear and require further investigation.

Intraprocedural Strategies

Intraprocedural strategies for approaching patients with CKD largely depend on three things: (1) the choice of contrast agent, (2) minimizing the volume that is used as much as possible, and (3) avoiding use of potentially nephrotoxic medications. Although useful, these strategies must always be used without sacrificing the operator's ability to adequately and safely perform the procedure. This requires a careful balance to weigh the clinical risks and benefits of different approaches. For example, appropriate visualization of the lesion and adjacent coronary anatomy is essential for success during PCI and should not be sacrificed.

General strategies to consider during the case include the use of smaller guiding catheters when possible because these are associated with lower volumes of contrast agents.[81] It is also important to minimize use of contrast agents during the diagnostic portion of the case if ad hoc PCI is performed. This can be done by potentially avoiding left ventriculograms and by using noninvasive tests, such as echocardiography, to evaluate systolic wall motion and function. The use of biplanar coronary angiography, which allows the operator to obtain two simultaneous views with one injection during cineangiography, is another commonly used tool. The use of automated contrast injector systems has been promoted as a strategy to reduce contrast use, but studies have shown that the small reduction in total contrast volume does not reduce adverse outcomes related to kidney function.[82] Other proposed intraprocedural strategies to limit CI-AKI include both coronary sinus cannulation with extracorporeal column filtration and intraprocedural hypothermia. Although the feasibility of the coronary cannulation system has been demonstrated in a swine model and in small human studies,[83-85] these results have not been widely validated. Intraprocedural hypothermia has also not been shown to be effective for the prevention of CI-AKI.[86]

The Choice and Use of Contrast Agents

The choice of contrast agent is an important intraprocedural consideration that has evolved considerably over the last several years with the development of low-osmolar and isoosmolar contrast agents. Traditional iodine-based contrast agents were hypertonic, including ionic compounds such as diatrizoate, which frequently caused mild hemodynamic changes in addition to CI-AKI. Given their substantially lower costs in recent years, most laboratories have switched to the routine use of low-osmolar, nonionic contrast agents (iopamidol, iohexol, ioxaglate), which improve hemodynamic effects and patient comfort. One important effect of low-osmolar agents is a reduction in CI-AKI. In a meta-analysis that included data from 25 trials, the risk of CI-AKI was 39% lower in patients who received low-osmolar contrast agents compared with those who received hyperosmolar contrast agents.[87] This benefit appeared to be even more pronounced in patients

with preexisting kidney disease who experienced a 50% relative risk reduction. The introduction of iodixanol, an isoosmolar contrast agent, has raised the question of whether the incidence of CI-AKI can be further reduced. In a widely cited study of patients with CKD and diabetes mellitus, the use of isoosmolar contrast agents reduced the incidence of CI-AKI by over 90% when compared with low-osmolar contrast agents.[88] An additional study compared these two types of contrast agents in patients undergoing high-risk PCI.[89] However, more recent clinical trials and registry analyses have shown no difference in outcomes.[90-94] Because the data comparing isoosmolar and low-osmolar contrast agents are not consistent, current PCI guidelines do not make formal recommendations regarding the choice of low-osmolar or isoosmolar contrast agents.

Finally, some investigators have begun to use alternative, noniodinated contrast agents such as gadolinium, particularly in peripheral angiography. Although case reports of its use in the coronary circulation do exist, many questions remain regarding the overall safety and feasibility of this approach, particularly given the high serum osmolality of these agents and the risk of nephrogenic systemic fibrosis in patients with severe kidney impairment.[95-97]

Regardless of the selection of a contrast agent, it is imperative to use the least amount of volume required for adequate visualization of the coronary artery and technical success of the procedure. In patients at particularly high risk, the suggested maximum allowable contrast dose (MACD, which is equal to three times the GFR estimated by the Cockroft-Gault equation) should be calculated before the procedure so that the interventional cardiologist and the catheterization laboratory team can be aware of its use during the procedure. Specific catheterization techniques have been described that vastly reduce the requirement for contrast in the renal-impaired patient to less than 10 mL (and even occasionally 0 mL in a case that involved prior diagnostic images as a roadmap and intravascular ultrasound) for both diagnostic and interventional procedures.[98] Recent contrast exposure for other radiologic studies should also be considered when determining the MACD before the procedure because it is increasingly common for patients to have multiple contrast-related procedures during a hospitalization. Many patients who come for coronary angiography have already received a large dose of contrast exposure within the previous 24 to 48 hours. Recent performance measures have suggested recording total contrast exposure for the admission prior to every procedure. This can alert operators to patients who may warrant more judicious use of contrast than their risk profile might otherwise suggest or who may benefit from a delay in their procedure to decrease adverse kidney outcomes.[99] Staging nonurgent procedures is a potential approach in many settings and will minimize the risk of patients developing CI-AKI. Unfortunately, few data are available on the optimal timing between sequential procedures.

SPECIAL POPULATIONS

End-Stage Renal Disease

Patients with ESRD who undergo cardiac catheterization and PCI represent an important group that may be at risk for intraprocedural, as well as short- and long-term, complications. Most patients with CKD will die of other nonrenal causes, especially cardiovascular disease, before they progress to ESRD. However, the number of patients with ESRD is growing rapidly, and these patients are increasingly encountered in the cardiac catheterization lab. In the United States, both the incidence and prevalence of ESRD have doubled in the past decade, and they are expected to increase significantly in the future.[100] In 2011, over 615,000 people required dialysis or transplantation for ESRD in the United States; however, by 2030, estimates suggest that this number will increase to more than 2 million.[100] The dramatically increased rates of cardiovascular disease and accelerated atherosclerosis have long been recognized in ESRD.[101] Approximately 42% of deaths among patients with ESRD are due to cardiovascular events. Sudden cardiac death, which is often precipitated by MI, is the most common cause of death in patients with ESRD, and 11% of cardiac deaths can be directly attributed to acute MI.[100] The 2-year mortality rate after acute MI among patients with ESRD on hemodialysis is 74%, or three times the mortality rate after MI in the general population.[100,102] This excess cardiovascular mortality risk ranges from 500-fold higher in individuals aged 25 to 35 to fivefold higher in individuals older than 85 years.[103]

In most patients who are chronically on dialysis, routine dialysis postprocedurally is not needed after exposure to contrast agents.[76,104] However, the studies in this area have involved only a select group of patients. So although it appears that most patients can be maintained on their routine schedules for dialysis, special care and attention may be needed for specific groups, such as those with poor cardiac function or evidence of residual renal function, which is more common among patients treated with peritoneal dialysis. Preservation of residual renal function is vital to successful treatment with peritoneal dialysis: once residual renal function is lost, patients often require hemodialysis.

An additional concern regarding patients with advanced CKD and ESRD is the anatomy of their coronary arteries, which are frequently diffusely diseased with a heavy atherosclerotic burden.[105] These issues can raise technical challenges in the delivery of coronary devices during routine PCI, particularly for those with ESRD where extensive coronary calcification is common. Additional strategies, such as rotational atherectomy, may be required under some circumstances for plaque modification prior to coronary stent delivery.

After PCI, the presence of CKD and ESRD has also been associated with higher rates of major adverse cardiovascular events, including restenosis and repeat target-vessel revascularization (TVR). In the era before routine stenting, restenosis was a substantial problem, with rates as high as 80% in patients with ESRD. Although the likelihood of these complications has diminished with newer devices, the risk still appears to be increased.[106,107] For example, Rubenstein and colleagues[107] demonstrated that CKD was independently predictive of worse outcomes, including repeat revascularization, in a cohort of 3334 patients who underwent PCI during a period when coronary stenting and atherectomy were being introduced. Within this study population, there also appeared to be no difference between patients with CKD and ESRD.[107] Evidence is accumulating to support the intuitive notion that drug-eluting stents may minimize the risk of restenosis even further in patients with CKD and ESRD.[108-111] In the Randomized Comparison of Xience V and Multi-Link Vision Coronary Stents in the Same Multivessel Patient With Chronic Kidney Disease (RENAL-DES) study, Tomai and colleagues[112] studied 215 patients with CKD and multivessel coronary artery disease. This unique intraindividual randomized study found a significantly lower rate of ischemia-driven TVR at 1 year (2.7% vs. 11.4%) in vessels treated with drug-eluting stents compared with those treated with bare-metal stents. Despite these promising results, optimal therapy among patients with CKD requires further investigation.

Determining the risks and benefits of PCI versus surgical revascularization in this population is also critical. This is a controversial area, and clinical trials have been unable to directly inform this issue because most have excluded patients with significant CKD and ESRD. In the absence of adequate clinical trial data, this decision is often individualized and relies on the goals of treatment, the likelihood of technical success with PCI, and the patient's operative risk with bypass surgery.[113-115] These patients may benefit from more collaborative discussions with multidisciplinary "heart teams" that include input by nephrologists.

Finally, it is important for the interventional cardiologist to appropriately select and dose adjunctive drug therapy in patients with CKD and ESRD. The risks and benefits of many drugs routinely used as adjunctive therapy in PCI, including glycoprotein IIb/IIIa inhibitors and bivalirudin, must be carefully weighed in this population because of the diminished renal clearance of such agents in these patients and the potential to increase the risk for bleeding.[116-118] Even statins, which are usually a pillar of medical therapy for primary and secondary prevention of cardiovascular disease in most patients, have not been

shown to decrease adverse clinical events in patients with ESRD and are no longer routinely recommended in some guidelines.[119]

Patients With Transplanted Kidneys

As the number of patients with transplanted kidneys increases, it is important to recognize the precautions that should be taken to avoid injuring the transplanted organs during cardiac catheterization. First, it is important to identify the location and laterality of the vascular anastomosis of the transplanted kidney. The anastomosis is commonly at the level of the external iliac artery and vein, but it can also be at the internal iliac artery and vein or at the aorta and inferior vena cava. When planning arterial and venous access, instrumentation of the vessels that supply the transplanted kidney should be avoided. If this is not possible, fluoroscopy should be used to make sure that wires and catheters are steered away from the vascular anastomoses. Additionally, contrast should be used judiciously because the consequences of CI-AKI could be devastating. It would be reasonable to have a lower threshold to implement the more aggressive preventative strategies outlined earlier, regardless of the eGFR, because these patients have only one functioning kidney. Extra care should also be taken to make sure that medications are dosed appropriately for kidney function and that potential drug interactions are anticipated before the start of the procedure because immunosuppressants can interact with many cardiac medications. Finally, because patients with transplanted organs are immunosuppressed, to lower the risk of infection, it is important to avoid leaving indwelling arterial and venous catheters and to avoid using vascular closure devices.

Congestive Heart Failure and the Risk of Acute Kidney Injury

Patients with advanced heart failure (New York Heart Association [NYHA] classes III and IV) are among the highest-risk populations for the development of CI-AKI, with an incidence of 38.5% and an odds ratio of 2.25 (95% confidence interval [CI], 1.68 to 3.01) compared with those who do not have advanced heart failure.[25] These patients pose a particularly difficult management dilemma because the use of volume-loading strategies is generally discouraged. Gentle diuresis of patients with pulmonary edema is often necessary to allow supine patient positioning for catheterization, and the relief of excess portal pressure in these patients may reduce the risk of CI-AKI.[120] Limited gentle hydration (e.g., 100 mL/hr for 2 to 4 hours) following cardiac catheterization may be considered in heart failure patients with low left ventricular end-diastolic pressures, and measures to limit contrast volume (e.g., biplanar angiography, selective angiographic views, noninvasive left ventricular functional assessment) are encouraged.

THE FUTURE

Assessment of AKI using serum markers of renal clearance, including serum creatinine and cystatin C, is inherently problematic and leads to the poor sensitivity and specificity observed when compared with biopsy-proven kidney injury. In fact, measures of structural injury are better markers of AKI and are able to detect smaller tubular insults than the current methods of relying on serum creatinine–based changes in renal clearance (i.e., function). In search of such improved biomarkers for detecting AKI, several new ones have been identified, with most of the current interest focused on a small handful of promising biomarkers: neutrophil gelatinase–associated lipocalin, interleukin-18, liver-type fatty acid binding protein, and kidney injury molecule 1.[10,33,121] Some early results are encouraging, but they have yet to be validated; therefore these tests cannot be recommended for routine clinical use.[122] Once validated in large studies that support their diagnostic and predictive capacities, however, such biomarkers are likely to complement assessment of AKI by changes in serum creatinine.

This evolution of kidney assessment moves closer to the paradigm within the field of cardiology, in which structural anatomic injury is assessed separately from overall physiologic function. Sudden changes in these new biomarkers will be used to detect AKI similar to how serum troponin and creatine kinase are used to evaluate acute coronary syndromes. Likewise, overall function will be assessed with estimating equations using serum creatinine (with or without new biomarkers, such as cystatin C), similar to the way in which ventricular function is evaluated with an ejection fraction and other measurements. In addition to clarifying the role of various alterations of the kidney, this evolution has the potential to improve clinical outcomes by helping to identify more successful treatments.[10]

REFERENCES

1. Persson PB, Tepel M: Contrast medium–induced nephropathy: the pathophysiology. *Kidney Int Suppl* (100):S8–S10, 2006.
2. Katholi RE, Woods WT, Jr, Taylor GJ, et al: Oxygen free radicals and contrast nephropathy. *Am J Kidney Dis Off J Natl Kidney Found* 32(1):64–71, 1998.
3. Toprak O, Cirit M: Risk factors for contrast-induced nephropathy. *Kidney Blood Press Res* 29(2):84–93, 2006.
4. Erley C: Concomitant drugs with exposure to contrast media. *Kidney Int Suppl* (100):S20–S24, 2006.
5. Mannesse CK, Blankestijn PJ, Man in 't Veld AJ, Schalekamp MA: Renal failure and cholesterol crystal embolization: a report of 4 surviving cases and a review of the literature. *Clin Nephrol* 36(5):240–245, 1991.
6. Hyman BT, Landas SK, Ashman RF, et al: Warfarin-related purple toes syndrome and cholesterol microembolization. *Am J Med* 82(6):1233–1237, 1987.
7. Cholesterol Embolism Study (CHEST) Investigators: The incidence and risk factors of cholesterol embolization syndrome, a complication of cardiac catheterization: a prospective study. *J Am Coll Cardiol* 42(2):211–216, 2003.
8. Kelly AM, Dwamena B, Cronin P, et al: Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. *Ann Intern Med* 148(4):284–294, 2008.
9. McCullough PA, Adam A, Becker CR, et al: Epidemiology and prognostic implications of contrast-induced nephropathy. *Am J Cardiol* 98(6A):5K–13K, 2006.
10. Hudson C, Hudson J, Swaminathan M, et al: Emerging concepts in acute kidney injury following cardiac surgery. *Semin Cardiothorac Vasc Anesth* 12(4):320–330, 2008.
11. Ferguson TB, Jr, Dziuban SW, Jr, Edwards FH, et al: The STS National Database: current changes and challenges for the new millennium. Committee to Establish a National Database in Cardiothoracic Surgery, the Society of Thoracic Surgeons. *Ann Thorac Surg* 69(3):680–691, 2000.
12. Kidney Disease Improving Global Outcomes (KDIGO): Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl* 2(1):1–138, 2012.
13. Mehta RL, Kellum JA, Shah SV, et al: Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 11(2):R31, 2007.
14. Acute Dialysis Quality Initiative workgroup: Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI). *Crit Care* 8(4):R204–R212, 2004.
15. Tsai TT, Patel UD, Chang TI, et al: Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the NCDR Cath-PCI Registry. *JACC Cardiovasc Interv* 7(1):1–9, 2014.
16. Fox CS, Muntner P, Chen AY, et al: Short-term outcomes of acute myocardial infarction in patients with acute kidney injury: a report from the National Cardiovascular Data Registry. *Circulation* 125(3):497–504, 2012.
17. McCullough PA, Sandberg KR: Epidemiology of contrast-induced nephropathy. *Rev Cardiovasc Med* 4(Suppl 5):S3–S9, 2003.
18. Freeman RV, O'Donnell M, Share D, et al: Nephropathy requiring dialysis after percutaneous coronary intervention and the critical role of an adjusted contrast dose. *Am J Cardiol* 90(10):1068–1073, 2002.
19. McCullough PA: Contrast-induced acute kidney injury. *J Am Coll Cardiol* 51(15):1419–1428, 2008.
20. McCullough PA, Wolyn R, Rocher LL, et al: Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med* 103(5):368–375, 1997.
21. Rihal CS, Textor SC, Grill DE, et al: Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 105(19):2259–2264, 2002.
22. Marenzi G, Lauri G, Assanelli E, et al: Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 44(9):1780–1785, 2004.
23. Bartholomew BA, Harjai KJ, Dukkipati S, et al: Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. *Am J Cardiol* 93(12):1515–1519, 2004.
24. Gupta R, Gurm HS, Bhatt DL, et al: Renal failure after percutaneous coronary intervention is associated with high mortality. *Catheter Cardiovasc Interv* 64(4):442–448, 2005.
25. Mehran R, Aymong ED, Nikolsky E, et al: A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 44(7):1393–1399, 2004.
26. Gurm HS, Seth M, Kooiman J, Share D: A novel tool for reliable and accurate prediction of renal complications in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 61(22):2242–2248, 2013.
27. Maioli M, Toso A, Gallopin M, et al: Preprocedural score for risk of contrast-induced nephropathy in elective coronary angiography and intervention. *J Cardiovasc Med (Hagerstown)* 11(6):444–449, 2010.
28. Chen Y-L, Fu N-K, Xu J, et al: A simple preprocedural score for risk of contrast-induced acute kidney injury after percutaneous coronary intervention. *Catheter Cardiovasc Interv* 83(1):E8–E16, 2014.
29. United States Renal Data System: 2013 Atlas of CKD & ERSD (vol 1). <http://www.usrds.org/atlas.aspx>. Accessed 25.02.15.
30. National Kidney Foundation Kidney Disease Outcome Quality Initiative Advisory B: KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. *Am J Kidney Dis* 39:S1–S246, 2002.
31. Levey AS, Bosch JP, Lewis JB, et al: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130(6):461–470, 1999.
32. Stevens LA, Coresh J, Greene T, Levey AS: Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med* 354(23):2473–2483, 2006.

33. McCullough PA, Shaw AD, Haase M, et al: Diagnosis of acute kidney injury using functional and injury biomarkers: workgroup statements from the tenth Acute Dialysis Quality Initiative Consensus Conference. *Contrib Nephrol* 182:13–29, 2013.
34. Knight EL, Verhave JC, Spiegelman D, et al: Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. *Kidney Int* 65(4):1416–1421, 2004.
35. Melloni C, Peterson ED, Chen AY, et al: Cockcroft-Gault versus modification of diet in renal disease: importance of glomerular filtration rate formula for classification of chronic kidney disease in patients with non–ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol* 51(10):991–996, 2008.
36. Go AS, Chertow GM, Fan D, et al: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351(13):1296–1305, 2004.
37. Sarnak MJ, Levey AS, Schoolwerth AC, et al: Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 108(17):2154–2169, 2003.
38. Patel UD, Young EW, Ojo AO, Hayward RA: CKD progression and mortality among older patients with diabetes. *Am J Kidney Dis Off J Natl Kidney Found* 46(3):406–414, 2005.
39. Anavekar NS, Gans DJ, Berl T, et al: Predictors of cardiovascular events in patients with type 2 diabetic nephropathy and hypertension: a case for albuminuria. *Kidney Int Suppl* (92):S50–S55, 2004.
40. James PA, Oparil S, Carter BL, et al: 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 311(5):507–520, 2014.
41. Shlipak MG, Fried LF, Cushman M, et al: Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. *JAMA* 293(14):1737–1745, 2005.
42. Best PJ, Reddan DN, Berger PB, et al: Cardiovascular disease and chronic kidney disease: insights and an update. *Am Heart J* 148(2):230–242, 2004.
43. Anavekar NS, McMurray JJ, Velazquez EJ, et al: Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 351(13):1285–1295, 2004.
44. Hiremath S, Akbari A, Shabana W, et al: Prevention of contrast-induced acute kidney injury: is simple oral hydration similar to intravenous? A systematic review of the evidence. *PLoS ONE* 8(3):e60009, 2013.
45. Maioli M, Toso A, Leoncini M, et al: Sodium bicarbonate versus saline for the prevention of contrast-induced nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *J Am Coll Cardiol* 52(8):599–604, 2008.
46. Mueller C, Buerkle G, Buettner HJ, et al: Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med* 162(3):329–336, 2002.
47. Brar SS, Aharonian V, Mansukhani P, et al: Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial. *Lancet* 383(9931):1814–1823, 2014.
48. Merten GJ, Burgess WP, Gray LV, et al: Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA* 291(19):2328–2334, 2004.
49. Brar SS, Shen AY-J, Jorgensen MB, et al: Sodium bicarbonate vs sodium chloride for the prevention of contrast medium–induced nephropathy in patients undergoing coronary angiography: a randomized trial. *JAMA* 300(9):1038–1046, 2008.
50. Hafiz AM, Jan MF, Mori N, et al: Prevention of contrast-induced acute kidney injury in patients with stable chronic renal disease undergoing elective percutaneous coronary and peripheral interventions: randomized comparison of two preventive strategies. *Catheter Cardiovasc Interv* 79(6):929–937, 2012.
51. Maioli M, Toso A, Leoncini M, et al: Effects of hydration in contrast-induced acute kidney injury after primary angioplasty: a randomized, controlled trial. *Circ Cardiovasc Interv* 4(5):456–462, 2011.
52. Zoungas S, Ninomiya T, Huxley R, et al: Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. *Ann Intern Med* 151(9):631–638, 2009.
53. Nallamothu BK, Shojania KG, Saint S, et al: Is acetylcysteine effective in preventing contrast-related nephropathy? A meta-analysis. *Am J Med* 117(12):938–947, 2004.
54. Tepel M, van der Giet M, Schwarzfeld C, et al: Prevention of radiographic-contrast-agent–induced reductions in renal function by acetylcysteine. *N Engl J Med* 343(3):180–184, 2000.
55. ACT Investigators: Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized Acetylcysteine for Contrast-induced nephropathy Trial (ACT). *Circulation* 124(11):1250–1259, 2011.
56. Berwanger O, Cavalcanti AB, Sousa AMG, et al: Acetylcysteine for the prevention of renal outcomes in patients with diabetes mellitus undergoing coronary and peripheral vascular angiography: a substudy of the acetylcysteine for contrast-induced nephropathy trial. *Circ Cardiovasc Interv* 6(2):139–145, 2013.
57. Droppa M, Desch S, Blase P, et al: Impact of N-acetylcysteine on contrast-induced nephropathy defined by cystatin C in patients with ST-elevation myocardial infarction undergoing primary angioplasty. *Clin Res Cardiol* 100(11):1037–1043, 2011.
58. Jaffery Z, Verma A, White CJ, et al: A randomized trial of intravenous N-acetylcysteine to prevent contrast induced nephropathy in acute coronary syndromes. *Catheter Cardiovasc Interv* 79(6):921–926, 2012.
59. Sun Z, Fu Q, Cao L, et al: Intravenous N-acetylcysteine for prevention of contrast-induced nephropathy: a meta-analysis of randomized, controlled trials. *PLoS ONE* 8(1):e55124, 2013.
60. Weisbord SD, Gallagher M, Kaufman J, et al: Prevention of contrast-induced AKI: a review of published trials and the design of the prevention of serious adverse events following angiography (PRESERVE) trial. *Clin J Am Soc Nephrol* 8(9):1618–1631, 2013.
61. Patti G, Ricottini E, Nusca A, et al: Short-term, high-dose atorvastatin pretreatment to prevent contrast-induced nephropathy in patients with acute coronary syndromes undergoing percutaneous coronary intervention (from the ARMYDA-CIN [atorvastatin for reduction of myocardial damage during angioplasty-contrast-induced nephropathy] trial. *Am J Cardiol* 108(1):1–7, 2011.
62. Quintavalle C, Fiore D, De Micco F, et al: Impact of a high loading dose of atorvastatin on contrast-induced acute kidney injury. *Circulation* 126(25):3008–3016, 2012.
63. Leoncini M, Toso A, Maioli M, et al: Early high-dose rosuvastatin for contrast-induced nephropathy prevention in acute coronary syndrome: results from the PRATO-ACS Study (Protective Effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome). *J Am Coll Cardiol* 63(1):71–79, 2014.
64. Han Y, Zhu G, Han L, et al: Short-term rosuvastatin therapy for prevention of contrast-induced acute kidney injury in patients with diabetes and chronic kidney disease. *J Am Coll Cardiol* 63(1):62–70, 2014.
65. Madyoon H, Croushore L, Weaver D, Mathur V: Use of fenoldopam to prevent radiocontrast nephropathy in high-risk patients. *Catheter Cardiovasc Interv* 53(3):341–345, 2001.
66. Kini AS, Mitre CA, Kamran M, et al: Changing trends in incidence and predictors of radiographic contrast nephropathy after percutaneous coronary intervention with use of fenoldopam. *Am J Cardiol* 89(8):999–1002, 2002.
67. Stone GW, McCullough PA, Tumlin JA, et al: Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. *JAMA* 290(17):2284–2291, 2003.
68. Sadat U, Usman A, Gillard JH, Boyle JR: Does ascorbic acid protect against contrast-induced acute kidney injury in patients undergoing coronary angiography? A systematic review with meta-analysis of randomized, controlled trials. *J Am Coll Cardiol* 62(23):2167–2175, 2013.
69. Spargias K, Adreanides E, Demerouti E, et al: Iloprost prevents contrast-induced nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation* 120(18):1793–1799, 2009.
70. Bagshaw SM, Ghali WA: Theophylline for prevention of contrast-induced nephropathy: a systematic review and meta-analysis. *Arch Intern Med* 165(10):1087–1093, 2005.
71. Dai B, Liu Y, Fu L, et al: Effect of theophylline on prevention of contrast-induced acute kidney injury: a meta-analysis of randomized controlled trials. *Am J Kidney Dis* 60(3):360–370, 2012.
72. Solomon R, Werner C, Mann D, et al: Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 331(21):1416–1420, 1994.
73. Briguori C, Visconti G, Focaccio A, et al: Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard System in high-risk patients for contrast-induced acute kidney injury. *Circulation* 124(11):1260–1269, 2011.
74. Marenzi G, Ferrari C, Marana I, et al: Prevention of contrast nephropathy by furosemide with matched hydration: the MYTHOS (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial. *JACC Cardiovasc Interv* 5(1):90–97, 2012.
75. Lee P-T, Chou K-J, Liu C-P, et al: Renal protection for coronary angiography in advanced renal failure patients by prophylactic hemodialysis. A randomized controlled trial. *J Am Coll Cardiol* 50(11):1015–1020, 2007.
76. Deray G: Dialysis and iodinated contrast media. *Kidney Int Suppl* (100):S25–S29, 2006.
77. Marenzi G, Marana I, Lauri G, et al: The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med* 349(14):1333–1340, 2003.
78. Cruz DN, Goh CY, Marenzi G, et al: Renal replacement therapies for prevention of radiocontrast-induced nephropathy: a systematic review. *Am J Med* 125(1):66–78.e3, 2012.
79. Er F, Nia AM, Dopp H, et al: Ischemic preconditioning for prevention of contrast medium-induced nephropathy: randomized pilot RenPro Trial (Renal Protection Trial). *Circulation* 126(3):296–303, 2012.
80. Deftereos S, Giannopoulos G, Tzalamouras V, et al: Renoprotective effect of remote ischemic post-conditioning by intermittent balloon inflations in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 61(19):1949–1955, 2013.
81. Grossman PM, Gurm HS, McNamara R, et al: Percutaneous coronary intervention complications and guide catheter size: bigger is not better. *JACC Cardiovasc Interv* 2(7):636–644, 2009. doi: 10.1016/j.jcin.2009.05.012.
82. Gurm HS, Smith D, Share D, et al: Impact of automated contrast injector systems on contrast use and contrast-associated complications in patients undergoing percutaneous coronary interventions. *JACC Cardiovasc Interv* 6(4):399–405, 2013.
83. Michishita I, Fujii Z: A novel contrast removal system from the coronary sinus using an adsorbing column during coronary angiography in a porcine model. *J Am Coll Cardiol* 47(9):1866–1870, 2006.
84. Danenberg HD, Lotan C, Varshitski B, et al: Removal of contrast medium from the coronary sinus during coronary angiography: feasibility of a simple and available technique for the prevention of nephropathy. *Cardiovasc Revasc Med* 9(1):9–13, 2008.
85. Duffy SJ, Ruygrok P, Juergens CP, et al: Removal of contrast media from the coronary sinus attenuates renal injury after coronary angiography and intervention. *J Am Coll Cardiol* 56(6):525–526, 2010.
86. Stone G, Dixon S, Foster M: Abstract 3794: Systemic Hypothermia to Prevent Contrast Nephropathy: the COOL RCN Pilot Trial. *Circulation* 114(II):811–812, 2006.
87. Barrett BJ, Carlisle EJ: Meta-analysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. *Radiology* 188(1):171–178, 1993.
88. Aspelin P, Aubry P, Fransson S-G, et al: Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med* 348(6):491–499, 2003. doi: 10.1056/NEJMoa021833.
89. Davidson CJ, Laskey WK, Hermiller JB, et al: Randomized trial of contrast media utilization in high-risk PTCA: the COURT trial. *Circulation* 101(18):2172–2177, 2000.
90. Kuhn MJ, Chen N, Sahani DV, et al: The PREDICT study: a randomized double-blind comparison of contrast-induced nephropathy after low- or isoosmolar contrast agent exposure. *AJR Am J Roentgenol* 191(1):151–157, 2008.
91. Laskey W, Aspelin P, Davidson C, et al: Nephrotoxicity of iodixanol versus iopamidol in patients with chronic kidney disease and diabetes mellitus undergoing coronary angiographic procedures. *Am Heart J* 158(5):822–828.e3, 2009.
92. Solomon RJ, Natarajan MK, Doucet S, et al: Cardiac Angiography in Renally Impaired Patients (CARE) study: a randomized double-blind trial of contrast-induced nephropathy in patients with chronic kidney disease. *Circulation* 115(25):3189–3196, 2007.
93. VALOR Trial Investigators: Nephrotoxicity of iodixanol versus ioversol in patients with chronic kidney disease: the Visipaque Angiography/Interventions with Laboratory Outcomes in Renal Insufficiency (VALOR) Trial. *Am Heart J* 156(4):776–782, 2008.
94. Reed M, Meier P, Tamhane UU, et al: The relative renal safety of iodixanol compared with low-osmolar contrast media: a meta-analysis of randomized controlled trials. *JACC Cardiovasc Interv* 2(7):645–654, 2009.
95. Sarkis A, Badaoui G, Azar R, et al: Gadolinium-enhanced coronary angiography in patients with impaired renal function. *Am J Cardiol* 91(8):974–975, A4, 2003.
96. Bokhari SW, Wen Y-HJ, Winters RJ: Gadolinium-based percutaneous coronary intervention in a patient with renal insufficiency. *Catheter Cardiovasc Interv* 58(3):358–361, 2003.
97. Kribben A, Witzke O, Hillen U, et al: Nephrogenic systemic fibrosis: pathogenesis, diagnosis, and therapy. *J Am Coll Cardiol* 53(18):1621–1628, 2009.
98. Nayak KR, Mehta HS, Price MJ, et al: A novel technique for ultra-low contrast administration during angiography or intervention. *Catheter Cardiovasc Interv* 75(7):1076–1083, 2010.
99. Nallamothu BK, Tommaso CL, Anderson HV, et al: ACC/AHA/SCAI/AMA–Convened PCPI/NCQA 2013 performance measures for adults undergoing percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures, the Society for Cardiovascular Angiography and Interventions, the American Medical Association–Convened Physician Consortium for Performance Improvement, and the National Committee for Quality Assurance. *J Am Coll Cardiol* 63(7):722–745, 2014.
100. United States Renal Data System: 2013 Atlas of CKD & ERSD (vol 2). <http://www.usrds.org/atlas.aspx>. Accessed 25.02.15.
101. Lindner A, Charra B, Sherrard DJ, Scribner BH: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 290(13):697–701, 1974.
102. Herzog CA, Ma JZ, Collins AJ: Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *N Engl J Med* 339(12):799–805, 1998.
103. Levey AS, Beto JA, Coronado BE, et al: Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. *Am J Kidney Dis* 32(5):853–906, 1998.
104. Hamani A, Petitclerc T, Jacobs C, Deray G: Is dialysis indicated immediately after administration of iodinated contrast agents in patients on haemodialysis? *Nephrol Dial Transplant* 13(4):1051–1052, 1998.
105. Bocksch W, Fateh-Moghadam S, Mueller E, et al: Percutaneous coronary intervention in patients with end-stage renal disease. *Kidney Blood Press Res* 28(5–6):275–279, 2005.
106. Azar RR, Prpic R, Ho KK, et al: Impact of end-stage renal disease on clinical and angiographic outcomes after coronary stenting. *Am J Cardiol* 86(5):485–489, 2000.
107. Rubenstein MH, Harrell LC, Sheynberg BV, et al: Are patients with renal failure good candidates for percutaneous coronary

revascularization in the new device era? *Circulation* 102(24): 2966–2972, 2000.
108. Daemen J, Lemos P, Aoki J, et al: Treatment of coronary artery disease in dialysis patients with sirolimus-eluting stents: 1-year clinical follow-up of a consecutive series of cases. *J Invasive Cardiol* 16(12):685–687, 2004.
109. Halkin A, Mehran R, Casey CW, et al: Impact of moderate renal insufficiency on restenosis and adverse clinical events after paclitaxel-eluting and bare metal stent implantation: results from the TAXUS-IV Trial. *Am Heart J* 150(6):1163–1170, 2005.
110. Abdel-Latif A, Mukherjee D, Mesgarzadeh P, Ziada KM: Drug-eluting stents in patients with end-stage renal disease: meta-analysis and systematic review of the literature. *Catheter Cardiovasc Interv* 76(7):942–948, 2010.
111. Douglas PS, Brennan JM, Anstrom KJ, et al: Clinical effectiveness of coronary stents in elderly persons: results from 262,700 Medicare patients in the American College of Cardiology-National Cardiovascular Data Registry. *J Am Coll Cardiol* 53(18):1629–1641, 2009.
112. Tomai F, Ribichini F, De Luca L, et al: Randomized Comparison of Xience V and Multi-Link Vision Coronary Stents in the Same Multivessel Patient With Chronic Kidney Disease (RENAL-DES) study. *Circulation* 129(10):1104–1112, 2014.
113. Reddan DN, Szczech LA, Tuttle RH, et al: Chronic kidney disease, mortality, and treatment strategies among patients with clinically significant coronary artery disease. *J Am Soc Nephrol* 14(9):2373–2380, 2003.
114. Williams ME: Coronary revascularization in diabetic chronic kidney disease/end-stage renal disease: a nephrologist's perspective. *Clin J Am Soc Nephrol* 1(2):209–220, 2006.
115. Charytan DM, Li S, Liu J, Herzog CA: Risks of death and end-stage renal disease after surgical compared with percutaneous coronary revascularization in elderly patients with chronic kidney disease. *Circulation* 126(11 Suppl 1):S164–S169, 2012.
116. Freeman RV, Mehta RH, Al Badr W, et al: Influence of concurrent renal dysfunction on outcomes of patients with acute coronary syndromes and implications of the use of glycoprotein IIb/IIIa inhibitors. *J Am Coll Cardiol* 41(5):718–724, 2003.
117. Alexander KP, Chen AY, Roe MT, et al: Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. *JAMA* 294(24): 3108–3116, 2005.
118. Tsai TT, Maddox TM, Roe MT, et al: Contraindicated medication use in dialysis patients undergoing percutaneous coronary intervention. *JAMA* 302(22):2458–2464, 2009.
119. Kidney Disease Improving Global Outcomes (KDIGO): Clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int Suppl* 3(3):1–305, 2013.
120. Damman K, van Deursen VM, Navis G, et al: Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol* 53(7):582–588, 2009.
121. Malyszko J, Bachorzewska-Gajewska H, Poniatowski B, et al: Urinary and serum biomarkers after cardiac catheterization in diabetic patients with stable angina and without severe chronic kidney disease. *Ren Fail* 31(10):910–919, 2009.
122. Tasanarong A, Hutayanon P, Piyayotai D: Urinary Neutrophil Gelatinase-Associated Lipocalin predicts the severity of contrast-induced acute kidney injury in chronic kidney disease patients undergoing elective coronary procedures. *BMC Nephrol* 14:270, 2013.

Radiation Safety During Cardiovascular Procedures

7

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KEY POINTS

- Interventional cardiologists who use fluoroscopy should be familiar with radiation risks and should know how to manage radiation appropriately.
- Incidents of patient skin injury following fluoroscopy-guided interventional procedures have been reported. Many reported skin effects resulting from fluoroscopic procedures were inadvertent, and the physician was unaware of the radiation dose and consequences.
- Interventional cardiologists must receive training in selection of appropriate fluoroscopic equipment configuration and utilization of dose-management tools. This training should include both general radiation dose-management practices and specific practices for the model of fluoroscopic equipment and personnel radiation protection tools they will use.
- Strategies for minimizing patient radiation dose include using a low dose rate and a low frame rate for fluoroscopy, keeping the image receptor close to the patient, using collimation and moderate x-ray beam angles, and minimizing fluoroscopy time and image acquisition.
- The cumulative radiation dose display provided by the fluoroscopic equipment should be utilized to keep track of patient dose.
- If reference point air *kerma* (kinetic energy released in material) exceeds 5 Gy for a procedure, the interventional cardiologist should inform the patient that a radiation skin effect may occur.
- Personnel present during fluoroscopy procedures should use x-ray shielding and should move back from the patient during fluoroscopy to reduce their radiation exposure.

Fluoroscopy-guided interventional cardiovascular procedures provide substantial benefit to patients by relieving symptoms, improving quality of life, and replacing the need for open surgical procedures. Procedure risks may also be substantial and include stroke, myocardial infarction (MI), renal failure, and death. The ionizing radiation required for fluoroscopic guidance also carries risk, particularly for prolonged procedures and obese patients. These radiation risks include radiogenic cancer and skin injury, although many other procedural risks are significantly greater than the radiation risks. Nevertheless, it is important to apply the basic principles of radiation protection for medical exposure to patients. These principles are *justification*—that is, use of radiation should provide more benefit than harm to the patient, and the procedure should be medically indicated—and *optimization*, meaning the patient dose should be managed to be commensurate with the medical purpose, and unnecessary radiation exposure should be avoided.[1] To follow these principles, practitioners who use fluoroscopy should be familiar with radiation risk and should know how to manage radiation appropriately.

RADIATION RISK

Two types of health effects result from radiation exposure, stochastic and deterministic. *Stochastic effects* include cancer and genetic mutations. These effects are caused by damage to cell DNA. Because an effect may result from misrepair of a single cell, stochastic effects are independent of the amount of radiation exposure and are thought to have no lower threshold limit. *Deterministic effects* are tissue reactions from radiation exposure. The severity of tissue reactions increases with dose, and a minimum dose exists below which no observable effect occurs. Tissue reactions of concern related to fluoroscopy use include skin burns, hair loss, and cataracts.

Radiation-induced cancer risk has been studied extensively in many different exposed populations, including survivors of the atomic bomb detonations over Hiroshima and Nagasaki in World War II, patients receiving medical treatments, and workers exposed to radiation. Although the relationship between cancer induction and radiation exposure has been well established for high doses, cancer risk at low dose levels, such as those encountered in diagnostic imaging or from natural sources, is uncertain. Because the latent period for most cancers is long, and the natural incidence of cancer is high, it is difficult to determine cancer risk levels for whole-body doses less than approximately 100 mSv (which is equivalent to the radiation delivered during several complex percutaneous cardiac interventions [PCIs]). As a result, a model is used to estimate cancer risk at low doses from observed high-dose cancer rates. The commonly accepted linear nonthreshold model predicts a fatal cancer risk of 5% per Sv whole-body exposure for a working-age adult.[2] Typical effective dose values (estimation of whole-body dose from a partial body exposure) are 15 mSv for PCI, 7 mSv for diagnostic coronary angiography, 7 mSv for chest computed tomography (CT), and 0.1 mSv for a chest radiography exam.[3] For comparison, natural background radiation levels in the United States average about 3 mSv per year.[4]

Genetic mutations from radiation exposure have been found in animal studies, but no human study has demonstrated any effect. Although radiation-induced heritable effects were initially thought to be a significant radiation risk, it is now accepted that the genetic risk is minimal.

Skin injury from radiation exposure has been thoroughly characterized for radiation therapy patients. Although fluoroscopy x-ray energies are lower than high-energy radiation therapy x-ray beams, skin effects and threshold dose levels are similar to that of orthovoltage radiation therapy (50 to 250 kilovolt peak [kVp]; Table 7-1). Transient erythema may occur within 24 hours after a radiation dose of 2 Gy or more. Between 2 and 8 weeks from an exposure, epilation may occur with main erythema present for doses greater than 5 Gy, and desquamation may occur for doses greater than 10 Gy. Longer term, for doses greater than 15 Gy, dermal atrophy and secondary ulceration may occur that may require surgical treatment.[5] Examples of fluoroscopic skin injuries are shown in Figures 7-1 and 7-2. It should be noted that time intervals and dose thresholds given in Table 7-1 are approximate and will vary depending on the patient's health, location of the exposed area, and condition of the lesion. Other factors may also be associated with increased skin response to irradiation, including diseases such as diabetes mellitus and hyperthyroidism and also ataxia, telangiectasia, connective tissue diseases, and exposure to various chemotherapy agents.[6]

Although rare, skin injury following fluoroscopy-guided interventional procedures has been reported.[5,7] Many of these injuries involve complex cardiology procedures such as PCI for the recanalization of chronic total vascular occlusions and radiofrequency ablations. A rise in the number of reports to the Food and Drug Administration (FDA) in the early 1990s led to the release of a public health advisory in 1994.[8]

TABLE 7-1 Tissue Reactions From Single-Delivery Radiation Dose to Skin of the Neck, Torso, Pelvis, Buttocks, or Arms*

Band	Single-Site Acute Skin-Dose Range (Gy)†,§,‖	NCI Skin Reaction Grade	APPROXIMATE TIME OF ONSET OF EFFECTS†,‡			
			Prompt <2 Weeks	Early 2-8 Weeks	Mid-Term 6-52 Weeks	Long Term >40 Weeks
A1	0-2	Not applicable	No observable effects expected at any time			
A2	2-5	1	Transient erythema	Epilation	Recovery from hair loss	None expected
B	5-10	1-2	Transient erythema	Erythema, epilation	Recovery; at higher doses, prolonged erythema, permanent partial epilation	Recovery; at higher doses, dermal atrophy or induration
C	10-15	2-3	Transient erythema	Erythema, epilation; possible dry or moist desquamation, recovery from desquamation	Prolonged erythema, permanent epilation	Telangiectasia,¶ dermal atrophy or induration, skin likely to be weak
D	>15	3-4	Transient erythema; after very high doses: edema and acute ulceration, long-term surgical intervention likely to be required	Erythema, epilation; moist desquamation	Dermal atrophy; secondary ulceration due to failure of moist desquamation to heal, surgical intervention likely to be required; at higher doses, dermal necrosis, surgical intervention likely to be required	Telangiectasia,¶ dermal atrophy, induration; possible late skin breakdown; wound can be persistent and may progress into a deeper lesion; surgical intervention likely to be required

NCRP: Report 168: Radiation dose management for fluoroscopically guided interventional procedures. Bethesda, MD: National Council on Radiation Protection and Measurements, 2010.
*This table is applicable to the normal range of patient radiosensitivities in the absence of mitigating or aggravating physical or clinical factors; this table does not apply to the skin of the scalp.
†The dose range and approximate time period are not rigid boundaries. Also, signs and symptoms can be expected to appear earlier as the skin dose increases.
‡Abrasion or infection of the irradiated area is likely to exacerbate radiation effects.
§*Skin dose* refers to actual skin dose (including backscatter). This quantity is *not* air kerma at the reference point ($K_{a,r}$).
‖Skin dosimetry based on $K_{a,r}$ or air kerma area product (P_{KA}) is unlikely to be more accurate than ±50%.
¶Refers to radiation-induced telangiectasia. Telangiectasia associated with an area of initial moist desquamation or the healing of ulceration may be present earlier.
NCI, National Cancer Institute.

Injury may also result from multiple procedures, even if individual sessions are below the threshold for skin effects. When exposure of the same skin location occurs over several episodes, injury threshold doses will depend on the dose level and the time interval between procedures.[5] It should be noted that many reported skin effects resulting from fluoroscopic procedures were inadvertent, and the physician was unaware of the radiation dose delivered.[9] As a result, patients were not made aware of the potential for skin injury, which caused a delay in the diagnosis of their wound.[7] Skin biopsy should not be performed in areas of suspected radiation skin injury because this leads to a delay in healing and/or to secondary infections.[6] Recording of patient dose, communication with the patient, and follow-up for significant dose levels are important radiation management methods that will be discussed later in this chapter.

RADIATION MANAGEMENT

Procedure optimization includes limiting radiation dose to a level that is as low as possible to accomplish the clinical task. This process requires attention to imaging equipment configuration and to radiation dose management practices. Interventional fluoroscopy systems contain many components that work together to form an image. For the most part, adjusting components to increase radiation dose will result in improved image quality. Although at first glance, achieving excellent image quality may appear to be the aim of procedure optimization, this objective will generally result in an unnecessary dose. Instead, the appropriate image quality level that is clinically acceptable should be the goal so that an appropriate radiation dose can be used. Some tasks within an interventional procedure can be accomplished using an image with reduced radiation dose and image quality. Whenever possible, equipment configurations with a lower dose rate should be selected. This is best accomplished by adjusting initial settings to a low dose rate before a procedure begins, then selecting higher dose-rate settings as needed in a limited fashion for a specific imaging task, such as placing a guidewire or deploying a stent, where high spatial resolution and low image noise are needed. Further details about fluoroscopic equipment components will be covered in the next section of this chapter.

Staff training is an important component of procedure optimization. Operators of fluoroscopic systems are in charge of the amount of radiation used during a procedure, which affects the dose to the patient, to themselves, and to other staff in the procedure room. It is important that operators receive training on how to select appropriate equipment configurations and how to utilize dose-management tools. Additional information regarding the components of this training are provided in this chapter.

FLUOROSCOPIC IMAGING EQUIPMENT

Because fluoroscopy-guided interventional procedures have the potential to deliver patient radiation dose levels that can cause skin injury, it is important that the fluoroscopic equipment used be suitable for the task. Several key equipment features are desirable to ensure proper management of patient and staff radiation dose. Some of these features include digital image acquisition, variable-rate pulsed fluoroscopy, added x-ray beam filtration, and patient radiation dose display.[10] Safe and effective patient care in complex interventional procedures is best realized when appropriate equipment is used. Fluoroscopy systems that comply with International Electrotechnical Commission (IEC)[11] standard IEC-60601-2-43 for interventional equipment include these and other elements appropriate for interventional procedures.

Image Chain Components

The basic components of a fluoroscopic imaging chain are an x-ray generator, tube, and beam filter; a collimator; the patient; a grid; and

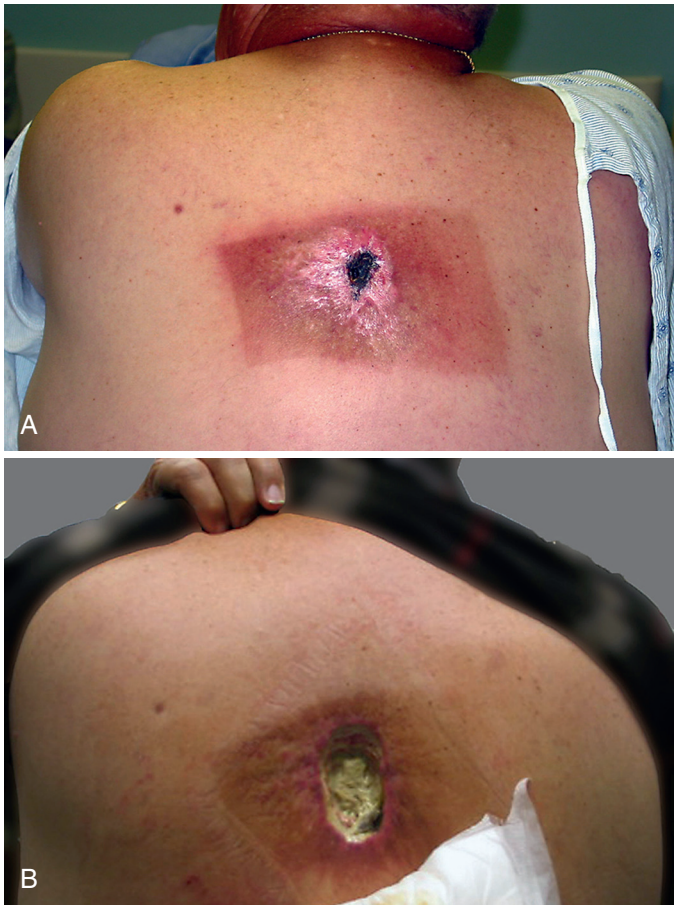


FIGURE 7-1 Radiation injury in a 60-year-old man resulting from coronary angioplasty. Images show a time sequence of the injury. **A,** At 30 weeks after exposure, a central area of deep necrosis surrounded by indurated and depigmented skin within an area of prolonged erythema is shown. **B,** At 38 weeks after exposure, area of deep necrosis has increased in size. (From Balter S, Hopewell JW, Miller DL, et al: Fluoroscopically guided interventional procedures: a review of radiation effects on patients' skin and hair. *Radiology* 254[2]:326-341, Fig. 8A, 2010.)

FIGURE 7-2 Radiation injury in a 60-year-old woman resulting from a coronary angioplasty. At 18 months after exposure, erythema with dusky coloration is shown.

the image receptor, processor, and displays (Fig. 7-3). The operator controls the fluoroscopy system through the exposure foot switch, table-side controls, and configuration selection; the operator monitors the output of the system on the image display and on the radiation use display.

The x-ray generator provides electrical power to the x-ray tube that allows for adjustment of x-ray beam kilovolt peak and tube current (in milliamperes [mA]). The x-ray beam produced is generally pulsed at a rate of 1 to 30 pulses per second with pulse widths between 3 and 20 ms. Another important feature of an x-ray generator is automatic exposure rate control (AERC), which acts to keep the x-ray flux at the image receptor at a constant level as it is panned over body parts of differing thickness and attenuation. This is achieved by automatically adjusting the kilovolt peak, tube current, pulse width, and beam filtration settings through a feedback signal from the image receptor to maintain the x-ray exposure level at the entrance to the image receptor.

Within the x-ray tube, x-rays are produced by accelerating electrons emitted from a filament (cathode) toward a rotating tungsten disk (anode). The housing that surrounds the x-ray tube contains lead shielding that absorbs x-rays not directed out the exit port. The x-ray production process is relatively inefficient, with less than 1% of the energy input into the x-ray tube converted into x-rays; most of the energy is converted into heat, and x-ray tube heat can build up quickly during clinical procedures that require the capture of multiple images. To achieve a large heat capacity, angiography x-ray tubes are equipped with high-speed anode rotation (over 10,000 rotations/min) and a circulating water or oil heat exchanger with cooling fans. The instantaneous heat capacity of the x-ray tube may become a limiting factor for the selection of technique factors when imaging thick body parts and large patients, particularly when using mobile C-arm fluoroscopy systems. Many systems include an indicator of the thermal condition of the anode, which notifies the operator when the heat level is approaching threshold values.

X-ray tubes for fluoroscopy systems typically contain two focal spots: the *small focal spot* (SF) is selected for all fluoroscopy and image acquisition of thin body parts; the *large focal spot* (LF) is required for imaging thicker body parts, for which higher kilovolt peak and tube current are needed. The smaller the focal spot, the less geometric blur occurs for better spatial resolution (Fig. 7-4). However, concentrating the focal spot into a smaller area results in increased heat concentration that could reach temperatures hot enough to melt the anode material. Therefore the larger focal spot size is needed for cine acquisition imaging.

The x-ray beam travels through a sheet of aluminum several millimeters thick before it exits the collimator assembly. This aluminum filtration material is present to attenuate low-energy X-rays from the beam, which are generally absorbed in the first few centimeters of patient tissue without being transmitted to the image receptor; this contributes to patient skin dose with little impact on image formation. Federal regulations specify a minimum thickness of filtration material be used for all fluoroscopy systems.[12] Additional filtration material, typically copper, is included in angiography and interventional fluoroscopy systems to further reduce patient skin dose. The filtration thickness may be fixed for a given program setting or it may be configured to vary automatically with changes in patient attenuation.

The collimator contains radiopaque shutter blades with two levels of control, primary and secondary, that define the shape of the x-ray beam. The *primary collimator control* automatically limits the x-ray beam field of view as operator changes are made in the magnification (zoom) mode selection or source-image receptor distance. The *secondary collimator control* allows the operator to further reduce the size of the x-ray beam to the area of clinical interest. Most fluoroscopy systems

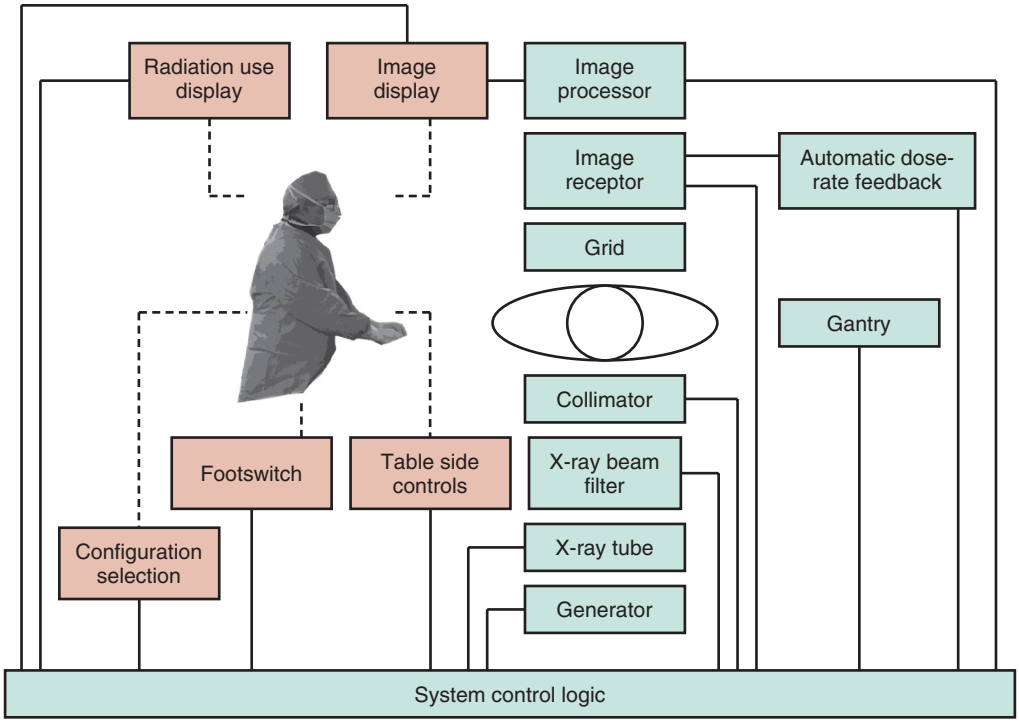


FIGURE 7-3 Block diagram of a fluoroscopic imaging system. The imaging chain components (generator, x-ray tube, x-ray beam filter, collimator, image receptor, and gantry) are controlled by the operator through the configuration selection, footswitch, and table-side controls through system control logic via automatic dose-rate feedback. The radiation use display and image display are available for use by the operator.

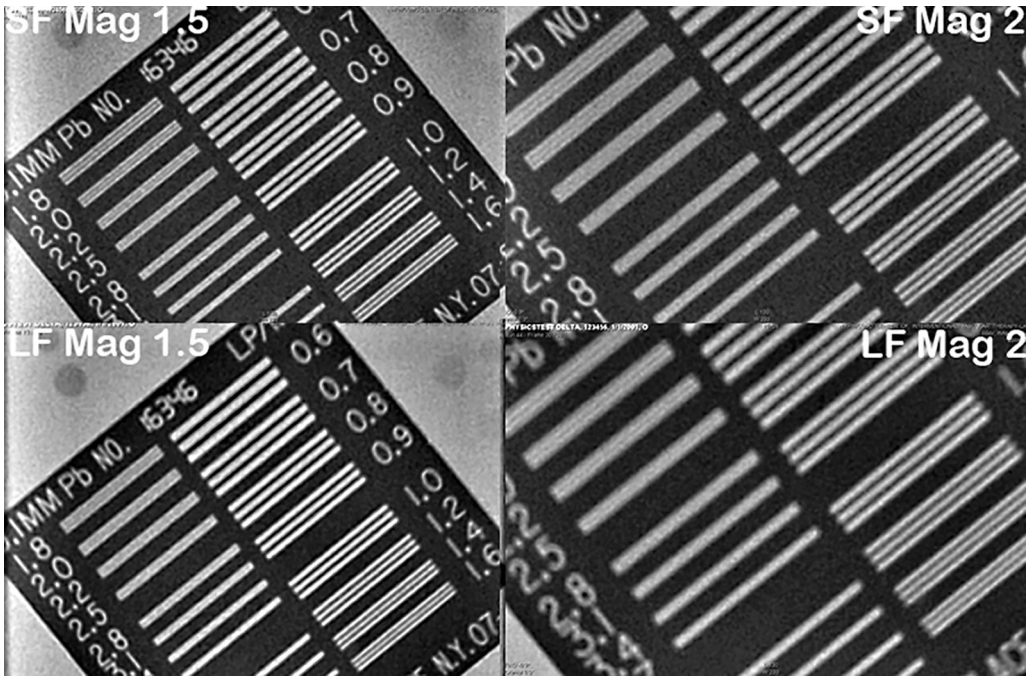


FIGURE 7-4 Focal spot size and geometric magnification effect on spatial resolution. Using a small focal (SF) spot and low geometric magnification (Mag 1.5) maximizes the visibility of the bars in this high-subject-contrast test pattern. The effects of using a large focal (LF) spot are seen in the lower left image, increasing geometric magnification (Mag 2) is seen in the upper right image, and the incorporation of both are shown in the lower right image.

used for interventional procedures also contain equalization filters. These filters, also called *contour filters* or *wedge filters*, are partially radiolucent blades used to provide modest beam attenuation, which serves to reduce x-ray intensity in areas with low patient attenuation that may otherwise lead to areas of white glare in the images. Use of secondary collimation and equalization filters are an important tool to improve image quality and also reduce patient dose.

The image receptor used for most modern fluoroscopy systems is a flat-panel digital detector. A grid is mounted in front of the image receptor to reduce the scatter contribution to the image. Most detectors for fluoroscopy are of the indirect conversion type, in which a cesium iodide phosphor layer absorbs incident x-rays and produces light photons. The light photons are then detected and converted to a stored charge by a matrix array of photodiodes to create a digital image. Flat-panel fluoroscopy detectors are available in square or rectangular formats with sizes that range from 17 to 40 cm square; typical pixel spacing is between 0.14 and 0.20 mm. Selection of magnification modes is also possible, although spatial resolution may not change. For large fields of view or high–frame-rate imaging, pixel binning (typically 2 by 2) to reduce data transfer rates can reduce spatial resolution. Although spatial resolution is decreased, image noise is also decreased because of the large effective pixel size. Spatial resolution may also be limited by the resolution of the display monitor; if this is the case, a digital zoom can be used to better visualize detail.

Image processing is commonly applied to fluoroscopy and acquired images prior to display and archive. Processing is applied to increase image contrast, improve spatial resolution, and decrease the appearance of image noise. Adjustment of image-processing parameter settings allows for fine-tuning of image appearance to the clinical application and user preference. However, it should be noted that image quality improvements from image processing usually require a compromise in some other image quality characteristic. Most fluoroscopy systems acquire cine images with a pixel matrix size of approximately 1024 by 1024. However, when images are archived, the matrix size is typically decreased to 512 by 512. As a result, images viewed on the acquisition display monitor will generally provide the best spatial resolution.

Imaging Modes

Fluoroscopy systems used for interventional cardiovascular procedures typically have three imaging modes: (1) fluoroscopy, (2) acquisition or cine mode, and (3) digital subtraction angiography (DSA). *Fluoroscopy* is used for real-time visualization of moving structures or interventional devices for relatively long periods of time (seconds to minutes); therefore the dose rates with fluoroscopy are the lowest of all the imaging modes. Generally, the operator can select from several different dose rates and frame rates so that the lowest dose rate acceptable for the clinical task can be used. Federal regulations limit the maximum patient entrance air kerma rate to 88 mGy/min under test conditions.[12] Typical patient entrance air kerma rates for fluoroscopy can be highly variable but are generally 20 to 35 mGy/min[13] with a frame rate of 7.5 to 15 feet per second (fps).

Acquisition or *cine mode* is used to acquire quality images for diagnostic and archival purposes. Consequently, cine dose rates are typically 10 to 20 times higher than those used for fluoroscopy, with no maximum regulatory limit. Similar to fluoroscopy, many systems provide several different dose rates for cine acquisition to allow for dose reduction when possible. Cine acquisition frame rates are also selectable, with 15 fps being the typical rate and patient entrance air kerma rates between 150 and 250 mGy/min.[13] Note that the maximum air kerma rate for large patients can exceed 1000 mGy/min.

Digital subtraction angiography is used for imaging noncardiac, stationary vessels. In DSA, a precontrast mask image is logarithmically subtracted from an image obtained at the same location after contrast media has been injected. The result is an image in which overlying bone and soft tissue are removed, leaving only vasculature. The process of subtracting images increases the appearance of noise, so DSA images require the highest air kerma rates, generally between 300 and 500 mGy/min using frame rates of 1 to 4 fps.

PATIENT RADIATION DOSE MANAGEMENT

Comprehensive patient radiation dose management requires consideration of both x-ray system technical parameters and the operator's procedural skills. As a result, formal training of physician and nonphysician staff should be considered essential. All staff should become familiar with concepts and practices that lead to a safe and effective clinical practice.[14-17] Staff education should include a combination of didactic and practical training. Practical, hands-on training in particular provides a controlled environment to teach and learn general concepts and specific practices that lead to safe radiation practices. All new staff should receive organized, formal, and documented training. All staff should receive incremental training when new x-ray equipment or features are introduced into the practice. Such training should broadly cover applicable x-ray imaging physics and image creation, best practices to ensure patient radiation safety, and best practices to ensure staff radiation safety, and it should be specific to the clinical practice and equipment.

Factors That Contribute to High Skin Dose

The two primary factors that determine skin dose are x-ray system output dose rate (air kerma rate) and duration of exposure. Each of these primary factors has several associated components. Dose rate is determined by a combination of x-ray system configuration, operator selection of operational mode, and patient thickness.[18] Exponential attenuation of the x-ray beam by the patient dictates that the x-ray tube output, and thereby the patient dose rate, increases rapidly as the x-ray beam path length through the patient increases. The instantaneous dose rate for large patients can be 10 or more times greater than that for small patients. Because x-ray intensity decreases as the square of the distance from the source increases, maintaining appropriate radiographic distances can significantly influence patient skin dose. The duration of x-ray exposure directly influences skin dose and varies substantially among patient procedures. X-ray duration varies greatly between procedure types and even among patients undergoing similar procedures.[19,20] It is critically important that nontarget anatomy is not in the x-ray beam. In particular, ensure that the patient's arms are never between the x-ray tube and the patient's thorax.

Radiation Dose Measurement

All modern interventional fluoroscopy systems display radiation dose metrics in the procedure room. These metrics include air kerma (K, in mGy) and air kerma area product (P_{KA}, in Gy cm^2 and μGy m^2). *Air kerma* is a measurement of primary x-ray beam intensity. In the procedure room, the air kerma is reported at a fixed point in space that approximates, although not exactly, the location of the patient's skin. When the x-ray beam is on, the instantaneous air kerma rate is reported, and when the x-ray beam is off, the procedure's cumulative air kerma is reported. The *air kerma area product* is the integrated x-ray intensity over the field of view. It can be approximated as the product of the air kerma and the x-ray field area. Because the x-ray beam size is generally constant for cardiovascular procedures, air kerma and air kerma area product provide equivalent indicators of patient radiation burden. However, neither is a good indicator of actual patient skin dose, and neither should be used as such. Converting these metrics to an estimate of skin dose is an area of active academic research and implementation by the manufacturers (Fig. 7-5).[21] The newest interventional x-ray systems may offer advanced features that approximate actual patient skin dose during a procedure, thereby providing the operator some guidance to help avoid radiation skin injury during complex procedures. Traditionally, x-ray fluoroscopy time was used to monitor patient radiation burden. However, fluoroscopy time has

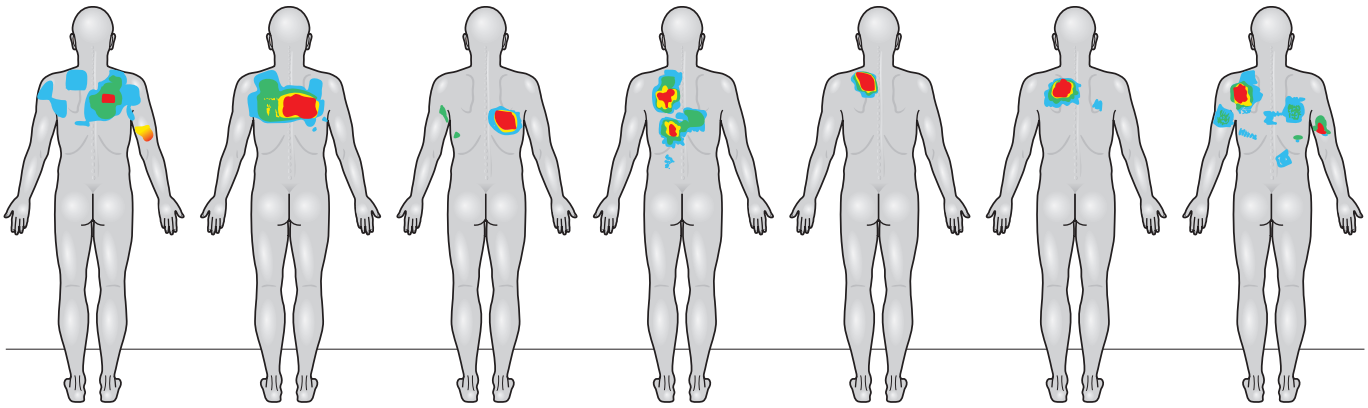


FIGURE 7-5 Sample patient skin dose maps for seven different patient exams. The area of highest skin dose is shown in *red*. Decreasing skin dose is indicated by *yellow, green,* and *light blue*. (From Johnson PB, Borrego D, Balter S, et al: Skin dose mapping for fluoroscopically guided interventions. *Med Phys* 38[10]:5490-5499, Fig. 4, 2011.)

important limitations for use as a dose metric. Specifically, it does not account for exposure from acquisition imaging or variation of fluoroscopy dose rate. Therefore fluoroscopy time is a poor indicator of patient radiation burden or skin dose and should not be used as a primary dose metric. Fluoroscopy time can be considered a useful secondary dose metric as a surrogate for procedure complexity or operator proficiency.

Best Practices for Patient Dose Management

Before starting a procedure, the patient record should be reviewed for prior instances of radiation exposure that could contribute to increased risk of radiation skin injury. No standard period of time exists over which the look-back should occur. Cellular injury from radiation commences immediately upon exposure, and repair mechanisms begin shortly thereafter.[22,23] If the radiation dose is sufficiently high, tissue damage can manifest over a period of several hours to several weeks after exposure.[5,24,25] Both cellular and tissue repair occur in the minutes, hours, days, and months following high exposure. When possible, multiple potentially high skin-dose procedures should be scheduled at least several weeks apart to minimize the potential for cumulative skin effects. When clinically necessary, repeat exposures over a period of a few days should be performed judiciously and should assume that the potential for radiation skin injury is cumulative.

Modern interventional x-ray systems include many features designed to result in a relatively low patient skin dose while still providing a clinically adequate image quality. System optimization for dose should be a collaborative effort between the clinical practice and the x-ray equipment manufacturer and should include a combination of a low detector-input dose, use of x-ray beam spectral filters, and a low frame rate.[26,27] Most invasive cardiac procedures can be performed using 7.5 fps fluoroscopy and 15 fps acquisition imaging. Operational modes should be created specifically for the variety of clinical tasks encountered in the invasive cardiology labs. Specific modes should be used for adult cardiac catheterization and ablation procedures, recognizing that the dose from catheterization procedures has approximately equal contributions from fluoroscopy and acquisition imaging and that the dose from ablation procedures is nearly entirely from fluoroscopy. Specific pediatric modes should be created with reduced detector input dose and should specify removal of the antiscatter grid for small patients (<20 kg).[28,29] System configuration and clinical use should recognize that some portions of procedures may require improved image quality. For these instances, it is useful to provide an operational mode that includes a higher radiation dose rate. As a matter of routine, the x-ray system should default to the lowest reasonable radiation dose rate mode, and the operator should be provided the option to temporarily switch to a higher dose-rate mode when improved image quality is required. Strategies for optimizing x-ray system settings to minimize patient radiation dose are summarized in Table 7-2.

TABLE 7-2 Strategies for Optimizing X-Ray System Settings to Minimize Patient Radiation Dose

Decrease frame rate	For at least most fluoroscopic imaging, 7.5 fps is adequate; for acquisition (cine) imaging, 15 fps is adequate.
Decrease detector target dose	Work with the x-ray system manufacturer to specify a lower dose target at the image receptor.
Increase use of x-ray spectral filtration	Ensure that both fluoroscopy and acquisition programs use x-ray beam spectral filters. A minimum of 0.1 mm copper should be used for acquisition imaging to reduce skin dose while maintaining image quality.[30]

For all x-ray imaging, it is important to minimize the time the x-ray beam is on to minimize the dose. Activate fluoroscopy only when necessary, and cease as soon as the live imaging is no longer needed clinically. For most cardiac operational modes, the dose rate associated with acquisition imaging is 10 to 20 times greater than that for fluoroscopic imaging. One method to reduce patient dose is to preferentially use and store fluoroscopic images obtained at a relatively low radiation dose rate, rather than acquisition imaging, when high-quality images are not required. Importantly, never use acquisition imaging to overcome poor fluoroscopic image quality. If fluoroscopic image quality is clinically inadequate, switch to a fluoroscopy mode with a higher radiation dose rate.

Especially for large patients, use of relatively shallow (posteroanterior) x-ray projection angles can help minimize the x-ray path length through the patient and thereby reduce the dose rate.[31,32] To help minimize skin dose, ensure that the patient's skin is positioned as far as reasonably possible away from the x-ray source and that the image receptor is positioned as close as reasonably possible to the patient (minimize the "air gap" between the patient and the image detector; Fig. 7-6). For patient safety, it is particularly important to ensure that the patient's arms are not in the x-ray beam.

Particularly for complex procedures, including ablation procedures, there is often a clinically preferred x-ray beam projection angle that is conducive to visualization of the anatomy. This can lead to high localized skin dose. When clinically possible, the effect can be reduced by using multiple x-ray projection angles such that the dose is distributed over a larger skin area. In this case, the projection angle must be changed enough (~15°) to avoid overlap of the irradiated skin areas.

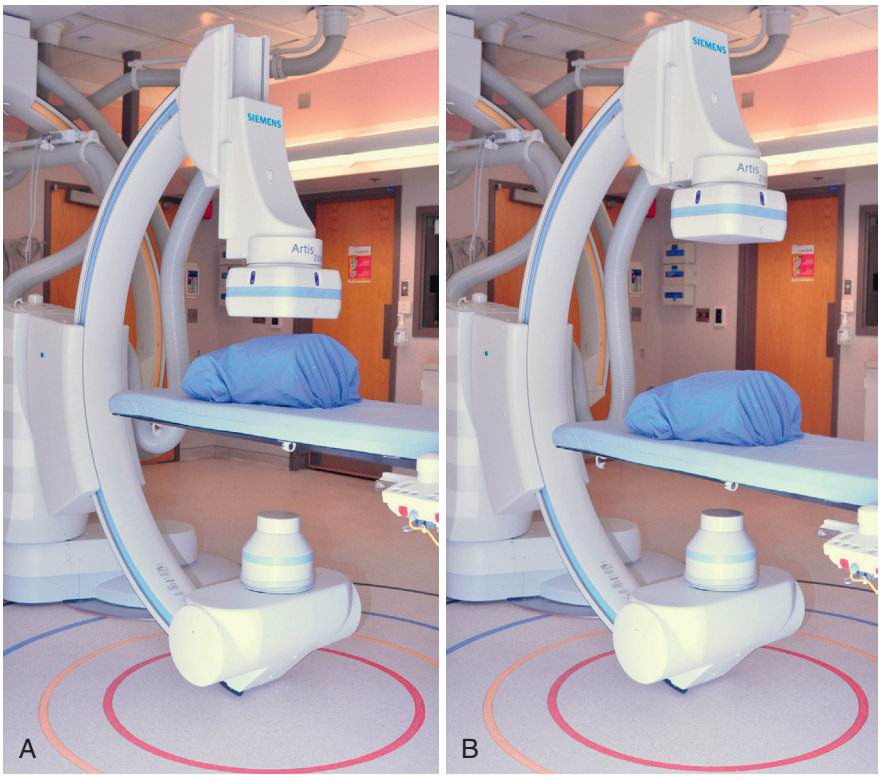


FIGURE 7-6 **A,** Good imaging geometry with the table elevated and a small air gap (<10 cm). **B,** Poor imaging geometry with a short distance between the x-ray tube and patient (table too low) and a great distance between the patient and image receptor (air gap). (Photographs courtesy Mayo Clinic, Rochester, MN.)

By default, x-ray systems are typically configured to modify the patient entrance air kerma rate with changes to the size of the primary field of view (magnification mode). Smaller fields of view (higher magnifications) are associated with increased patient skin-dose rates. Systems should be configured to operate using the most clinically useful x-ray beam size. This is typically a 20-cm diagonal field of view (at the image detector) for catheterization procedures and a 25-cm or larger field for ablation procedures. Magnification modes should be used sparingly as necessary to support the clinical procedure. The operator should be familiar with and should use secondary collimator control. Secondary collimators reduce the x-ray beam area and thereby reduce patient dose and x-ray scatter to the operator and to the image receptor. Particularly for large patients, x-ray scatter to the image receptor contributes to reduced image contrast; therefore decreasing the size of the x-ray beam area with the secondary collimators can result in a notable improvement in image quality. Furthermore, systems equipped with a large screen monitor may be configured to use the wide display mode for increased dose optimization. By using a larger field of view with collimation and zooming the image to a wide display, the use of magnification mode can be avoided.[33] Strategies to minimize patient radiation dose during a procedure are summarized in Table 7-3.

Active monitoring of the cumulative air kerma should be incorporated into the clinical practice for all procedures. Intraprocedure announcement of air kerma starting at 3 Gy and then in increments of 1 Gy thereafter is recommended.[10] After the procedure, air kerma and air kerma area product values should be included in the patient record for future reference. Each practice should routinely audit patient radiation dose metrics to recognize trends in patient dose and to facilitate relevant quality improvement. Detailed recommendations for a facility's quality assurance–peer review (QA-PR) process and recommendations for administrative practices for the evaluation of known or suspected radiation injuries can be found in the reference section.[34]

Patients for whom the air kerma exceeded 5 Gy should receive postprocedure instruction and appropriate follow-up. Informing such patients that they received a substantial dose of radiation and asking them to have a family member check their back in 1 month are simple and effective first-level assessment steps. The patient should report the appearance of a red patch the size of a hand to the physician who performed the procedure. The physician should then arrange to see the patient to continue evaluation and management. Physicians should also consider prospectively contacting patients who received a substantial dose 1 to 2 months after the index procedure. Physicians should regard any such signs as being of radiogenic origin until an alternative diagnosis is established.

TABLE 7-3 Intraprocedure Strategies to Minimize Patient Radiation Dose

Default to low-dose-rate fluoroscopy.	Configure the x-ray system to use the lowest reasonable fluoroscopy dose rate. Table-side controls provide access to modes with a higher dose rate when a higher quality fluoroscopic image is required.
Be attentive to x-ray geometry.	Maintaining a long x-ray source–patient distance and a short patient–image receptor distance can substantially reduce patient skin dose.
Activate x-ray imaging judiciously.	Activate x-ray only when clinically indicated, and cease irradiation immediately after clinical utility has passed.
Use moderate x-ray beam angles.	When possible, use less x-ray beam angulation to decrease the path length through the patient, thereby decreasing x-ray attenuation and reducing dose rate.
Use secondary collimators.	The patient will receive less radiation, operator dose from scatter will go down, and the quality of images of large patients will improve.
Never use acquisition imaging to overcome poor fluoroscopic image quality.	Acquisition dose rates can be as much as 20× greater than for fluoroscopy. When necessary to improve image quality, temporarily switch to a higher dose rate fluoroscopy mode.

TABLE 7-4 Occupational Dose Limits

Dose Quantity	Dose Limit
Effective Dose	
Annual	50 mSv
Cumulative	10 mSv × age in years
Equivalent Dose (Annual)	
Lens of the eye	150 mSv
Skin, hands, and feet	500 mSv
Embryo and fetus, equivalent dose (monthly) once pregnancy is known	0.5 mSv

From National Council on Radiation Protection and Measurements (NCRP): *Report 116: Limitation of exposure to ionizing radiation,* Bethesda, MD, 1993, NCRP.

Straightforward procedures, including diagnostic procedures, are typically not associated with a high skin dose that could lead to skin injury. However, it is important to practice low-dose radiation techniques during all procedures to master the skills necessary to maintain low skin dose during difficult procedures. It is important that all procedure room staff understand radiographic imaging and radiation safety principles, and physicians should foster a collaborative effort to ensure patient radiation safety.

STAFF RADIATION PROTECTION

Studies that report measurements of staff radiation dose during cardiac catheterization procedures show that high levels are possible.[35] Particular concern has been noted with regard to radiation doses to the lens of the eye,[36] the hands,[37] and lower extremities[38] of the operator. It is possible for personnel to reduce occupational radiation exposure with careful attention to their actions during the procedure; such actions include knowledge of the sources of radiation exposure and methods that can be used to decrease exposure levels.

Occupational Dose Monitoring

Radiation monitors are worn by personnel who work in fluoroscopy procedure rooms to determine their individual occupational exposure level. In order to provide an estimate of personnel radiation risk when protective aprons are worn, the use of two radiation monitors is recommended.[10] One monitor is worn under the apron at the waist or chest level, and a second monitor is worn outside the apron at the neck. The values from both monitors are used to estimate effective dose, and the neck monitor provides an estimate of the dose to the lens and thyroid if protective glasses and a thyroid shield are not worn. Because the exposure reading under the apron will be much lower than the reading at the neck, it is essential that the monitors be clearly labeled to avoid accidental exchange.

Dose limits to personnel are set by regulatory agencies to prevent tissue reactions and to limit the risk of stochastic effects. Table 7-4 lists the current National Council on Radiation Protection and Measurements (NCRP) dose limits for occupational workers. When attention is paid to radiation safety and optimal work habits practices, a fluoroscopy operator's effective dose is likely to be between 2 and 4 mSv per year.[39]

Fluoroscopy operators should take special note of dose limits for the lens of the eye. Until recently, it has been generally accepted that radiation-induced cataracts do not form below a threshold lens dose of 2 to 5 Gy. This threshold provided the basis for the maximum permissible dose of 150 mSv per year for the lens. However, new data on the radiosensitivity of the eye indicate that the threshold dose may be significantly lower, and the International Commission on Radiological Protection (ICRP) has recommended a lower lens-dose limit of 20 mSv per year averaged over 5 years, with no single year exceeding 50 mSv.[40] Although U.S. regulatory agencies have not adopted a lower lens-dose limit, careful attention to radiation protection of the eye is warranted to minimize cataract risk. Protective shielding to reduce radiation exposure to the eye from scatter includes leaded eyewear and ceiling-suspended upper body shields. Additional information on lens-dose reduction is included later in this section.

For pregnant personnel, a lower dose limit is applied to minimize radiation exposure of the embryo/fetus. To monitor the conceptus dose, a radiation monitor is provided when a worker has declared her pregnancy. This monitor is worn at the waist level under a protective apron and is exchanged on a monthly basis. Because current data do not suggest a significant increased risk to the fetus of pregnant personnel in the cardiac catheterization laboratory, it is not necessary—nor is it legal—to restrict pregnant workers from working in fluoroscopy procedure areas.[41] However, additional radiation safety precautions and monitoring of radiation exposure among pregnant personnel are warranted.

Sources of Personnel Radiation Exposure

Radiation exposure during fluoroscopy procedures comes from three sources: (1) the primary x-ray beam, (2) scattered x-rays, and (3) x-ray tube leakage x-rays. Occupational exposure to the *primary beam* may occur when the operator manipulates devices positioned within the imaging field of view. Dose rates in this region are in the range of 5 to 20 mGy/hour at the surface, where the x-ray beam *exits* the patient during fluoroscopy. Dose rates to the operator's hands when they are placed in the unattenuated x-ray beam (patient-entrance side) can exceed 5000 mGy/hour. *Scattered x-rays* are produced when tissue is exposed to the primary x-ray beam, and the rays travel in all directions from the point of origin. Scatter dose rates are typically 1 to 10 mGy/hour at the operator's position. The third source of radiation is from *leakage x-rays* emitted from the x-ray tube in areas other than the primary beam port. Leakage is several orders of magnitude lower than scatter-dose rates.

In general, scatter levels decrease in proportion to the inverse squared distance from the irradiated patient tissue volume. However, it should be noted that the radiation distribution surrounding the patient is not uniform. Figure 7-7 shows a typical scatter isodose plot for a C-arm. For a lateral x-ray beam, note that radiation intensity is concentrated in the area near the x-ray tube. This distribution is caused by higher levels of scattered x-rays produced at the primary beam patient-input port. Forward scattered rays from the first few centimeters of tissue depth are heavily attenuated by the rest of the patient tissue, which results in higher radiation levels in the direction back toward the x-ray tube.

Personal Protective Equipment

X-ray scatter from the patient is the primary source of radiation dose to in-room personnel, and it should be minimized to reduce the likelihood of long-term health effects. Occupational radiation dose can be minimized through a combination of radiation safety devices and practices. These are often summarized by the concepts of reducing *time* duration of exposure, increasing *distance* from the scatter source (the patient), and use of *shielding* to block x-ray scatter. In addition, it is important to recognize that the occupational radiation dose *rate* that originates from the patient is directly proportional to dose rate to the patient. A primary step to reducing occupational dose is to reduce patient dose. For most interventional cardiac lab personnel, the amount of time spent in the procedure room is determined by the number and type of procedures performed and is not readily controlled on an individual basis. The inverse square law dictates that the intensity of radiation decreases in proportion to the square of the distance from the source. When the x-ray beam is on, personnel should position themselves as far as reasonably possible from the patient. It is recognized, however, that patient care necessitates that some personnel remain close to the patient during exposure. Therefore the most important concept for personnel radiation dose reduction is shielding.

Shielding refers to placement of any device between the patient and personnel with the purpose of absorbing x-ray scatter. All in-room

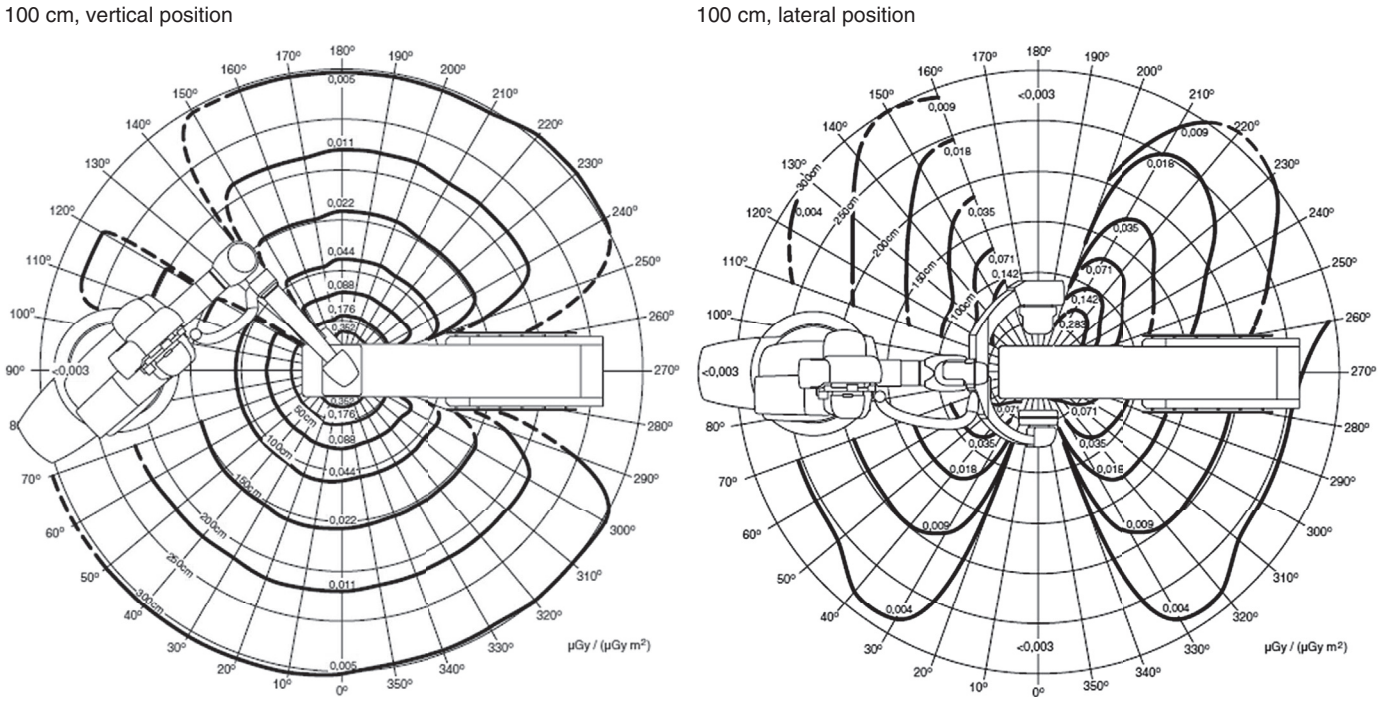


FIGURE 7-7 Scatter isodose curves for a fluoroscopic system. Scatter levels at a height of 1 m is shown for a vertical (*left*) and lateral (*right*) orientation. Isodose lines are in units of Gy per Gy m^2 of patient P_{KA}. (Courtesy Siemens Medical Systems.)

personnel are required to wear a protective garment over the trunk of the body. A typical 0.5 mm lead-equivalent garment blocks about 98% of the x-ray scatter incident upon it. Radiation shields or drapes attached to the patient table provide excellent protection of the lower body (Fig. 7-8). Use of optional vertical extension of these drapes provides additional protection to the operator's midsection for femoral-access procedures, but they interfere with the patient for radial-access procedures. Ceiling-mounted, leaded-glass upper body shields can provide up to 80% protection of the upper body, including the otherwise unprotected neck and head.[20,42] For femoral artery–access procedures, the upper body shield should be positioned nominally perpendicular to the patient head-foot direction, tight to the patient abdomen, and just superior to the access point to minimize the angular size of the gap in protection under the shield occupied by the patient. For radial-access procedures, the upper body shield is best positioned nominally parallel to the patient's head-foot direction and close to the patient's arm. For upper body shields, flexible extensions attached to the bottom of the leaded-glass shield provide a soft and contoured contact between the shield and patient. A good guideline for use of the upper body shield is that the operator should have to look through the shield to see the volume of the patient being irradiated. Floor-mounted mobile shields should be available for protection of in-room personnel, particularly nursing staff. Physician operators should wear leaded glasses to reduce the dose to the lens of the eye and thereby minimize lifetime risk of radiation-induced cataracts.[40,43] Glasses with a large surface area, including side shields, are most effective.[44]

Disposable radiation-absorbing towels or drapes can provide up to 60% upper body protection in situations where the upper body shield cannot be readily used, including in the hybrid operating room.[20,45] These must be thoughtfully positioned to maximize protection. Other novel radiation protection devices are commercially available and may also be considered.[46,47] Generally, these novel systems are floor mounted or suspended and are designed to provide whole-body protection, thereby removing the weight burden of a protective garment.[48-50] Other novel technologies, such as robot-guided interventional systems, provide an opportunity for both operator radiation protection and ergonomic comfort.[51,52] Strategies to reduce occupational radiation dose are summarized in Table 7-5.

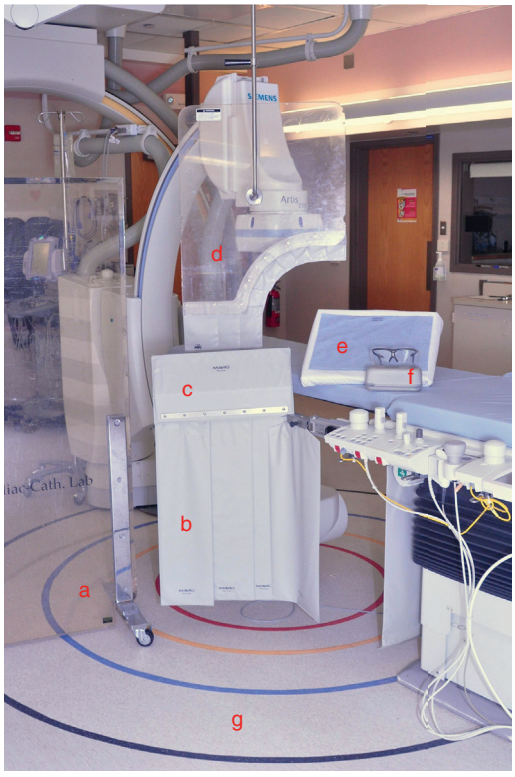


FIGURE 7-8 Personnel radiation safety devices: a) portable leaded-glass shield; b) lower body shield; c) vertical extension to lower body shield; d) upper body shield with patient contour extensions; e) sterile, disposable radiation-absorbing drape; and f) leaded-glass safety glasses. The lines on the floor (g) indicate distance from the patient corresponding to 2× changes in scatter dose rate, providing a visual reminder of the protective effects of increased distance from the scatter source. Mandatory lead-equivalent garments and thyroid shield are not shown. (Photograph courtesy Mayo Clinic, Rochester, MN.)

TABLE 7-5 Strategies to Reduce Occupational Radiation Dose

Reduce patient dose.	Occupational radiation dose is proportional to patient dose. Efforts to reduce patient dose will positively affect occupational dose.
Use x-ray shields judiciously.	*Operators:* When properly used, the ceiling mounted upper body shield can substantially reduce operator dose. *Nursing staff:* Remain behind a lead barrier when possible.
Wear your radiation monitoring badge.	Consistent use of the radiation monitoring badge is the best way to know how well your occupational dose-reduction efforts are working.
Maintain situational awareness.	*Operators:* Do not activate the x-ray unnecessarily when a nurse or technologist is tending to the patient. *In-room staff:* When possible, step back from the patient when the x-ray beam is on.
Wear leaded glasses.	Operators should wear leaded glasses with large side shields to reduce the dose to the lens of the eye and thereby reduce the lifetime risk of developing cataracts.

REFERENCES

1. International Commission on Radiological Protection (ICRP): Report 103: The 2007 Recommendations of the ICRP.
2. National Academy of Sciences: *Health risks from exposure to low levels of ionizing radiation: BEIR VII—Phase 2 Committee to Assess Health Risks from Exposure*, Washington, DC, 2006, National Academies Press.
3. Mettler FA, Huda W, Yoshizumi TT, Mahesh M: Effective doses in radiology and diagnostic nuclear medicine. *Radiology* 248:254–262, 2008.
4. National Council on Radiation Protection and Measurements (NCRP): *Report 160: Ionizing radiation exposure of the population of the United States*, Bethesda, MD, 2009, NCRP.
5. Balter S, Hopewell JW, Miller DL, et al: Fluoroscopically guided interventional procedures: a review of radiation effects on patients' skin and hair. *Radiology* 254(2):326–341, 2010.
6. Koenig TR, Wolff D, Mettler FA, Wagner LK: Skin injuries from fluoroscopically guided procedures: Part 1, characteristics of radiation injury. *AJR Am J Roentgenol* 177(1):3–11, 2001.
7. Wagner LK: Radiation injury is potentially a severe consequence of fluoroscopically guided complex interventions. *Health Phys* 95(5):645–649, 2008.
8. Food and Drug Administration (FDA): *Important information for physicians and other health care professionals. Avoidance of serious x-ray–induced skin injuries to patients during fluoroscopically-guided procedures*, 1994, FDA. <http://www.fda.gov/downloads/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/MedicalX-Rays/ucm116677.pdf>. Accessed 03.25.15.
9. Shope TB: Radiation-induced skin injuries from fluoroscopy. *Radiographics* 16(5):1195–1199, 1996.
10. National Council on Radiation Protection and Measurements (NCRP): *Report 168: Radiation dose management for fluoroscopically-guided interventional procedures*, Bethesda, MD, 2010, NCRP.
11. International Electrotechnical Commission (IEC): *IEC 60601. Medical electrical equipment: Part 2-43, ed 2, Particular requirements for the safety of x-ray equipment for interventional procedures*, 2010.
12. Food and Drug Administration: U.S. Food and Drug Administration Center for Devices and Radiological Health. Code of Federal Regulations, Title 21 Part 1020, Section 1020.30-32, Performance standards for ionizing radiation–emitting products. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. Accessed 25.03.15.
13. Conference of Radiation Control Program Directors (CRCPD): *Proceedings of the 42nd annual national conference on radiation control: opportunities and innovations in radiation control*, Frankfort, KY, 2010, CRCPD. CRCPD Publication E-10-5.
14. Hirshfeld JW, Jr, Balter S, Brinker JA, et al: ACCF/AHA/HRS/SCAI clinical competence statement on physician knowledge to optimize patient safety and image quality in fluoroscopically guided invasive cardiovascular procedures. A report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on Clinical Competence and Training. *J Am Coll Cardiol* 44(11):2259–2282, 2004.
15. Lakkireddy D, Nadzam G, Verma A, et al: Impact of a comprehensive safety program on radiation exposure during catheter ablation of atrial fibrillation: a prospective study. *J Interv Card Electrophysiol* 24(2):105–112, 2009.
16. Chambers CE, Fetterly KA, Holzer R, et al: Radiation safety program for the cardiac catheterization laboratory. *Catheter Cardiovasc Interv* 77(4):546–556, 2011.
17. Kuon E, Weitmann K, Hoffmann W, et al: Efficacy of a mini-course in radiation-reducing techniques in invasive cardiology: a multicenter field study. *JACC Cardiovasc Interv* 7(4):382–390, 2014.
18. Ector J, Dragusin O, Adriaenssens B, et al: Obesity is a major determinant of radiation dose in patients undergoing pulmonary vein isolation for atrial fibrillation. *J Am Coll Cardiol* 50(3):234–242, 2007.
19. Padovani R, Bernardi G, Malisan MR, et al: Patient dose related to the complexity of interventional cardiology procedures. *Radiat Prot Dosimetry* 94(1–2):189–192, 2001.
20. Fetterly KA, Magnuson DJ, Tannahill GM, et al: Effective use of radiation shields to minimize operator dose during invasive cardiology procedures. *JACC Cardiovasc Interv* 4(10):1133–1139, 2011.
21. Khodadadegan Y, Zhang M, Pavlicek W, et al: Automatic monitoring of localized skin dose with fluoroscopic and interventional procedures. *J Digit Imaging* 24(4):626–639, 2011.
22. Geisel D, Heverhagen JT, Kalinowski M, Wagner HJ: DNA double-strand breaks after percutaneous transluminal angioplasty. *Radiology* 248(3):852–859, 2008.
23. Beels L, Bacher K, De Wolf D, et al: gamma-H2AX foci as a biomarker for patient x-ray exposure in pediatric cardiac catheterization: are we underestimating radiation risks? *Circulation* 120(19):1903–1909, 2009.
24. Wagner LK, Eifel P, Geise R: Effects of ionizing radiation. *J Vasc Interv Radiol* 6(6):988–989, 1995.
25. Geleijns J, Wondergem J: X-ray imaging and the skin: radiation biology, patient dosimetry and observed effects. *Radiat Prot Dosimetry* 114(1–3):121–125, 2005.
26. Kuon E, Glaser C, Dahm JB: Effective techniques for reduction of radiation dosage to patients undergoing invasive cardiac procedures. *Br J Radiol* 76(906):406–413, 2003.
27. Fetterly KA, Mathew V, Lennon R, et al: Radiation dose reduction in the invasive cardiovascular laboratory: implementing a culture and philosophy of radiation safety. *JACC Cardiovasc Interv* 5(8):866–873, 2012.
28. Onnasch DG, Schemm A, Kramer HH: Optimization of radiographic parameters for paediatric cardiac angiography. *Br J Radiol* 77(918):479–487, 2004.
29. Mauriello DA, Fetterly KA, Lennon RJ, et al: Radiation reduction in pediatric and adult congenital patients during cardiac catheterization. *Catheter Cardiovasc Interv* 84(5):801–808, 2014.
30. Fetterly KA: Investigation of the practical aspects of an additional 0.1 mm copper x-ray spectral filter for cine acquisition mode imaging in a clinical care setting. *Health Phys* 99(5):624–630, 2010.
31. Kuon E, Dahm JB, Empen K, et al: Identification of less-irradiating tube angulations in invasive cardiology. *J Am Coll Cardiol* 44(7):1420–1428, 2004.
32. Vano E, Gonzalez L, Fernandez JM, et al: Influence of patient thickness and operation modes on occupational and patient radiation doses in interventional cardiology. *Radiat Prot Dosimetry* 118(3):325–330, 2006.
33. Gailloud P: A large display is a powerful tool to reduce radiation exposure during single-plane fluoroscopically guided procedures. *AJR Am J Roentgenol* 204(4):W483–W485, 2015.
34. National Council on Radiation Protection and Measurements (NCRP): *Statement X (currently under review). Administrative policies for managing substantial dose procedures and tissue reactions associated with fluoroscopically-guided interventions*, Bethesda, MD, 2014, NCRP.
35. Kim KP, Miller DL, Balter S, et al: Occupational radiation doses to operators performing cardiac catheterization procedures. *Health Phys* 94(3):211–227, 2008.
36. Vano E, Gonzalez L, Fernandez JM, Haskal ZJ: Eye lens exposure to radiation in interventional suites: caution is warranted. *Radiology* 248:945–953, 2008.
37. Whitby M, Martin CJ: A study of the distribution of dose across the hands of interventional radiologists and cardiologists. *Br J Radiol* 78:219–229, 2005.
38. Whitby M, Martin CJ: Radiation doses to the legs of radiologists performing interventional procedures: Are they a cause for concern? *Br J Radiol* 76:321–327, 2003.
39. Miller DL, Vano E, Bartal G, et al: Occupational radiation protection in interventional radiology: a joint guideline of the Cardiovascular and Interventional Radiology Society of Europe and the Society of Interventional Radiology. *Cardiovasc Intervent Radiol* 33(2):230–239, 2010.
40. International Commission on Radiation Protection: Statement on tissue reactions/early and late effects of radiation in normal tissues and organs—threshold doses for tissue reactions in a radiation protection context. Publication 118. *Ann ICRP* 2012.
41. Best PJ, Skelding KA, Mehran R, et al: SCAI consensus document on occupational radiation exposure to the pregnant cardiologist and technical personnel. *Catheter Cardiovasc Interv* 77(2):232–241, 2011.
42. Maeder M, Brunner-La Rocca HP, Wolber T, et al: Impact of a lead glass screen on scatter radiation to eyes and hands in interventional cardiologists. *Catheter Cardiovasc Interv* 67(1):18–23, 2006.
43. Jacob S, Michel M, Spaulding C, et al: Occupational cataracts and lens opacities in interventional cardiology (O'CLOC study): are X-rays involved? Radiation-induced cataracts and lens opacities. *BMC Public Health* 10:537, 2010.
44. Sturchio GM, Newcomb RD, Molella R, et al: Protective eyewear selection for interventional fluoroscopy. *Health Phys* 104(2 Suppl 1):S11–S16, 2013.
45. Dromi S, Wood BJ, Oberoi J, Neeman Z: Heavy metal pad shielding during fluoroscopic interventions. *J Vasc Interv Radiol* 17(7):1201–1206, 2006.
46. Dragusin O, Weerasooriya R, Jaïs P, et al: Evaluation of a radiation protection cabin for invasive electrophysiological procedures. *Eur Heart J* 28(2):183–189, 2007.
47. Fattal P, Goldstein JA: A novel complete radiation protection system eliminates physician radiation exposure and leaded aprons. *Catheter Cardiovasc Interv* 82(1):11–16, 2013.
48. Ross AM, Segal J, Borenstein D, et al: Prevalence of spinal disc disease among interventional cardiologists. *Am J Cardiol* 79(1):68–70, 1997.
49. Moore B, vanSonnenberg E, Casola G, Novelline RA: The relationship between back pain and lead apron use in radiologists. *AJR Am J Roentgenol* 158(1):191–193, 1992.
50. Fadl YY, Ellenbogen KA, Grubb RL, Jr, et al: A review of spinal injuries in the invasive cardiologist II: prevention and treatment. *Pacing Clin Electrophysiol* 30(9):1149–1157, 2007.
51. Jeron A, Fredersdorf S, Debl K, et al: First-in-man (FIM) experience with the Magnetic Medical Positioning System (MPS) for intracoronary navigation. *EuroIntervention* 5(5):552–557, 2009.
52. Kautzner J, Peichl P, Cihák R, et al: Early experience with robotic navigation for catheter ablation of paroxysmal atrial fibrillation. *Pacing Clin Electrophysiol* 32(Suppl 1):S163–S166, 2009.

Preoperative Coronary Intervention

8

CRAIG R. NARINS

KEY POINTS

- Perioperative myocardial infarction (PMI) can result from either coronary plaque rupture or a myocardial oxygen supply-demand mismatch related to a preexisting coronary stenosis. This typically occurs in the first 48 hours following surgery, and even if clinically silent, it is a powerful predictor of future adverse cardiac events.
- Routine administration of beta-blockers prior to noncardiac surgery for all at-risk patients who are not on chronic beta-blocker therapy can be harmful and is no longer recommended.
- The indications for performing preoperative coronary angiography are limited and are the same as in the nonoperative setting.
- Because no prospective trial has demonstrated short- or long-term benefits from a strategy of routine preoperative revascularization among patients with coronary disease, the indications for preoperative percutaneous coronary intervention (PCI) are very limited. The use of PCI to "get a patient through" noncardiac surgery is unproven and potentially harmful.
- Noncardiac surgery performed within 4 to 6 weeks of stent implantation is associated with a substantial risk of major adverse cardiac events (MACEs). Surgery should be delayed if possible for 2 weeks after balloon angioplasty, 4 to 6 weeks after bare-metal stenting, and 12 months following drug-eluting placement.
- Among patients with recent stent placement who subsequently require unanticipated noncardiac surgery, the decision whether to continue or suspend antiplatelet therapy for surgery requires individualized assessment of the competing risks of bleeding complications and stent thrombosis. This decision should be made with multidisciplinary input from the cardiologist, surgeon, and other involved subspecialists.
- Perioperative "bridging," in which a parenteral glycoprotein IIb/IIIa receptor antagonist is administered during the interval between $P2Y_{12}$ receptor inhibitor discontinuation and surgery, is a potential strategy to reduce ischemic events among individuals at high risk for stent thrombosis.
- Prompt recognition and treatment of postoperative cardiac complications is a critical element in optimizing surgical outcomes.
- Randomized trials are lacking and are greatly needed to clarify issues fundamental to the management of patients with coronary stents who require subsequent noncardiac surgery, such as the proper timing of surgery and perioperative management of antiplatelet medications.

Of the more than 30 million surgical procedures performed annually in the United States that require the use of general anesthesia, approximately one third involve patients who are at risk for or have known coronary artery disease. Given the physiologic stresses that accompany surgery, the perioperative period is a time of substantially heightened risk for adverse cardiac events. Current evidence suggests that the routine use of coronary revascularization in the preoperative setting is unlikely to reduce the incidence of subsequent cardiac events. Nevertheless, selected patients at particularly increased risk for cardiac complications related to noncardiac surgery may benefit from preoperative PCI. Additionally, up to 12% of individuals who undergo coronary stenting require unanticipated noncardiac surgery within the subsequent year. For these patients, decisions that regard the management of antiplatelet therapy require careful consideration of the competing risks of perioperative bleeding and stent thrombosis.

This chapter will provide a clinically oriented review of preoperative PCI that includes the indications for coronary angiography and revascularization prior to upcoming surgery, the utility of various medical and interventional strategies to reduce perioperative risk among patients with known or suspected coronary disease, technical approaches to performing angioplasty and stenting prior to noncardiac surgery, and strategies for managing patients with recent stent placement who subsequently require unanticipated noncardiac surgery.

PERIOPERATIVE MYOCARDIAL INFARCTION

As with myocardial infarction (MI) outside the context of surgery, PMI can result either from atherosclerotic plaque rupture with thrombotic occlusion of the involved coronary artery (type 1 MI) or from a transient stress-induced mismatch of myocardial oxygen supply and demand, possibly in the setting of a fixed coronary artery stenosis or occlusion (type 2 MI).[1,2] Thrombosis of a previously implanted coronary stent represents another potential mechanism for PMI.[3-5] In the vast majority of instances, PMI does not occur during the surgical procedure but rather within the first 48 hours following surgery. This period is associated with multiple hemodynamic stresses and hematologic alterations that can predispose to plaque rupture, myocardial oxygen supply-demand mismatch, and a hypercoagulable state (Fig. 8-1).[6,7] The risk of MI can remain elevated for several weeks following major surgery.[8]

PMI, whether clinically apparent or silent, is associated with increased mortality in both the short and long term. In-hospital survival rates for PMI typically exceed 90%; however, even smaller infarcts detected following noncardiac surgery are associated with substantial increases in intermediate and late-term mortality independent of other clinical factors.[9] In a study of over 15,000 patients undergoing noncardiac surgery, even small elevations in troponin T (0.02 ng/mL) were associated with a fourfold increase in 30-day mortality, and higher levels (≥0.30 ng/mL) were linked to a sixteenfold escalation in 30-day death.[10] Among 2502 individuals who underwent carotid endarterectomy or stenting in the randomized Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST), PMI was associated with an independent greater than threefold increase in 4-year all-cause mortality.[11]

INDICATIONS FOR PREOPERATIVE CORONARY ANGIOGRAPHY

For clinically stable patients, the current appropriate use criteria (AUC) for diagnostic catheterization offer quite limited indications for performing coronary angiography prior to noncardiac surgery (Fig. 8-2).[12] In accordance with current U.S. and European guideline statements, the indications for performing coronary angiography as part of a preoperative assessment are identical to those in the nonoperative setting.[13,14] Specific instances when preoperative coronary angiography should be considered include:

1. Noninvasive test results suggesting a high risk of adverse outcomes, such as extensive (multivessel distribution) myocardial ischemia, prior to high-risk surgery

2. The presence of Canadian Cardiovascular Society Class III or IV angina not responsive to appropriate medical therapy
3. The presence of unstable angina or recent MI

It must be emphasized that, given the absence of prospective data indicating that surgical risk can be favorably influenced by preoperative coronary revascularization, the concept that PCI or coronary artery bypass grafting (CABG) should be undertaken to "get the patient through" a subsequent noncardiac surgery is not supported by evidence-based standards. The American College of Cardiology (ACC)/American Hospital Association (AHA) consensus guidelines assert that preoperative coronary revascularization is "appropriate for only a small subset of patients at very high risk" and should be used sparingly if at all. Likewise, the current AUC document for coronary revascularization does not consider upcoming noncardiac surgery as a rationale to supersede otherwise inappropriate indications for revascularization.[15]

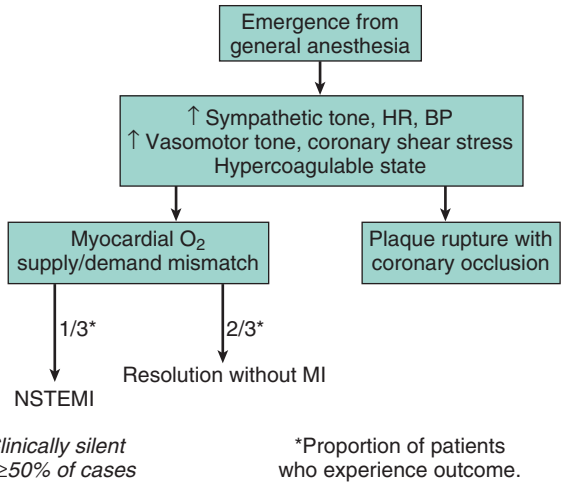


FIGURE 8-1 Pathophysiologic events contributing to the genesis of perioperative myocardial infarction (MI). *BP,* Blood pressure; *HR,* heart rate; *STEMI,* non-ST-segment elevation myocardial infarction.

PHARMACOLOGIC THERAPY

Because all individuals with known or suspected coronary disease have the potential to benefit from appropriate pharmacologic therapy at the time of surgery regardless of whether preoperative coronary revascularization is undertaken, current principles regarding the use of perioperative beta-blocker and statin therapy will briefly be reviewed.

Beta-Blockers

The routine use of perioperative beta-blocker therapy in all at-risk surgical patients to reduce cardiac events, once considered dogma, has come under scrutiny and is no longer recommended. Beta-blockers are thought to ameliorate cardiac stress in the perioperative setting by a number of mechanisms, including reduction of adrenergic stimulation, improvements in the balance of myocardial oxygen demand and supply, diminution of arrhythmic potential, and potential antiinflammatory and plaque-stabilizing effects.[16] Two relatively small trials published in the 1990s demonstrated significant reductions in mortality associated with perioperative beta-blocker therapy among patients at risk for coronary events.[17,18] The emergence of strong evidence that challenged the veracity of data from at least one of these initial Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE)-I trials—coupled with ensuing studies that failed to demonstrate consistent benefit, and in some instances displayed harm, from routine perioperative beta-blocker therapy—has raised serious questions regarding therapeutic efficacy.[19-22]

The Patients Undergoing Noncardiac Surgery (POISE) trial,[23] currently the largest randomized trial of perioperative beta-blocker therapy with data that are considered secure and valid, examined

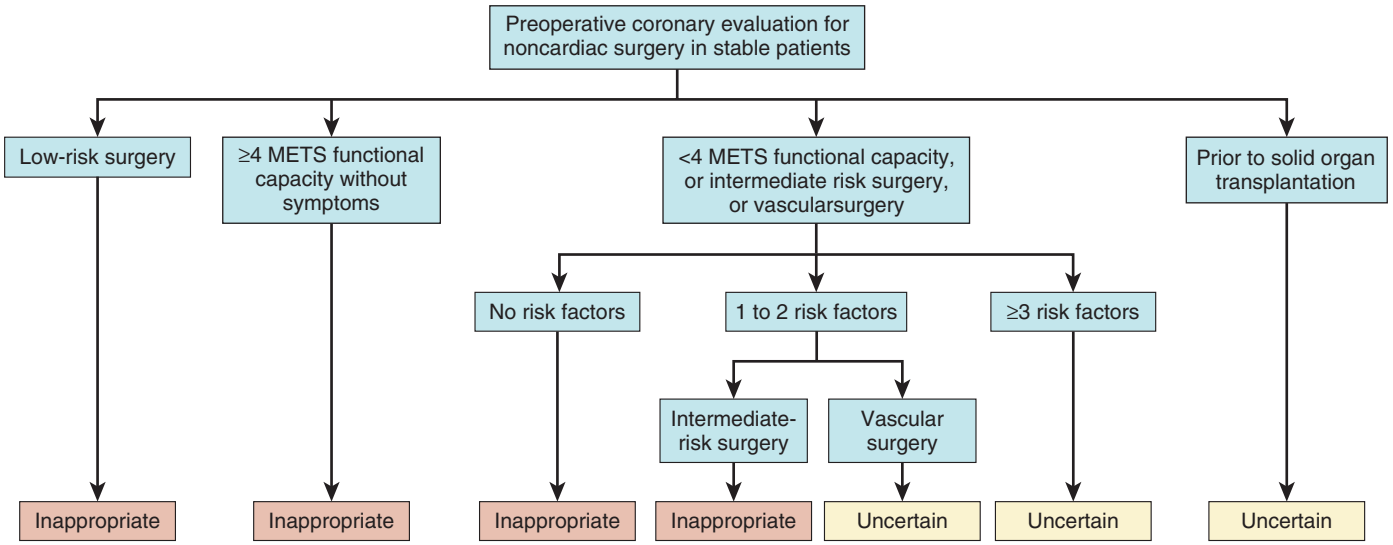


FIGURE 8-2 Appropriate use criteria for preoperative coronary angiography for patients without prior noninvasive stress testing. From the Appropriate Use Criteria for Diagnostic Catheterization guidelines. (From Patel MR, Bailey SR, Bonow RO, et al: ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 59[22]:1995-2027, 2012.)

8351 patients at risk for or with known coronary artery disease. Extended-release metoprolol started 2 to 4 hours before noncardiac surgery was associated with a reduction of cardiovascular death, MI, or cardiac arrest at 30 days; however, this advantage was offset by significantly increased frequencies of both all-cause mortality and stroke among individuals treated with beta-blockers rather than placebo. In a recent meta-analysis that included only data from trials not discredited by evidence of misconduct, initiation of beta-blocker therapy prior to noncardiac surgery was associated with a 27% increased risk of 30-day mortality, as well as significantly increased incidences of stroke and hypotension.[20] Two contemporary registries that in aggregate examined more than 80,000 individuals undergoing noncardiac surgery showed that benefit from perioperative beta-blocker therapy was inconsistent and was confined only to higher-risk individuals.[24,25] Although beta-blockers may protect the myocardium from adrenergic stressors, therapy can also produce unwanted bradycardia, hypotension, and impaired myocardial capacity to adaptively respond to surgical events such as blood loss or systemic vasodilation. Based on current data, the lone class I recommendation for beta-blockade in the present ACC/AHA guidelines states that "beta-blockers should be continued in patients undergoing surgery who are [already] receiving beta-blockers" for appropriate indications. The routine administration of high-dose beta-blockers in the absence of dose titration is now contraindicated (class III) for patients undergoing noncardiac surgery who are not already taking beta-blockers.

Statin Therapy

Proposed mechanisms by which statins may reduce perioperative cardiac complications relate to the plaque-stabilizing effects of these agents, including their antiinflammatory and antithrombotic properties, and the favorable influences these drugs exert on plaque-related endothelial dysfunction.[26] The withdrawal of statin therapy in the perioperative period has been associated with increased cardiac events.[27] A meta-analysis of 15 trials of perioperative statin therapy among patients undergoing cardiac or noncardiac surgery indicated that statin use was associated with a significant reduction in the risk of perioperative MI (relative risk [RR], 0.53; 95% confidence interval [CI], 0.38 to 0.74) but not death (RR, 0.62; 95% CI, 0.34 to 1.14).[28] Unfortunately, as with the beta-blocker literature, the two major randomized trials of perioperative statin therapy—DECREASE-III and -IV—have fallen under the same specter of misconduct as other publications in the DECREASE family.[29,30] Current ACC/AHA guidelines recommend, with a class I indication, that patients currently taking statins who are scheduled for noncardiac surgery should continue therapy. In addition, the guidelines provide class II support for statin use among patients undergoing vascular surgery, with or without clinical risk factors, and for patients undergoing intermediate-risk procedures who have at least one clinical risk factor for coronary disease.[13]

PREOPERATIVE CORONARY REVASCULARIZATION

Because perioperative MI is often related to the presence of preexisting coronary stenosis, coronary revascularization prior to surgery conceivably could represent a means to limit the occurrence of ischemic events during and after surgery. Randomized trials, however, have failed to demonstrate clinical benefit from a strategy of routine coronary revascularization prior to noncardiac surgery, and the indications for preoperative CABG or PCI are currently quite limited.

Coronary Artery Bypass Grafting

Noncardiac surgery appears safe for individuals with remote CABG who subsequently require a major noncardiac surgical procedure. Among patients followed in the Coronary Artery Surgery Study (CASS) registry who required high-risk noncardiac surgery during follow-up, prior CABG was associated with reduced postoperative MI and mortality compared with medically managed coronary disease.[30a] Whereas a history of remote coronary bypass grafting may be protective during future surgical procedures, the role of CABG undertaken as a preemptive measure among patients discovered to have severe coronary artery disease during a preoperative risk assessment remains unproven. Performance of CABG can substantially delay subsequent noncardiac surgery, and prophylactic CABG may not be feasible if the required noncardiac surgical procedure is urgent. Attempting to perform noncardiac surgery very shortly after CABG may be associated with further increased operative risks. For example, in one observational study, patients undergoing vascular surgery within 1 month of CABG demonstrated a fivefold increase in operative mortality compared with matched controls who underwent vascular surgery without preceding CABG (20.6 vs. 3.9%, $P < .005$).[31]

Percutaneous Coronary Intervention

Risks of Preoperative Percutaneous Coronary Intervention

Decision analyses have suggested that coronary angiography and intervention prior to vascular surgery should be carried out only when the risk of the vascular surgery is relatively high (>5%) and the anticipated risk of angiography and revascularization is relatively low (<3%). Unfortunately, the mere presence of peripheral vascular disease is associated with an increased risk of adverse events during PCI. In a pooled analysis of 19,867 patients enrolled in eight large PCI trials, patients with concomitant peripheral arterial disease experienced a greater than twofold increase in procedural, 6-month, and 1-year mortality.[31a] Likewise, peripheral arterial disease consistently has emerged as an independent predictor of mortality following PCI in large registries and risk-prediction models.[31b]

Observational Studies of Preoperative Percutaneous Coronary Intervention

A variety of retrospective analyses extending from the prestent era to current practice have addressed the relationship between preoperative PCI and the likelihood of adverse cardiac events during subsequent noncardiac surgery (Tables 8-1 through 8-3). Conclusions that can be drawn from these studies are limited, however, because most reports suffer from small size, retrospective design, frequent absence of standardized indications to determine which patients were referred for PCI, a wide variety of noncardiac surgical procedures, variable timing between preoperative PCI and subsequent noncardiac surgery (days to years), and most important, the lack of control groups. Also, because in most reports, patients who died following PCI did not go

TABLE 8-1 Complication Rates of Noncardiac Surgery Following Balloon Angioplasty

First Author, (Year)	*N*	MI (%)	Death (%)	Interval Between Angioplasty and Surgery
Allen (1991)[32]	148	0.7	2.7	11 months
Huber (1992)[33]	50	5.6	1.9	9 days
Elmore (1993)[34]	14	0	0	10 days
Jones (1993)[35]	108	3.7	0.9	14 days
Gottlieb (1998)[36]	194	0.5	0.5	11 days
Posner (1999)[37]	686	2.2	2.6	1 year
Hassan (2001)[38]	251	0.8	0.8	21 months
Brilakis (2005)[39]	350	0.6	0.3	<2 months
Leibowitz (2006)[40]	122	2.9 6.8	14.7 9.1	Early (0 to 14 days) Late (14 to 62 days)

Adapted (and expanded) from Fleisher LA, Beckman JA, Brown KA, et al: 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 120(21):e169-276, 2009.

TABLE 8-2 Complication Rates of Noncardiac Surgery Following Coronary Bare-Metal Stent Placement

First Author (Year)	N	MI (%)	Death (%)	Major Bleeding (%)	Comments
Kaluza (2000)[4]	40	17.5	20	27.5	All deaths and MI occurred when surgery was performed <2 weeks after stenting.
Wilson (2003)[5]	207	1.4	2.9	33	All deaths and MI occurred when surgery was performed <6 weeks after stenting.
Sharma (2004)[41]	47	NR	17.0	25.6	A fivefold increase in mortality was noted when surgery was performed early (<3 weeks) versus late (>3 weeks) after stenting.
Reddy (2005)[42]	56	10.7	7.1	5.4	Death or MI occurred in 38% who had surgery within 2 weeks of stenting but in none who had surgery after 6 weeks.
Leibowitz (2006)[40]	94	7.4	13.8	16	Significantly more adverse events occurred when surgery was performed within 2 weeks of PCI.
Vicenzi (2006)*[43]	103	11.7	4.9	3.9	When surgery was performed early (<35 days) rather than late (>90 days) after stenting, 2.1-fold more events were reported.
Schouten (2007)*[44]	192	2.6	0	23	MACE rate was 13.3% versus 0.6% when surgery was performed early (<30 days) versus late (>30 days) after stenting.
Brotman (2007)*[45]	114	1.8	0	NR	MACE rate was low.
Kim (2008)[46]	101	0	0	NR	No MACEs occurred.
Nuttall (2008)[47]	899	2.0	3.4	4.8	MACE rate was more than threefold greater when surgery was performed early (<30 days) rather than late (>30 days) after stenting.
Cruden (2010)[48]	1383	0.7	0.6	NR	Surgery was done late (median 503 days) post stent.
CREDO-Kyoto (2012)[49]	1103	0.6	3.0	3.2	Surgery occurred within 3 years of PCI.

Adapted and expanded from Fleisher LA, Beckman JA, Brown KA, et al: 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 120(21):e169-276, 2009.
*Studies marked by an asterisk included patients with bare-metal or drug-eluting stents. Unmarked studies include data only for patients who received bare-metal stents.
MACE, Major adverse cardiac event; *MI,* myocardial infarction; *NR,* not reported; *PCI,* percutaneous coronary intervention.

TABLE 8-3 Complication Rates of Noncardiac Surgery Following Coronary Drug-Eluting Stent Placement

First Author (Year)	N	MI (%)	Death (%)	Major Bleeding (%)	Comments
Assali (2009)[50]	78	5.1	2.6	16.7	Frequency of MACE did not differ significantly between those with early (<1 yr) versus late (>1 yr) NCS following DES placement.
Rabbitts (2008)[51]	520	2.7	2.7	14.8	Frequency of MACE was not significantly associated with the time between PCI and NCS.
Rhee (2008)[52]	141	1.4	3.5	NR	Only patients undergoing NCS <1 year post DES were included. The strongest MACE predictor was discontinuance of clopidogrel ≥7 days preoperatively.
Godot (2008)[53]	96	12.5	2.1	0	Frequency of MACE was not significantly associated with the time between PCI and NCS.
Compton (2006)[54]	38	0	0	NR	No MACE was noted in this small series. Clopidogrel was stopped prior to NCS in 60% of patients.
Kim (2008)[46]	138	1.4	0.7	NR	The adverse events occurred 6, 264, and 367 days after stent placement.
Anwarruddin (2009)[55]	481	4.1	5.0	NR	MACE rate was highest during the first 30 days after PCI.
Berger (2010)[3]	206	1.5	0.5	NR	All surgery was done within 1 year of DES placement.
Cruden (2010)[48]	570	1.2	0.5	NR	Surgery was done late (median 371 days) post stent.
CREDO-Kyoto (2012)[49]	1295	0.6	2.5	2.1	Surgery was done within 3 years of PCI.

DES, Drug-eluting stent; *MACE,* major adverse cardiac events; *MI,* myocardial infarction; *N,* number of patients; *NCS,* noncardiac surgery; *NR,* not reported; *PCI,* percutaneous coronary intervention.

on to noncardiac surgery and thus were not included in follow-up, the true complication rates from a strategy of preoperative PCI were underreported.

Among studies of preoperative balloon angioplasty performed in the present era, in-hospital mortality following subsequent noncardiac surgery ranged from 0% to 2.7% for patients who underwent surgery following either recent (within 2 weeks) or remote (up to 29 months) preoperative angioplasty. Higher perioperative mortality rates (ranging from 2.9% to 20%) were initially reported in studies that examined outcomes following coronary bare-metal or drug-eluting stent implantation prior to noncardiac surgery, although the incidence of adverse outcomes appears to have fallen over time.

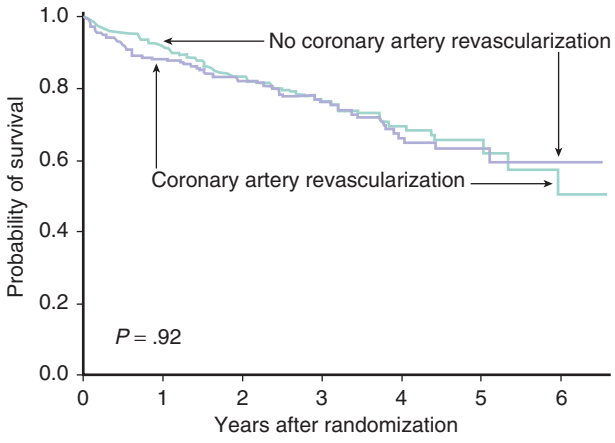
Randomized Trials of Preoperative Revascularization

Two randomized trials have examined the role of coronary revascularization as a means to reduce the likelihood of perioperative events among individuals with coronary artery disease scheduled to undergo vascular surgery.[56,57] Despite their modest size (<200 subjects in the two studies combined underwent PCI) and documentation of investigator misconduct in one of the two studies (DECREASE-V),[20] these

trials have become the foundation for current recommendations that are critical of preoperative coronary revascularization.

The Coronary Artery Revascularization Prophylaxis (CARP) trial compared the strategy of preoperative coronary revascularization to that of stand-alone medical therapy for the reduction of early and late cardiac events following major vascular surgery.[56] The trial enrolled 510 patients scheduled for vascular surgery at one of 18 Veterans Affairs (VA) Medical Centers. Patients were eligible if angiography-proven coronary artery disease with a 70% or more stenosis in at least one major epicardial coronary artery was present, and they were randomized to either coronary revascularization followed by vascular surgery or to vascular surgery without preceding coronary revascularization. Among the group randomized to coronary revascularization, 41% of patients underwent CABG, and 59% were treated with PCI.

The majority of patients enrolled in the CARP trial were at low to intermediate rather than high risk for perioperative coronary events. The median age was 66 years, and whereas 42% had a prior MI, only 38% noted the presence of angina at the time of study entry. Most patients had one- or two-vessel coronary disease with preserved left ventricular (LV) function, and those with left main stenosis of 50% or greater, a left ventricular ejection fraction (LVEF) of less than 20%, or severe aortic stenosis were excluded. The results of the CARP trial indicated that preoperative revascularization was not associated with any apparent benefit over conservative therapy. Although patients assigned to coronary revascularization had a significantly longer delay between randomization and vascular surgery (54 vs. 18 days), neither preoperative PCI nor CABG was associated with a reduction in the occurrence of adverse cardiac events or overall survival following vascular surgery at 30-day or 2.7-year follow-up (Fig. 8-3). One criticism of the CARP trial was that the process of preoperative risk stratification used in the study did not follow the ACC/AHA preoperative guidelines, in which coronary angiography is generally considered only after noninvasive testing has demonstrated moderate or severe inducible ischemia. In the CARP study, noninvasive testing was not mandated, and less than 50% of enrolled subjects underwent a stress imaging study that documented moderate or severe ischemia prior to coronary angiography.



No. at risk						
Revascularization	226	175	113	65	18	7
No revascularization	229	172	108	55	17	12

FIGURE 8-3 Kaplan-Meier survival curve for patients enrolled in the CARP trial. There was no difference in early or late mortality following noncardiac surgery among patients with coronary artery disease who were randomized to undergo preoperative coronary revascularization rather than conservative therapy. (From McFalls EO, Ward HB, Moritz TE, et al: Coronary-artery revascularization before elective major vascular surgery, *New Engl J Med* 351[27]:2795-2804, 2004.)

The DECREASE-V pilot study was designed to evaluate the effectiveness of prophylactic coronary revascularization prior to major vascular surgery among a higher-risk group of patients than those enrolled in the CARP trial.[57] A total of 101 patients with extensive myocardial ischemia on noninvasive stress imaging were randomized to either revascularization (65% had PCI, 35% had CABG) or no revascularization prior to vascular surgery. Within this small cohort, preoperative coronary revascularization was not associated with significant differences in the occurrence of death or MI either at 30 days or 1 year following noncardiac surgery.

Despite their potential shortcomings, the CARP and DECREASE-V results lend support to the concept that performing prophylactic coronary revascularization for the purpose of "getting a patient through" noncardiac surgery is generally not appropriate. At present, preoperative PCI should be considered only among patients who have an indication for coronary revascularization unrelated to the noncardiac surgery, particularly those with medically refractory angina, unstable angina, or recent MI. For these limited patient groups at the highest risk for adverse cardiac events, sufficient data regarding the efficacy and safety of preoperative revascularization are lacking, and the potential risks and benefits of preoperative revascularization need to be carefully weighed on an individual basis. Multidisciplinary communication involving the patient's primary care physician, cardiologist, cardiac surgeon, anesthesiologist, and surgeon intending to perform the noncardiac procedure can be crucial in determining a rational preoperative strategy. Such a discussion can allow consideration of issues such as the anticipated risks and benefits of preoperative PCI or CABG; the risks, necessity, and urgency of the planned noncardiac surgical procedure; and the potential risks that antiplatelet agents such as aspirin or $P2Y_{12}$ receptor–blocker therapy may pose during the operation.

Technical Aspects of Preoperative Percutaneous Coronary Intervention

When the decision has been made to perform preoperative PCI, several important technical considerations exist. Foremost is the length of delay that is permissible between PCI and the subsequent noncardiac surgical procedure, which often dictates whether stand-alone balloon angioplasty, bare-metal stenting, or drug-eluting stent implantation is performed (Fig. 8-4).

Balloon Angioplasty

Because of less reliable short- and long-term results, balloon angioplasty without stent placement has become an infrequently used strategy for most patients undergoing PCI. Stand-alone balloon angioplasty may, however, have a role in the preoperative setting because this approach does not introduce the possibility of perioperative stent thrombosis, nor does it mandate the use of $P2Y_{12}$ receptor–blocker therapy, permitting surgery with little delay following PCI (see Table 8-1). Current ACC/AHA guidelines recommend delaying surgery for 2 to 4 weeks following balloon angioplasty to allow for initial healing at the site of vessel injury and to overcome the usual time frame during which acute vessel closure and recoil typically occur. Surgery should not be delayed for more than 8 to 12 weeks following angioplasty because restenosis becomes a potential concern after this interval. Thus for a patient in whom PCI is deemed necessary prior to surgery, but delaying surgery for more than 2 weeks is undesirable, balloon angioplasty without stenting may represent a reasonable option. It should be kept in mind, however, that abrupt vessel closure or an inadequate angiographic result can occur in up to 10% to 20% of attempts at stand-alone balloon angioplasty and that unplanned stenting may become necessary.

Bare-Metal Stents

Among patients undergoing PCI, routine stent implantation is associated with improved immediate and late results compared with balloon angioplasty alone. In the face of noncardiac surgery, however, the

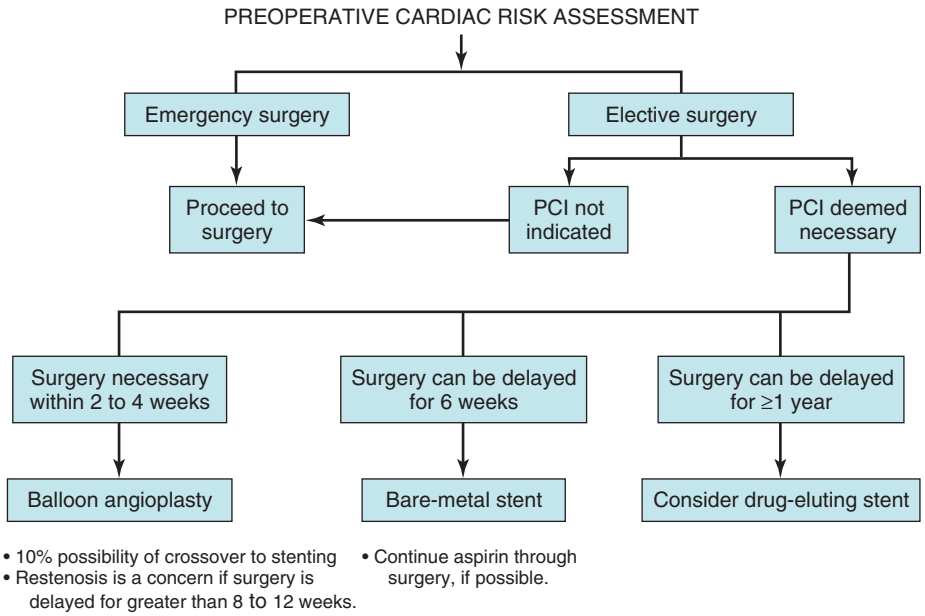


FIGURE 8-4 Algorithm outlining device selection for preoperative percutaneous coronary intervention (PCI).

presence of a recently placed coronary stent introduces the possibility of stent thrombosis during the perioperative period, an event associated with substantial morbidity and mortality. Antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor blocker is recommended for at least 4 weeks following placement of a bare-metal stent (BMS) to reduce the likelihood of stent thrombosis while stent endothelialization occurs. When noncardiac surgery is undertaken soon (within 4 to 6 weeks) after coronary stent implantation, the risk of adverse cardiac events is substantial, and MACE rates range from 10% to 30% in various registries. Consequently, noncardiac surgery should be delayed for 6 weeks following BMS implantation, if possible, to permit at least partial endothelialization of the stent, as well as completion of a full course of $P2Y_{12}$ receptor antagonist therapy.

Drug-Eluting Stents

Drug-eluting stents (DESs) have further reduced the likelihood of restenosis following PCI compared with BMSs yet are poorly suited for use in the preoperative setting. By inhibiting cellular proliferation, DESs limit the development of fibrointimal hyperplasia and clinical restenosis, but at the same time they inhibit the protective process of stent endothelialization.[58] Therefore stent thrombosis remains a concern for months to years (instead of weeks) following DES implantation, making interruption of dual-antiplatelet therapy (DAPT) for noncardiac surgery problematic.[59,60] Current ACC/AHA guidelines for perioperative care recommend delaying elective noncardiac surgery when possible for at least 12 months following DES placement. Hence, prior to all PCI procedures, patients should routinely be asked whether any noncardiac surgical procedure is planned or likely within the next year, and if so, balloon angioplasty or bare-metal stenting should be performed in lieu of DES placement if the impending surgery cannot be postponed.

With the introduction of second-generation DESs, the likelihood of stent thrombosis now appears no greater than that with BMSs, and DAPT durations of less than a year may be safe in some instances.[61-65] Three large, randomized controlled trials that examined contemporary DES platforms demonstrated no difference in late ischemic events following DES placement when DAPT was continued for only 3 or 6 months rather than for longer durations of 12 or 24 months.[66-68] The impact of this observation on perioperative stent thrombosis requires further evaluation because none of these trials specifically examined patients undergoing noncardiac surgery.

UNANTICIPATED SURGERY AFTER STENTING

Even if DES use is avoided among patients with impending surgery, roughly 4% to 12% of patients who receive a DES will require an unplanned surgical procedure during the first 12 months after stent placement.[3,43,49,67,69,70] For these individuals, the decision whether to continue or suspend antiplatelet therapy during surgery involves a presumptive trade-off between perioperative ischemic events and bleeding complications. The likelihood of ischemic events, particularly stent thrombosis, appears especially high if surgery is performed within the first 4 to 6 weeks following either BMS or DES placement. After 6 weeks, perioperative cardiac event rates fall substantially and in most analyses reach a stable nadir after 6 to 12 months after stent placement (Fig. 8-5). Although early stoppage of antiplatelet therapy is among the strongest predictors of stent thrombosis, it remains uncertain to what degree and under what circumstances continuation of DAPT in the perioperative setting reduces ischemic cardiac events.[71] Maintenance of aspirin and/or $P2Y_{12}$ receptor–blocker therapy during major noncardiac surgery, however, is associated with a well-documented increased likelihood of hemorrhagic complications.[72,73] Whether the increased bleeding risk associated with DAPT continuation during surgery is offset by a reduced incidence of cardiac ischemic events or stent thrombosis among patients with previous stent placement remains a subject of active investigation.

Cardiac Events With Unplanned Surgery

When surgery must be performed within 6 weeks following PCI, the likelihood of cardiac adverse events is substantial. In a Scottish registry of 1953 individuals who underwent noncardiac surgery following coronary BMS or DES placement, when surgery was performed within 42 days of stenting, the incidence of perioperative death or cardiac ischemic events was quite high (42.4%, vs. 12.8% when surgery was performed after 42 days; $P < .001$).[48] Mortality rates fell after 6 weeks but remained fourfold greater when surgery was performed between 42 days and 1 year compared with after 1 year post PCI. Notably, no association was found between stent type (BMS vs. DES) and adverse events. Among 41,989 VA patients who underwent noncardiac surgery within 24 months of coronary stenting, MACE rates fell from 11.6% when surgery was performed within 6 weeks of stenting to 6.4% when surgery was undertaken 6 weeks to 6 months after stent

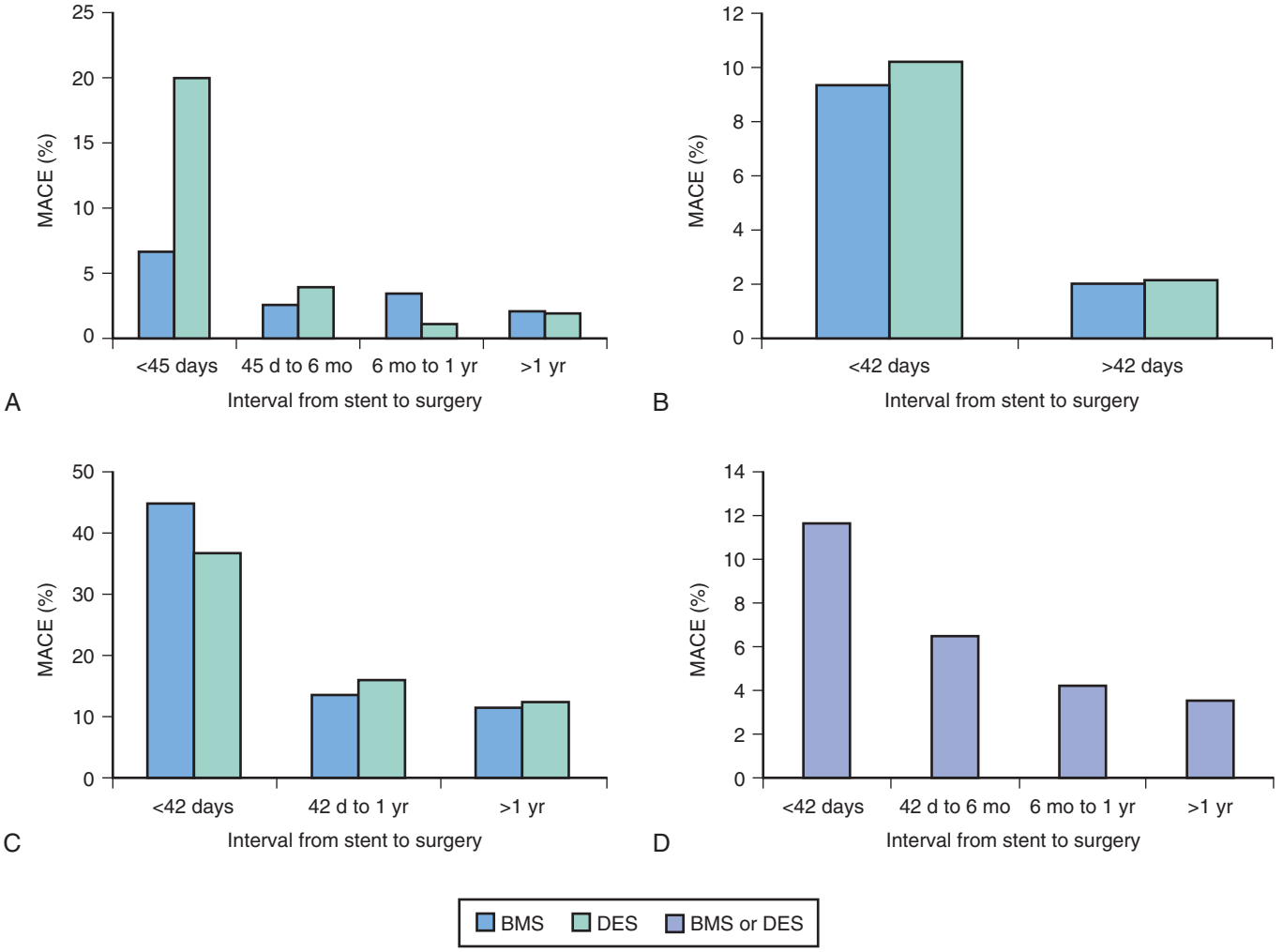


FIGURE 8-5 Death and cardiac ischemic event rates by interval between stent placement and noncardiac surgery, as reported in several large registries. **A,** Wijeysundera et al.[74] **B,** CREDO-Kyoto PCI/CABG registry cohort-2 investigators.[49] **C,** Cruden et al.[48] **D,** Hawn et al.[75] *BMS,* Bare-metal stent; *DES,* drug-eluting stent; *MACE,* major adverse cardiac event.

placement and to 4.2% when surgery was delayed by more than 6 months.[75] The three factors most strongly associated with MACE were nonelective surgery, history of MI in the 6 months preceding surgery, and higher cardiac risk index score. Event rates did not differ by stent type (bare metal vs. drug eluting), and after both BMS and DES placement, the risk of perioperative cardiac events remained stable after 6 months.

In another large group of 2725 patients who underwent stent placement prior to noncardiac surgery, MACE rates were likewise high when surgery was performed within 45 days of PCI (6.7% following BMS, 20.0% following DES).[74] Adverse event rates following BMS placement fell to 2.6% between 45 to 180 days post PCI and rose again after 180 days, possibly related to the occurrence of in-stent restenosis among some individuals. Following DES placement, surgical MACE rates remained greater than 3.0% until 180 days post PCI.

Antiplatelet Drug Interruption Prior to Surgery

Several large, "real world" registries have specifically examined the incidence and implications of DAPT interruption following DES placement in current practice and suggest that the risks associated with antiplatelet drug stoppage prior to noncardiac surgery may be less than previously thought. Among 1622 patients in a Spanish registry who received either a first- or second-generation DES, discontinuation of at least one antiplatelet drug (aspirin and/or $P2Y_{12}$ receptor antagonist) was observed among 10.6% of individuals during the first year.[76,77] Almost all interruptions in DAPT occurred beyond 1 month following stent placement, 76% were related to the need for an invasive procedure, and most stoppages were temporary (mean duration of 7 days). Antiplatelet drug discontinuation was not associated with increased 1-year MACE rates in this population (4.1%. vs. 5.5% for interrupted vs. uninterrupted DAPT therapy, respectively). In an industry-sponsored registry of 4896 patients who received a zotarolimus-eluting stent, DAPT interruption or discontinuation was documented among 21.8% of subjects during the first 12 months.[78] Most instances of DAPT stoppage were physician recommended and occurred after 6 months; however, 15.5% of interruptions occurred within the first month following stent placement, and 42.2% of all interruptions were undertaken prior to a medical, dental, or surgical procedure. DAPT interruption within the first month was associated with a substantial rate of definite or probable stent thrombosis (3.6%) and cardiac death or target-vessel MI (6.8%), but antiplatelet drug interruption after 1 month was not associated with an increased risk of stent thrombosis or adverse clinical events. DAPT usage was likewise tracked following BMS or DES implantation among 5018 individuals in the Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients (PARIS) registry.[79] Within 2 years of stent placement, 10.5% of patients had interruption of at least one antiplatelet drug (aspirin and/or a $P2Y_{12}$

receptor blocker) prior to a surgical procedure. Although it did not achieve statistical significance, a trend toward increased MACE among patients with DAPT interruption for surgery was observed (hazard ratio [HR], 1.41; 95% CI, 0.94 to 2.12; $P = .10$), and target-lesion revascularization (TLR) was significantly greater among individuals who had DAPT interrupted compared with the overall cohort (HR, 1.97; 95% CI, 1.23 to 3.17).

The intentional withdrawal of antiplatelet therapy prior to surgery has been identified as a significant risk factor for stent thrombosis and MACE in some studies but not in others. Among 1134 consecutive patients with coronary stents who underwent noncardiac surgery at one of 47 French centers, 10.4% suffered a postoperative major adverse cardiac or cerebrovascular event, and such events were independently associated with cessation of antiplatelet therapy 5 or more days prior to surgery.[80] Conversely, in a Japanese registry of 2398 patients who underwent surgery within 3 years of coronary BMS or DES placement, continuation of DAPT during surgery was associated with neither a decrease in the rates of perioperative death, MI, or stent thrombosis nor an increase in bleeding events.[49]

Antiplatelet Therapy and Surgical Bleeding Risk

Substantial variability currently exists in perioperative antiplatelet drug management among physicians, which reflects the lack of adequate studies and conclusive recommendations.[81-83] For "closed space" procedures—including intracranial, spinal, and retinal surgery—even small amounts bleeding into a confined area can have devastating consequences, and cessation of all antiplatelet agents is typically considered mandatory. Otherwise, decisions regarding antiplatelet therapy among patients with coronary stents are typically made on a case-by-case basis by which the risks and consequences of bleeding and stent thrombosis are weighed.

In a large retrospective evaluation of nearly 50,000 patients who underwent a variety of surgical procedures, aspirin use was associated with a 1.5-fold increase in overall bleeding complications.[84] Despite the increase in overall bleeding, no increase was found in fatal bleeding among aspirin users except during intracranial surgery and transurethral prostatectomy. In a randomized trial of 220 high-risk patients undergoing noncardiac surgery, perioperative aspirin therapy resulted in an 80% relative reduction in postoperative MACE compared with placebo, without an increase in bleeding events.[85] However, in the large POISE-2 trial 10,010 patients at risk for vascular complications were randomized to aspirin or placebo immediately prior to noncardiac surgery, and the administration of aspirin significantly increased the risk of major bleeding compared with placebo (HR, 1.23; 95% CI, 1.01 to 1.49) but had no significant effect on the rate of perioperative death or nonfatal MI (HR, 0.99; 95% CI, 0.86 to 1.15).[86] Smaller studies of perioperative clopidogrel use with noncardiac and cardiac surgery have demonstrated similar findings, with greater likelihoods of perioperative bleeding events and blood transfusions but no increase in bleeding-related mortality.[87-92] Even if not associated with increased surgical mortality rates, the excess bleeding that occurs with continuation of antiplatelet agents can render surgery more cumbersome and technically demanding, often leading surgeons to strongly favor stoppage of antiplatelet drugs whenever possible.[93]

SUMMARY AND RECOMMENDATIONS

Given the lack of randomized trials, the variability of findings among retrospective studies, and inconsistencies among current subspecialty guideline statements, the decision whether to suspend or continue antiplatelet therapy during noncardiac surgery requires an individualized approach.[94] Consideration of the potential risks and consequences of perioperative stent thrombosis versus bleeding complications should be carried out on a patient-by-patient basis (Table 8-4). Communication between the surgeon and cardiologist is crucial. In considering whether to stop or continue aspirin and/or $P2Y_{12}$ receptor–blocker therapy prior to surgery, the following factors should be taken into account: First, the amount of time that has elapsed since the stent was placed must be considered, because continuation of DAPT appears especially important when surgery cannot be deferred for 4 to 6 weeks following BMS or 6 to 12 months after DES implantation. If $P2Y_{12}$ receptor–blocker therapy must be stopped, ACC/AHA guidelines urge that "aspirin be continued if possible and the $P2Y_{12}$ platelet receptor-inhibitor therapy be restarted as soon as possible after the surgery," and the American College of Chest Physicians similarly recommend continuing aspirin around the time of noncardiac surgery among patients at moderate to high risk for cardiovascular events.[13,95] A meta-analysis of multiple cases of late or very late DES thrombosis supports the concept that short-term discontinuation of thienopyridine therapy may be safer if aspirin is continued.[96] Second, the patient-specific risk of stent thrombosis should be considered, and it should be determined whether the patient possesses any additional risk factors for stent thrombosis such as recent MI, renal insufficiency, diabetes, or "off label" stent use, all of which have been associated with an increased propensity for stent thrombosis.[97-99] Third, the potential consequences of stent thrombosis for the particular patient merit consideration. For instance, stent occlusion may be especially devastating for patients with preexisting left ventricular dysfunction or in circumstances when the stent is located in a vessel with a large territory of supply. Fourth, the potential risks and consequences of excess surgical bleeding for the proposed operation are important factors. For operations that involve closed spaces, for example, temporary cessation of antiplatelet therapy is usually mandatory.

When the decision is made to discontinue $P2Y_{12}$ receptor–antagonist therapy in advance of surgery, pharmacokinetic and clinical data suggest that clopidogrel and ticagrelor be stopped 5 days and prasugrel 7 days before the operation to allow adequate time for recovery of platelet function.[100-102] Likewise, these agents should be restarted with an appropriate bolus as soon as possible following surgery.

TABLE 8-4 Considerations for Management of Antiplatelet Therapy Prior to Noncardiac Surgery for Individuals With a Coronary Stent

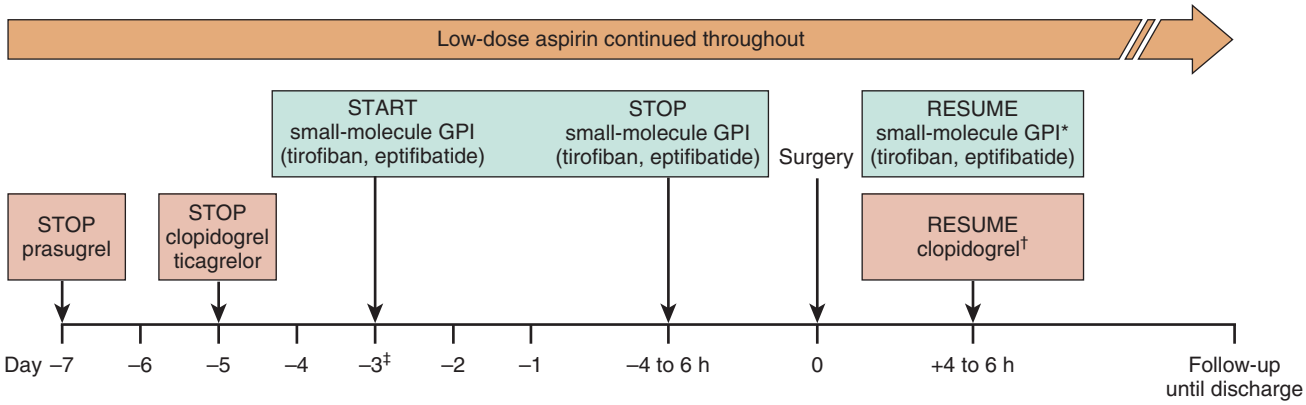
Favors Continuing Antiplatelet Therapy	Favors Interrupting Therapy
Recent stent placement (BMS within past 4 to 6 weeks, DES within past 6 to 12 months)	Remote stent placement
Higher risk of stent thrombosis (e.g., multiple stents and/or complex stent anatomy, recent MI)	Minimal risk factors for stent thrombosis
Consequences of stent thrombosis high (e.g., poor baseline LVEF, large myocardial territory subtended by stent)	Consequences of bleeding are severe (e.g., "closed space" surgery)
Surgical procedure with low bleeding risk	Surgical procedure with higher likelihood of substantial bleeding

BMS, Bare-metal stent; *DES,* drug-eluting stent; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction.

EMERGING STRATEGIES

Perioperative Bridging

Among patients receiving DAPT who are considered to be at particularly elevated risk for stent thrombosis but for whom antiplatelet agents must be stopped prior to surgery, perioperative bridging—in which a parenteral glycoprotein (GP) IIb/IIIa receptor antagonist is administered during the later part of the interval between cessation of the $P2Y_{12}$ receptor inhibitor and surgery—has been proposed as a means to reduce the risk of perioperative stent thrombosis (Fig. 8-6).[103-105] The small-molecule GP IIb/IIIa receptor antagonists eptifibatide and tirofiban both have relatively short physiologic half-lives with near



*If oral administration is not possible.

†With a 300- to 600-mg loading dose as soon as oral administation is possible; prasugrel and ticagrelor are discouraged.

‡Tirofiban: 0.1 μg/kg/min; if creatinine clearance <50 mL/min, adjust to 0.05 μg/kg/min. Eptifibatide: 2.0 μg/kg/min; if creatinine clearance is <50 mL/min, adjust to 1.0 μg/kg/min.

FIGURE 8-6 Proposed bridging protocol for patients on dual-antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor inhibitor referred for noncardiac surgery. *GPI,* Glycoprotein IIb/IIIa receptor inhibitor. –, Time before surgery; +, time after completion of surgery. (From Capodanno D, Angiolillo DJ: Management of antiplatelet therapy in patients with coronary artery disease requiring cardiac and noncardiac surgery. *Circulation* 128[25]:2785-2798, 2013.)

TABLE 8-5 Pharmacokinetics of Antiplatelet Agents

Drug	Route of Administration	Reversible Platelet Inhibition?	Time to Peak Activity After Loading Dose*	Elimination Half-Life*	Time to Platelet Recovery After Discontinuation*
Ticlopidine	Oral	No	3-4 days	4-5 days	5 days
Clopidogrel	Oral	No	2-6 hours	8 hours	5 days
Prasugrel	Oral	No	2-4 hours	8 hours	7 days
Ticagrelor	Oral	Yes	2-4 hours	8 hours	5 days
Cangrelor	Intravenous	Yes	<10 minutes	3 minutes	<60 minutes
Tirofiban	Intravenous	Yes	<10 minutes	2 hours	3-4 hours
Eptifibatide	Intravenous	Yes	<10 minutes	2.5 hours	4 hours

*Times are approximate and demonstrate interindividual variability.

complete recovery of platelet function within several hours of drug cessation, and they represent suitable bridging agents (Table 8-5).[106,107] Because a continuous intravenous (IV) infusion of drug is required, a bridging strategy requires hospitalization.

Although theoretically attractive, published experience with perioperative bridging is predominantly confined to nonrandomized case series.[108-113] In a meta-analysis of eight studies of perioperative bridging that included 280 patients, the overall incidence of stent thrombosis was 1.3% with an in-hospital mortality rate of 3.5%, a major bleeding rate of 7.4%, and a need for blood transfusions among 13.9% of patients.[114] Thus stent thrombosis and bleeding events still can occur despite bridging, and given the absence of control groups in any of these studies, the relative efficacy and safety of this approach compared with simply interrupting DAPT without interval bridging remains unknown.

Cangrelor, a reversible P2Y12 receptor antagonist that is administered intravenously, has a very rapid onset of action and a half-life of only 3 to 6 minutes with recovery of platelet function within 60 minutes; this renders the drug a potentially attractive perioperative bridging agent.[115] In the Maintenance of Platelet Inhibition with Cangrelor After Discontinuation of Thienopyridines in Patients Undergoing Surgery (BRIDGE) trial, 210 patients with recent coronary stent placement who were awaiting CABG surgery had oral $P2Y_{12}$ receptor–antagonist therapy discontinued 5 to 7 days preoperatively and were randomized to receive either a continuous infusion of either cangrelor or placebo for 2 to 7 days prior to surgery.[116] Cangrelor therapy was associated with consistent inhibition of platelet reactivity during the treatment period as assessed by point-of-care testing without an associated increase in major bleeding events, although minor bleeding was more frequent in the treatment group. The efficacy of cangrelor in preventing perioperative ischemic events remains to be established in larger trials. Pending further data, a bridging strategy might be considered for patients who are at particularly high risk for stent thrombosis, such as when surgery is required within 1 month of stent placement, or when the consequences of stent thrombosis would be dire—for example, in a vessel that supplies a large myocardial territory, such as an unprotected left main stent or a stent in a sole patent bypass graft.

Newer Antiplatelet Agents

It remains uncertain whether newer-generation oral platelet antagonists provide any advantages over clopidogrel for the prevention of ischemic and bleeding complications in the perioperative setting (see Table 8-5). Among 368 patients enrolled in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) trial who underwent CABG surgery, prasugrel therapy was associated with significantly increased rates of major and minor bleeding events compared with clopidogrel even when the drug was stopped

up to 7 days prior to surgery.[117] Ticagrelor is an orally administered nonthienopyridine platelet antagonist that, unlike clopidogrel and prasugrel, binds reversibly to the $P2Y_{12}$ receptor.[102,118] Among a small subgroup of patients who required CABG in an early dose-finding trial, major bleeding events were less common among those randomized to ticagrelor, rather than to clopidogrel, when surgery was performed within 5 days of drug cessation (36% vs. 64%) with little difference when surgery was delayed beyond 5 days (50% vs. 60%).[119] In a subgroup analysis that included 1261 patients who underwent CABG in the randomized Platelet Inhibition and Patient Outcomes (PLATO) trial, among patients who had surgery within 7 days of receiving study drug, ticagrelor was associated with a 50% relative reduction in total and cardiovascular mortality compared with clopidogrel, and fewer deaths occurred from cardiovascular, bleeding, and infectious complications.[120,121]

Platelet Function Testing

Because substantial individual variability exists in the degree of platelet inhibition and speed of platelet recovery following cessation of oral antiplatelet therapy, some patients are left vulnerable to ischemic events for a longer duration while awaiting surgery. In addition, a rebound state of hypercoagulability may occur shortly after cessation of antiplatelet therapy, which renders patients especially susceptible to thrombotic events, although this concept remains controversial.[122-126] A variety of assays are available to rapidly assess the level of platelet inhibition on a patient-specific basis, and these may be of value in determining the ideal timing for surgery following discontinuation of antiplatelet therapy.[127-129] To date, only a few small studies have examined the relationship of platelet function testing and operative bleeding events, all in CABG surgery.[130-132] Both the European Society of Cardiology (ESC) and the Society of Thoracic Surgery (STS) have given the premise of point-of-care testing of platelet inhibition for determining timing of surgery a class II recommendation in their most recent guidelines; however, the ideal assay and specific platelet reactivity cut-points to optimize clinical outcomes remain unknown.[133] Although intuitively attractive, the concept of using platelet function testing following antiplatelet therapy cessation to determine timing of surgery requires evaluation in larger scale clinical trials among post-PCI patients before its widespread use can be strongly recommended.

POSTOPERATIVE CARE

Although prevention of operative complications through proper patient selection and management remains the cornerstone of achieving low surgical mortality rates, prompt recognition and treatment of postoperative complications when they do occur represents another critical element in optimizing surgical outcomes. In a provocative multicenter study of over 84,000 patients who underwent inpatient general or vascular surgery, major surgical complication rates were similar among various hospitals. Ultimate mortality rates among patients with major complications, however, varied dramatically from 12.5% among hospitals in the lowest mortality quintile to 21.4% among hospitals in the highest mortality quintile.[134] These findings suggest that variations in mortality rates among hospitals may not result primarily from differences in initial surgical complication rates but from the care that patients receive after complications have occurred.

Because the vast majority of perioperative cardiac events occur within the first 24 to 48 hours following surgery, close surveillance of patients at increased risk for such events is essential during the early postoperative period. Continuous telemetry monitoring and routine assessment of serum troponin levels are recommended for patients with signs or symptoms suggestive of myocardial ischemia or MI during this interval. If aspirin and/or $P2Y_{12}$ receptor–blocker therapy was suspended prior to surgery, these agents should be resumed as soon as safely possible because the prothrombotic milieu engendered by surgery persists into the postoperative period. If an acute ST-segment elevation MI does occur early postoperatively, primary PCI is the treatment of choice. Thrombolytic therapy is contraindicated after all but the most minor surgical procedures because of the potential for hemorrhagic complications related to the surgical site. For this reason, patients at heightened risk for perioperative MI—including those with prior DES placement and those in whom DAPT must be suspended prior to surgery—should have their surgical procedure performed at an institution with the on-site ability to perform primary PCI on a continuous basis. Among patients who require emergency PCI in the very early postoperative period, bleeding complications related to the surgical site remain a concern; however, angioplasty can be performed safely in most instances with the use of only aspirin and a single dose of unfractionated heparin or a bolus and brief infusion of bivalirudin.

REFERENCES

1. Landesberg G, Beattie WS, Mosseri M, et al: Perioperative myocardial infarction. *Circulation* 119(22):2936–2944, 2009.
2. Sandoval Y, Smith S, Thordsen S, Apple F: Supply/demand type 2 myocardial infarction: should we be paying more attention? *J Am Coll Cardiol* 63:2079–2087, 2014.
3. Berger PB, Kleiman NS, Pencina MJ, et al: Frequency of major noncardiac surgery and subsequent adverse events in the year after drug-eluting stent placement results from the EVENT (Evaluation of Drug-Eluting Stents and Ischemic Events) Registry. *JACC Cardiovasc Interv* 3(9):920–927, 2010.
4. Kaluza GL, Joseph J, Lee JR, et al: Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J Am Coll Cardiol* 35(5):1288–1294, 2000.
5. Wilson SH, Fasseas P, Orford JL, et al: Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. *J Am Coll Cardiol* 42(2):234–240, 2003.
6. Rajagopalan S, Ford I, Bachoo P, et al: Platelet activation, myocardial ischemic events and postoperative non-response to aspirin in patients undergoing major vascular surgery. *J Thromb Haemost* 5(10):2028–2035, 2007.
7. Samama CM, Thiry D, Elalamy I, et al: Perioperative activation of hemostasis in vascular surgery patients. *Anesthesiology* 94(1):74–78, 2001.
8. Lalmohamed A, Vestergaard P, Klop C, et al: Timing of acute myocardial infarction in patients undergoing total hip or knee replacement: a nationwide cohort study. *Arch Intern Med* 172(16):1229–1235, 2012.
9. Devereaux PJ, Xavier D, Pogue J, et al: Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med* 154(8):523–528, 2011.
10. The Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators: association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 307(21):2295–2304, 2012.
11. Blackshear JL, Cutlip DE, Roubin GS, et al: Myocardial infarction after carotid stenting and endarterectomy: results from the carotid revascularization endarterectomy versus stenting trial. *Circulation* 123(22):2571–2578, 2011.
12. Patel MR, Bailey SR, Bonow RO, et al: ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 59(22):1995–2027, 2012.
13. Fleisher LA, Fleischmann KE, Auerbach AD, et al: 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* 64(22):e77–e137, 2014.
14. Kristensen SD, Knuuti J, Saraste A, et al: 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J* 35:2383–2431, 2014.
15. Patel MR, Dehmer GJ, Hirshfeld JW, et al: ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 Appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 59(9):857–881, 2012.
16. Priebe HJ: Perioperative myocardial infarction–aetiology and prevention. *Br J Anaesth* 95(1):3–19, 2005.
17. Poldermans D, Boersma E, Bax JJ, et al: The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med* 341(24):1789–1794, 1999.
18. Mangano DT, Layug EL, Wallace A, Tateo I: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. *N Engl J Med* 335(23):1713–1720, 1996.
19. Chopra V, Eagle KA: Perioperative mischief: the price of academic misconduct. *Am J Med* 125(10):953–955, 2012.
20. Bouri S, Shun-Shin MJ, Cole GD, et al: Meta-analysis of secure randomised controlled trials of beta-blockade to prevent perioperative death in non-cardiac surgery. *Heart* 100(6):456–464, 2014.
21. Flynn BC, Vernick WJ, Ellis JE: (-Blockade in the perioperative management of the patient with cardiac disease undergoing non-cardiac surgery. *Br J Anaesth* 107(Suppl 1):i3–i15, 2011.
22. Nowbar AN, Cole GD, Shun-Shin MJ, et al: International RCT-based guidelines for use of preoperative stress testing and perioperative beta-blockers and statins in non-cardiac surgery. *Int J Cardiol* 172(1):138–143, 2014.
23. Devereaux PJ, Yang H, Yusuf S, et al: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 371(9627):1839–1847, 2008.

24. Andersson C, Merie C, Jorgensen M, et al: Association of beta-blocker therapy with risks of adverse cardiovascular events and deaths in patients with ischemic heart disease undergoing non-cardiac surgery: a Danish nationwide cohort study. *JAMA Intern Med* 174(3):336–344, 2014.
25. London M, Hur K, Schwartz G, Henderson W: Association of perioperative beta-blockade with mortality and cardiovascular morbidity following major noncardiac surgery. *JAMA* 309:1704–1713, 2013.
26. Biccard BM: A peri-operative statin update for non-cardiac surgery. Part I: The effects of statin therapy on atherosclerotic disease and lessons learnt from statin therapy in medical (non-surgical) patients. *Anaesthesia* 63(1):52–64, 2008.
27. Le Manach Y, Godet G, Coriat P, et al: The impact of postoperative discontinuation or continuation of chronic statin therapy on cardiac outcome after major vascular surgery. *Anesth Analg* 104(6):1326–1333, 2007.
28. Chopra V, Wesorick DH, Sussman JB, et al: Effect of perioperative statins on death, myocardial infarction, atrial fibrillation, and length of stay: a systematic review and meta-analysis. *Arch Surg* 147(2):181–189, 2012.
29. Dunkelgrun M, Boersma E, Schouten O, et al: Bisoprolol and fluvastatin for the reduction of perioperative cardiac mortality and myocardial infarction in intermediate-risk patients undergoing noncardiovascular surgery: a randomized controlled trial (DECREASE-IV). *Ann Surg* 249(6):921–926, 2009.
30. Schouten O, Boersma E, Hoeks SE, et al: Fluvastatin and perioperative events in patients undergoing vascular surgery. *N Engl J Med* 361(10):980–989, 2009.

30a. Eagle KA, Rihal CS, Mickel MC, et al: Cardiac risk of noncardiac surgery: influence of coronary disease and type of surgery in 3368 operations. CASS Investigators and University of Michigan Heart Care Program. Coronary Artery Surgery Study. *Circulation* 96(6):1882–1887, 1997.

31. Breen P, Lee JW, Pomposelli F, Park KW: Timing of high-risk vascular surgery following coronary artery bypass surgery: a 10-year experience from an academic medical centre. *Anaesthesia* 59(5):422–427, 2004.

31a. Saw J, Bhatt DL, Moliterno DJ, et al: The influence of peripheral arterial disease on outcomes: a pooled analysis of mortality in eight large randomized percutaneous coronary intervention trials. *J Am Coll Cardiol* 48(8):1567–1572, 2006.

31b. Hannan EL, Farrell LS, Walford G, et al: The New York State risk score for predicting in-hospital/30-day mortality following percutaneous coronary intervention. *JACC Cardiovasc Interv* 6(6):614–622, 2013.

32. Allen JR, Helling TS, Hartzler GO: Operative procedures not involving the heart after percutaneous transluminal coronary angioplasty. *Surg Gynecol Obstet* 173(4):285–288, 1991.
33. Huber KC, Evans MA, Bresnahan JF, et al: Outcome of noncardiac operations in patients with severe coronary artery disease successfully treated preoperatively with coronary angioplasty. *Mayo Clin Proc* 67(1):15–21, 1992.
34. Elmore JR, Hallett JW, Jr, Gibbons RJ, et al: Myocardial revascularization before abdominal aortic aneurysmorrhaphy: effect of coronary angioplasty. *Mayo Clin Proc* 68(7):637–641, 1993.
35. Jones SE, Raymond RE, Simpfendorfer CC, Whitlow PL: Cardiac outcome of major noncardiac surgery in patients undergoing preoperative coronary angioplasty. *J Invasive Cardiol* 5(6):212–218, 1993.
36. Gottlieb A, Banoub M, Sprung J, et al: Perioperative cardiovascular morbidity in patients with coronary artery disease undergoing vascular surgery after percutaneous transluminal coronary angioplasty. *J Cardiothorac Vasc Anesth* 12(5):501–506, 1998.
37. Posner KL, Van Norman GA, Chan V: Adverse cardiac outcomes after noncardiac surgery in patients with prior percutaneous transluminal coronary angioplasty. *Anesth Analg* 89(3):553–560, 1999.
38. Hassan SA, Hlatky MA, Boothroyd DB, et al: Outcomes of noncardiac surgery after coronary bypass surgery or coronary angioplasty in the Bypass Angioplasty Revascularization Investigation (BARI). *Am J Med* 110(4):260–266, 2001.
39. Brilakis ES, Orford JL, Fasseas P, et al: Outcome of patients undergoing balloon angioplasty in the two months prior to noncardiac surgery. *Am J Cardiol* 96(4):512–514, 2005.
40. Leibowitz D, Cohen M, Planer D, et al: Comparison of cardiovascular risk of noncardiac surgery following coronary angioplasty with versus without stenting. *Am J Cardiol* 97(8):1188–1191, 2006.
41. Sharma AK, Ajani AE, Hamwi SM, et al: Major noncardiac surgery following coronary stenting: when is it safe to operate? *Catheter Cardiovasc Interv* 63(2):141–145, 2004.
42. Reddy PR, Vaitkus PT: Risks of noncardiac surgery after coronary stenting. *Am J Cardiol* 95(6):755–757, 2005.
43. Vicenzi MN, Meislitzer T, Heitzinger B, et al: Coronary artery stenting and non-cardiac surgery—a prospective outcome study. *Br J Anaesth* 96(6):686–693, 2006.
44. Schouten O, van Domburg RT, Bax JJ, et al: Noncardiac surgery after coronary stenting: early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events. *J Am Coll Cardiol* 49(1):122–124, 2007.
45. Brotman DJ, Bakhru M, Saber W, et al: Discontinuation of antiplatelet therapy prior to low-risk noncardiac surgery in patients with drug-eluting stents: a retrospective cohort study. *J Hosp Med* 2(6):378–384, 2007.
46. Kim HL, Park KW, Kwak JJ, et al: Stent-related cardiac events after non-cardiac surgery: drug-eluting stent vs. bare metal stent. *Int J Cardiol* 123(3):353–354, 2008.
47. Nuttall GA, Brown MJ, Stombaugh JW, et al: Time and cardiac risk of surgery after bare-metal stent percutaneous coronary intervention. *Anesthesiology* 109(4):588–595, 2008.
48. Cruden NL, Harding SA, Flapan AD, et al: Previous coronary stent implantation and cardiac events in patients undergoing noncardiac surgery. *Circ Cardiovasc Interv* 3(3):236–242, 2010.
49. CREDO-Kyoto PCI/CABG registry cohort-2 investigators: Incidence and outcome of surgical procedures after coronary bare-metal and drug-eluting stent implantation: a report from the CREDO-Kyoto PCI/CABG registry cohort-2. *Circ Cardiovasc Interv* 5(2):237–246, 2012.
50. Assali A, Vaknin-Assa H, Lev E, et al: The risk of cardiac complications following noncardiac surgery in patients with drug eluting stents implanted at least six months before surgery. *Catheter Cardiovasc Interv* 74(6):837–843, 2009.
51. Rabbitts JA, Nuttall GA, Brown MJ, et al: Cardiac risk of noncardiac surgery after percutaneous coronary intervention with drug-eluting stents. *Anesthesiology* 109(4):596–604, 2008.
52. Rhee SJ, Yun KH, Lee SR, et al: Drug-eluting stent thrombosis during perioperative period. *Int Heart J* 49(2):135–142, 2008.
53. Godet G, Le Manach Y, Lesache F, et al: Drug-eluting stent thrombosis in patients undergoing non-cardiac surgery: is it always a problem? *Br J Anaesth* 100(4):472–477, 2008.
54. Compton PA, Zankar AA, Adesanya AO, et al: Risk of noncardiac surgery after coronary drug-eluting stent implantation. *Am J Cardiol* 98(9):1212–1213, 2006.
55. Anwaruddin S, Askari AT, Saudye H, et al: Characterization of post-operative risk associated with prior drug-eluting stent use. *JACC Cardiovasc Interv* 2(6):542–549, 2009.
56. McFalls EO, Ward HB, Moritz TE, et al: Coronary-artery revascularization before elective major vascular surgery. *New Engl J Med* 351(27):2795–2804, 2004.
57. Poldermans D, Schouten O, Vidakovic R, et al: A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V Pilot Study. *J Am Coll Cardiol* 49(17):1763–1769, 2007.
58. Hara M, Nishino M, Taniike M, et al: Difference of neointimal formational pattern and incidence of thrombus formation among 3 kinds of stents: an angioscopic study. *JACC Cardiovasc Interv* 3(2):215–220, 2010.
59. Luscher TF, Steffel J, Eberli FR, et al: Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. *Circulation* 115(8):1051–1058, 2007.
60. Brilakis ES, Patel VG, Banerjee S: Medical management after coronary stent implantation: a review. *JAMA* 310(2):189–198, 2013.
61. Feres F, Costa RA, Abizaid A, et al: Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA* 310(23):2510–2522, 2013.
62. Tandjung K, Sen H, Lam MK, et al: Clinical outcome following stringent discontinuation of dual antiplatelet therapy after 12 months in real-world patients treated with second-generation zotarolimus-eluting resolute and everolimus-eluting Xience V stents: 2-year follow-up of the randomized TWENTE trial. *J Am Coll Cardiol* 61(24):2406–2416, 2013.
63. Varenhorst C, Jensevik K, Jernberg T, et al: Duration of dual antiplatelet treatment with clopidogrel and aspirin in patients with acute coronary syndrome. *Eur Heart J* 35(15):969–978, 2014.
64. Bangalore S, Kumar S, Fusaro M, et al: Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. *Circulation* 125(23):2873–2891, 2012.
65. Palmerini T, Biondi-Zoccai G, Della Riva D, et al: Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 379(9824):1393–1402, 2012.
66. Gwon HC, Hahn JY, Park KW, et al: Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation* 125(3):505–513, 2012.
67. Kim BK, Yoon JH, Shin DH, et al: Prospective and systematic analysis of unexpected requests for non-cardiac surgery or other invasive procedures during the first year after drug-eluting stent implantation. *Yonsei Med J* 55(2):345–352, 2014.
68. Valgimigli M, Campo G, Monti M, et al: Short- versus long-term duration of dual antiplatelet therapy after coronary stenting: a randomized multicentre trial. *Circulation* 125:2015–2026, 2012.
69. Gandhi NK, Abdel-Karim AR, Banerjee S, Brilakis ES: Frequency and risk of noncardiac surgery after drug-eluting stent implantation. *Catheter Cardiovasc Interv* 77(7):972–976, 2011.
70. Hawn MT, Graham LA, Richman JR, et al: The incidence and timing of noncardiac surgery after cardiac stent implantation. *J Am Coll Surg* 214(4):658–666, discussion 666-657, 2012.
71. Hollis RH, Graham LA, Richman JS, et al: Adverse cardiac events in patients with coronary stents undergoing noncardiac surgery: a systematic review. *Am J Surg* 204(4):494–501, 2012.
72. Capodanno D, Angiolillo DJ: Management of antiplatelet therapy in patients with coronary artery disease requiring cardiac and noncardiac surgery. *Circulation* 128(25):2785–2798, 2013.
73. Vaclavik J, Taborsky M: Antiplatelet therapy in the perioperative period. *Eur J Intern Med* 22(1):26–31, 2011.
74. Wijeysundera DN, Wijeysundera HC, Yun L, et al: Risk of elective major noncardiac surgery after coronary stent insertion: a population-based study. *Circulation* 126(11):1355–1362, 2012.
75. Hawn MT, Graham LA, Richman JS, et al: Risk of major adverse cardiac events following noncardiac surgery in patients with coronary stents. *JAMA* 310(14):1462–1472, 2013.
76. Ferreira-Gonzalez I, Marsal JR, Ribera A, et al: Background, incidence, and predictors of antiplatelet therapy discontinuation during the first year after drug-eluting stent implantation. *Circulation* 122(10):1017–1025, 2010.
77. Ferreira-Gonzalez I, Marsal JR, Ribera A, et al: Double antiplatelet therapy after drug-eluting stent implantation: risk associated with discontinuation within the first year. *J Am Coll Cardiol* 60(15):1333–1339, 2012.
78. Silber S, Kirtane AJ, Belardi JA, et al: Lack of association between dual antiplatelet therapy use and stent thrombosis between 1 and 12 months following resolute zotarolimus-eluting stent implantation. *Eur Heart J* 35(29):1949–1956, 2014.
79. Mehran R, Baber U, Steg PG, et al: Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. *Lancet* 382(9906):1714–1722, 2013.
80. Albaladejo P, Marret E, Samama CM, et al: Non-cardiac surgery in patients with coronary stents: the RECO study. *Heart* 97(19):1566–1572, 2011.
81. Erez G, Leitersdorf E, Szalat A, et al: Peri-procedural management of antiplatelet therapy, a survey. *Eur J Intern Med* 21:569–574, 2010.
82. Khair T, Garcia B, Banerjee S, Brilakis ES: Contemporary approaches to perioperative management of coronary stents and to preoperative coronary revascularization: a survey of 374 interventional cardiologists. *Cardiovasc Revasc Med* 12(2):99–104, 2011.
83. Vetter TR, Boudreaux AM, Papapietro SE, et al: The perioperative management of patients with coronary artery stents: surveying the clinical stakeholders and arriving at a consensus regarding optimal care. *Am J Surg* 204(4):453–461 e452, 2012.
84. Burger W, Chemnitius JM, Kneissl GD, Rucker G: Low-dose aspirin for secondary cardiovascular prevention: cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation—review and meta-analysis. *J Intern Med* 257(5):399–414, 2005.
85. Oscarsson A, Gupta A, Fredrikson M, et al: To continue or discontinue aspirin in the perioperative period: a randomized, controlled clinical trial. *Br J Anaesth* 104(3):305–312, 2010.
86. Devereaux PJ, Mrkobrada M, Sessler DI, et al: Aspirin in patients undergoing noncardiac surgery. *N Engl J Med* 370(16):1494–1503, 2014.
87. Chernoguz A, Telem DA, Chu E, et al: Cessation of clopidogrel before major abdominal procedures. *Arch Surg* 146(3):334–339, 2011.
88. Ozao-Choy J, Tammaro Y, Fradis M, et al: Clopidogrel and bleeding after general surgery procedures. *Am Surg* 74(8):721–725, 2008.
89. Chassot PG, Delabays A, Spahn DR: Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. *Br J Anaesth* 99(3):316–328, 2007.
90. Ferraris VA, Ferraris SP, Moliterno DJ, et al: The Society of Thoracic Surgeons practice guideline series: aspirin and other antiplatelet agents during operative coronary revascularization (executive summary). *Ann Thorac Surg* 79(4):1454–1461, 2005.
91. Fox KA, Mehta SR, Peters R, et al: Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE). *Circulation* 110(10):1202–1208, 2004.
92. Kapetanakis EI, Medlam DA, Petro KR, et al: Effect of clopidogrel premedication in off-pump cardiac surgery: are we forfeiting the benefits of reduced hemorrhagic sequelae? *Circulation* 113(13):1667–1674, 2006.
93. McFadden DW: Between a rock and a hard place: commentary on "adverse cardiac events in patients with coronary stents undergoing noncardiac surgery: a systematic review.". *Am J Surg* 204(4):502, 2012.
94. Darvish-Kazem S, Gandhi M, Marcucci M, Douketis JD: Perioperative management of antiplatelet therapy in patients with a coronary stent who need noncardiac surgery: a systematic review of clinical practice guidelines. *Chest* 144(6):1848–1856, 2013.
95. Douketis JD, Spyropoulos AC, Spencer FA, et al: Perioperative Management of Antithrombotic Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141(2 Suppl):e326S–e350S, 2012.
96. Eisenberg MJ, Richard PR, Libersan D, Filion KB: Safety of short-term discontinuation of antiplatelet therapy in patients with drug-eluting stents. *Circulation* 119(12):1634–1642, 2009.
97. Daemen J, Wenaweser P, Tsuchida K, et al: Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* 369(9562):667–678, 2007.

98. Iakovou I, Schmidt T, Bonizzoni E, et al: Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 293(17):2126–2130, 2005.
99. Win HK, Caldera AE, Maresh K, et al: Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA* 297(18):2001–2009, 2007.
100. Bernlochner I, Morath T, Brown PB, et al: A prospective randomized trial comparing the recovery of platelet function after loading dose administration of prasugrel or clopidogrel. *Platelets* 24(1):15–25, 2013.
101. Price MJ, Walder JS, Baker BA, et al: Recovery of platelet function after discontinuation of prasugrel or clopidogrel maintenance dosing in aspirin-treated patients with stable coronary disease: the recovery trial. *J Am Coll Cardiol* 59(25):2338–2343, 2012.
102. Gurbel PA, Bliden KP, Butler K, et al: Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 120(25): 2577–2585, 2009.
103. Abualsaud A, Eisenberg M: Peroperative management of patients with drug-eluting stents. *JACC Cardiovasc Interv* (3): 131–142, 2010.
104. May AE, Geisler T, Gawaz M: Individualized antithrombotic therapy in high risk patients after coronary stenting: a double-edged sword between thrombosis and bleeding. *Thromb Haemost* 99(3):487–493, 2008.
105. Singla S, Sachdeva R, Uretsky BF: The risk of adverse cardiac and bleeding events following noncardiac surgery relative to antiplatelet therapy in patients with prior percutaneous coronary intervention. *J Am Coll Cardiol* 60(20):2005–2016, 2012.
106. Kondo K, Umemura K: Clinical pharmacokinetics of tirofiban, a nonpeptide glycoprotein IIb/IIIa receptor antagonist: comparison with the monoclonal antibody abciximab. *Clin Pharmacokinet* 41(3):187–195, 2002.
107. Gretler DD: Pharmacokinetic and pharmacodynamic properties of eptifabatide in healthy subjects receiving unfractionated heparin or the low-molecular-weight heparin enoxaparin. *Clin Ther* 25(10):2564–2574, 2003.
108. Alshawabkeh LI, Prasad A, Lenkovsky F, et al: Outcomes of a preoperative "bridging" strategy with glycoprotein IIb/IIIa inhibitors to prevent perioperative stent thrombosis in patients with drug-eluting stents who undergo surgery necessitating interruption of thienopyridine administration. *EuroIntervention* 9(2):204–211, 2013.
109. Ben Morrison T, Horst BM, Brown MJ, et al: Bridging with glycoprotein IIb/IIIa inhibitors for periprocedural management of antiplatelet therapy in patients with drug eluting stents. *Catheter Cardiovasc Interv* 79(4):575–582, 2012.
110. Rassi AN, Blackstone E, Militello MA, et al: Safety of "bridging" with eptifibatide for patients with coronary stents before cardiac and non-cardiac surgery. *Am J Cardiol* 110(4):485–490, 2012.
111. Savonitto S, D'Urbano M, Caracciolo M, et al: Urgent surgery in patients with a recently implanted coronary drug-eluting stent: a phase II study of 'bridging' antiplatelet therapy with tirofiban during temporary withdrawal of clopidogrel. *Br J Anaesth* 104(3):285–291, 2010.
112. Wessler JD, Saldana F, Giugliano RP: Bridging therapy after recent stent implantation: case report and review of data. *Cardiovasc Revasc Med* 13(1):30–38, 2012.
113. Xia JG, Qu Y, Shen H, Liu XH: Short-term follow-up of tirofiban as alternative therapy for urgent surgery patients with an implanted coronary drug-eluting stent after ST-elevation myocardial infarction. *Coron Artery Dis* 24(6):522–526, 2013.
114. Warshauer J, Patel VG, Christopoulos G, et al: Outcomes of preoperative bridging therapy for patients undergoing surgery after coronary stent implantation: a weighted meta-analysis of 280 patients from eight studies. *Catheter Cardiovasc Interv* 85(1):25–31, 2014.
115. Ferreiro JL, Ueno M, Angiolillo DJ: Cangrelor: a review on its mechanism of action and clinical development. *Expert Rev Cardiovasc Ther* 7(10):1195–1201, 2009.
116. Angiolillo DJ, Firstenberg MS, Price MJ, et al: Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. *JAMA* 307(3):265–274, 2012.
117. Wiviott SD, Braunwald E, McCabe CH, et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 357(20):2001–2015, 2007.
118. Storey RF, Bliden KP, Ecob R, et al: Earlier recovery of platelet function after discontinuation of treatment with ticagrelor compared with clopidogrel in patients with high antiplatelet responses. *J Thromb Haemost* 9(9):1730–1737, 2011.
119. Cannon CP, Husted S, Harrington RA, et al: Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol* 50(19):1844–1851, 2007.
120. Held C, Asenblad N, Bassand JP, et al: Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. *J Am Coll Cardiol* 57(6):672–684, 2011.
121. Varenhorst C, Alstrom U, Scirica BM, et al: Factors contributing to the lower mortality with ticagrelor compared with clopidogrel in patients undergoing coronary artery bypass surgery. *J Am Coll Cardiol* 60(17):1623–1630, 2012.
122. Biondi-Zoccai GG, Lotrionte M, Agostoni P, et al: A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. *Eur Heart J* 27(22):2667–2674, 2006.
123. Diehl P, Halscheid C, Olivier C, et al: Discontinuation of long term clopidogrel therapy induces platelet rebound hyperaggregability between 2 and 6 weeks post cessation. *Clin Res Cardiol* 100(9):765–771, 2011.
124. Frelinger AL, 3rd, Barnard MR, Fox ML, Michelson AD: The Platelet Activity After Clopidogrel Termination (PACT) study. *Circ Cardiovasc Interv* 3(5):442–449, 2010.
125. Sibbing D, Stegherr J, Braun S, et al: A double-blind, randomized study on prevention and existence of a rebound phenomenon of platelets after cessation of clopidogrel treatment. *J Am Coll Cardiol* 55(6):558–565, 2010.
126. Yedidya I, Netzer A, Vaduganathan M, et al: Clopidogrel tapering as a strategy to attenuate platelet rebound phenomenon in patients with bare-metal stents. *J Thromb Thrombolysis* 33(1):16–21, 2012.
127. Angiolillo DJ, Ferreiro JL, Price MJ, et al: Platelet function and genetic testing. *J Am Coll Cardiol* 62(17 Suppl):S21–S31, 2013.
128. Bernlochner I, Byrne RA, Kastrati A, Sibbing D: The future of platelet function testing to guide therapy in clopidogrel low and enhanced responders. *Expert Rev Cardiovasc Ther* 9(8):999–1014, 2011.
129. Rollini F, Tello-Montoliu A, Angiolillo DJ: Advances in platelet function testing assessing bleeding complications in patients with coronary artery disease. *Platelets* 23(7):537–551, 2012.
130. Mahla E, Raggam R, Toller W: Platelet function testing to time surgery in patients on dual antiplatelet therapy? *Hamostaseologie* 34(1):40–45, 2014.
131. Mahla E, Suarez TA, Bliden KP, et al: Platelet function measurement-based strategy to reduce bleeding and waiting time in clopidogrel-treated patients undergoing coronary artery bypass graft surgery: the timing based on platelet function strategy to reduce clopidogrel-associated bleeding related to CABG (TARGET-CABG) study. *Circ Cardiovasc Interv* 5(2):261–269, 2012.
132. Kwak Y, Kim J, Choi Y, et al: Clopidogrel responsiveness regardless of the discontinuation date predicts increased blood loss and transfusion requirement after off-pump coronary artery bypass graft surgery. *J Am Coll Cardiol* 56:1994–2002, 2010.
133. Ferraris VA, Saha SP, Oestreich JH, et al: 2012 update to the Society of Thoracic Surgeons guideline on use of antiplatelet drugs in patients having cardiac and noncardiac operations. *Ann Thorac Surg* 94(5):1761–1781, 2012.
134. Ghaferi A, Birkmeyer J, Dimick J: Variation in hospital mortality associated with inpatient surgery. *New Engl J Med* 361:1368–1375, 2009.

Sex and Ethnicity Issues in Interventional Cardiology

9

SAHAR NADERI | LESLIE CHO

KEY POINTS

- Women who present for percutaneous coronary intervention (PCI) are older and have more comorbidities compared with men. Women and men have similar short-term and long-term benefits with bare-metal stents (BMSs) and drug-eluting stents (DESs). Moreover, women and men have similar mortality rates after PCI. However, women have higher rates of vascular complications and bleeding after PCI.
- Women who present with unstable angina or non–ST-elevation myocardial infarction (NSTEMI) with negative biomarkers are less likely to benefit from an invasive strategy and should be risk stratified with stress testing.
- Women and men derive similar benefit from glycoprotein (GP) IIb/IIIa inhibitors, $P2Y_{12}$ inhibitors, and direct thrombin inhibitors.
- Women and men derive similar benefit from primary PCI for ST-elevation MI (STEMI).
- Race-specific analyses of PCI are limited. However, black patients who present for PCI are younger and are more likely to be women, they have comorbidities, and they present with an acute coronary syndrome (ACS).

OVERVIEW

Cardiovascular disease (CVD) remains the leading cause of death regardless of sex and race. Until recently, information has been extrapolated from large studies and registries and has been applied to all populations irrespective of sex, race, or ethnicity. However, a growing body of literature shows sex and race differences in CVD manifestations and treatment effects. In this chapter, we will explore some of these differences as they pertain specifically to interventional cardiology.

SEX

CVD is the leading cause of mortality and morbidity among women in the United States. It claims the lives of more women than the next five major causes of death combined. CVD occurs about 10 years later in women than in men, and this has in part contributed to the misconception that CVD is predominately a man's condition. Increasing data show worse outcomes in women after a cardiovascular event, which may be explained by differences in comorbidities and pathophysiology as well as disparities in treatment.[1]

Characteristics and Outcomes of Women Undergoing Intervention

More than 1.3 million PCIs are performed annually in the United States, with an estimated 33% performed in women. Compared with men, women undergoing PCI are 5 years older and have a higher prevalence of hypertension, diabetes, and other comorbidities.[2] They are less likely to have a history of myocardial infarction (MI), PCI, or coronary artery bypass graft (CABG) surgery. Women were more likely to present with an NSTEMI or unstable angina, whereas men are more likely to present with a STEMI.[3] Compared with men, women have similar lesion types but less multivessel disease and substantially smaller vessels.[4,5] Despite a lower prevalence of left ventricular dysfunction at baseline, women tend to have a higher incidence of congestive heart failure (CHF), and they have more functional impairment after revascularization than men.[6]

Early reports of patients undergoing balloon angioplasty showed lower procedural success rates in women. In addition, early registry data found that women had higher in-hospital mortality after PCI even after adjusting for baseline comorbidities.[5] However, more recent studies report similar procedural success rates in both groups, with an increase in the number of women undergoing PCI over the last several decades.[5,7,8] These studies demonstrate that both in-hospital and long-term mortality rates after PCI are similar between men and women despite women being older and having more complex lesion types (Tables 9-1 and 9-2). This is likely due to heightened awareness of the effects of CVD on women, as well as advances within the field (i.e., newer-generation stents and balloons, smaller sheath sizes and catheters, and advances in adjunctive pharmacotherapies).[5,8,9] In addition, much controversy has surrounded less frequent use of diagnostic catheterization and delays in PCI in women compared with men.[10] These issues will be addressed further in the section on ACS later in the chapter.

Sex and Devices

No sex-based comparisons were made in the earlier randomized clinical trials comparing BMSs with balloon angioplasty. Restenosis and revascularization rates were not well defined for women after bare-metal stenting because of the small sample of women in prospective trials with systematic angiographic follow-up. Even though women tend to have smaller vessel size, shorter lesions, and a higher prevalence of diabetes, some intriguing initial studies reported that women had similar or lower target-vessel revascularization (TVR) rates compared with their male counterparts after PCI.[11] However, systematic angiographic and clinical follow-up has not validated these findings. In the DES era, both sirolimus and taxus stents have shown favorable outcomes in women. The Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions trial (SIRIUS) and the TAXUS IV trial demonstrated the superiority of DESs with reduction in restenosis, TVR, and major adverse cardiac events (MACEs) at 1-year follow-up in women and men.[12] In TAXUS IV,[13,14] patients with severe coronary artery stenosis were randomized to DES (paclitaxel) versus BMS. Women accounted for 27.9% of the study population. Restenosis rates were similar in women and men treated with the TAXUS stent (7.6% vs. 8.6%, $P = .80$), as were measurements of late luminal loss (0.23 mm vs. 0.22 mm, $P = .90$). Compared with BMSs, women treated with the TAXUS stent had a significant reduction in 9-month restenosis (29.2% vs. 8.6%, $P < .001$) and 1-year target-lesion revascularization (TLR) rates (14.9% vs. 7.6%, $P = .02$). Of note, women had higher unadjusted TLR rates compared with men at 1 year; however, female sex was not an independent predictor of TLR (odds radio [OR], 1.72; 95% confidence interval [CI], 0.68 to 4.37; $P = .25$).[14a] A pooled analysis from four randomized sirolimus versus BMS trials was done to assess for sex differences.[14] In 1748 patients, 497 of whom were women, sirolimus-coated stents were associated with a significant reduction in the rates of in-segment binary restenosis in women (6.3% vs. 43.8%) as well as

TABLE 9-1 Odds of In-Hospital Death and Myocardial Infarction After Percutaneous Coronary Interventions, by Sex

Study	Women/Men (*N*)	Women (%)	Men (%)	Adjusted Odds Ratio (95% CI)
Peterson 2001				
In-hospital death	35,571/74,137	1.8	1.0	1.07 (0.9 to 1.2)
In-hospital MI		1.5	1.2	1.25 (1.1 to 1.4)
Jacobs 2002				
In-hospital death	895/1629	2.2	1.3	1.6 (0.76 to 3.35)
In-hospital MI		0.2	0.7	
Lansky 2002				
In-hospital death	2077/5295	1.4	0.7	2.28 (1.15 to 4.55)
Watanabe 2001				
In-hospital death	29,227/53,556	1.2	0.6	1.65 (1.33 to 2.04)
Malenka 2002				
In-hospital death	3983/8057	1.04	0.79	1.24 (0.96 to 1.60)
In-hospital MI		1.71	1.36	1.02 (0.85 to 1.24)

CI, Confidence interval; *MI,* myocardial infarction.

TABLE 9-2 Long-Term Percutaneous Coronary Intervention Outcomes in Acute Coronary Syndrome Patients, by Sex

Study	Women/Men (*N*)	Women (%)	Men (%)	Adjusted Odds Ratio (95% CI)
Jacobs 2002				
1-year death	895/1629	6.5	4.3	1.26 (0.85 to 1.87)
1-year death/MI		11.1	9.0	1.14 (0.86 to 1.50)
Lansky 2002				No difference between sexes was noted; however OR was not reported.
1-year death	2077/5295	4.4	3.3	
1-year MACE		29.2	32.7	
Mehili 2000				
1-year death	1001/3263	4.0	4.1	0.99 (0.54 to 1.13)
1-year MACE		6.0	5.8	—
Chiu 2004				
1-year death	5301/12,738	7	5	1.14 (0.93 to 1.41)
1-year MACE		—	—	1.05 (0.97 to 1.13)

CI, Confidence interval; *MACE,* major adverse cardiac event; *MI,* myocardial infarction; *OR,* odds ratio.

in men (6.4% vs. 35.6%), which resulted in significant reduction in 1-year MACE rates ($P < .0001$). A recent pooled analysis of 11,557 women in 26 trials showed decreased mortality, MI, in-stent thrombosis, and TVR in those treated with a DES versus a BMS. In addition, a significant benefit was found with newer-generation over early-generation DESs.[15] Few sex-based studies on the efficacy of directional coronary atherectomy (DCA) exist. DCA is no longer used, but from a historical perspective, it appears to have been associated with lower procedural success and more bleeding complications in women.[16] Likewise, large devices such as the excimer laser are also associated with higher coronary perforation rates and increased morbidity in women.[16] No sex-specific data on rotational atherectomy, cutting balloon angioplasty, extraction atherectomy, or gamma brachytherapy are available, although the value of these techniques outside of specialized circumstances is currently debated for the population as a whole.

VASCULAR COMPLICATIONS

Women experience greater vascular and bleeding complications during PCI. Compared with men, they have an increased risk of major hematoma, retroperitoneal bleeding, bleeding that requires transfusion, and vascular injury that requires surgery after PCI.[9,17,18] Much of this may be explained by smaller vessel size, lower body mass index, and differences in platelet biology, drug distribution, and bioavailability. With the development of weight-adjusted heparin dosing, introduction of smaller sheath sizes, and early sheath removal, vascular complications have decreased.[18] However, even in the current era, women continue to have a 1.5 to 4 times higher risk of vascular complications compared with men.[14a,17,18] Table 9-3 shows different vascular complication rates by sex as reported in recently published large studies. Given that women have higher rates of vascular complications, they might be ideal

TABLE 9-3 Vascular Complications, by Sex

Study	Women/Men (*N*)	Women (%)	Men (%)	*P* value
Chiu 2004				
Blood transfusion	5301/12,738	12	4	<.001
Major hematoma		5	2	<.001
Pseudoaneurysm		0.6	0.3	.005
Lansky 2002				
Major hematoma	562/1520	2.5	1.5	.005
Retroperitoneal bleed		0.5	0.2	.05
Surgical repair		3.8	2.4	.001
Welty 2001				
Vascular injury	2101/3888	1.6	0.6	.001
Peterson 2001				
Vascular injury	35,571/74,137	5.4	2.7	.001

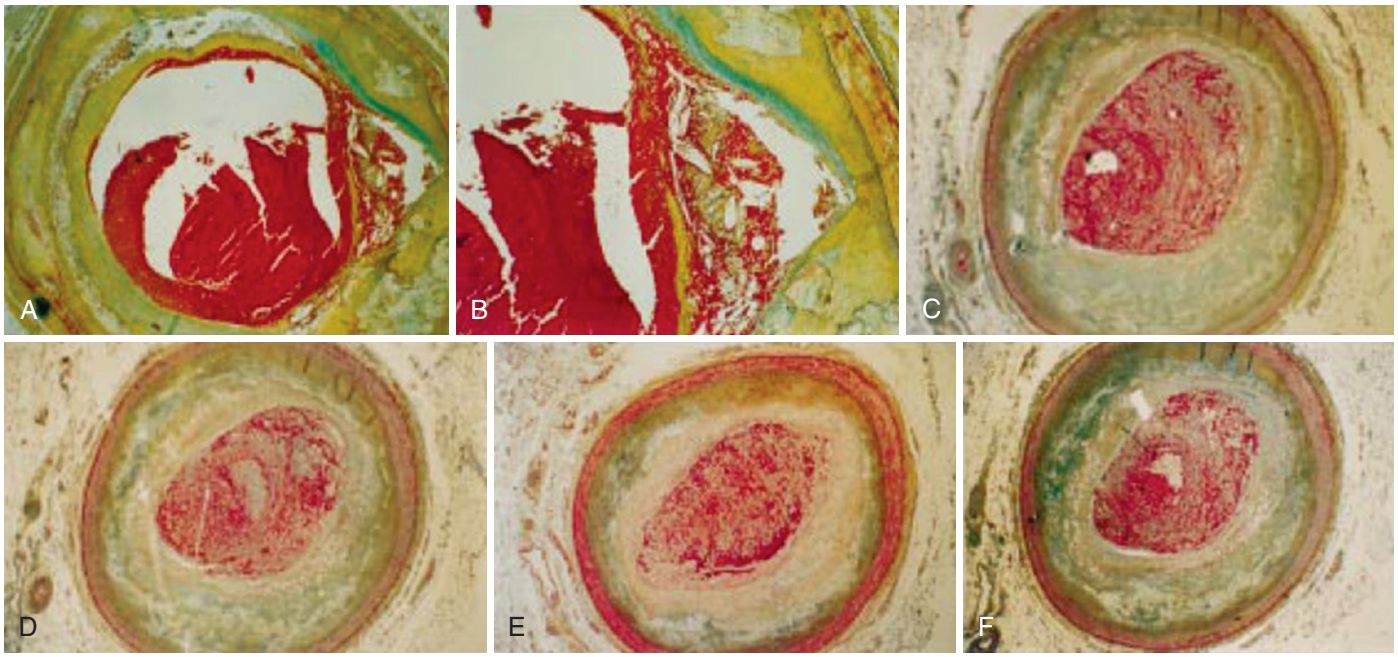


FIGURE 9-1 **A** and **B,** Plaque ulcer with hemorrhagic core. **C** through **F,** Plaque erosion. Note the lack of continuity between the thrombus and the plaque. (From Arbustini E, Dall Bello B, Morbini P, et al: Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. *Heart* 82[3]:269-272, 1999.)

candidates for radial access. Preliminary Data From the Study of Access Site for Enhancement of PCI for Women (SAFE-PCI) showed that the radial approach significantly decreased complications and bleeding rates compared with the femoral approach for women undergoing diagnostic left heart catheterizations. A trend was also seen toward decreased bleeding and complications for a subgroup who received PCI. Of note, an approximately 6% crossover to the femoral approach was reported, mostly as a result of radial artery spasm; this is consistent with a crossover of 7% for the population as a whole.[19] Data are sparse on sex differences in vascular complications related to arterial vascular closure devices. However, subgroup analyses of a number of studies have shown that the odds of a vascular complication related to a closure device is two to eight times higher in women than in men. Again, this is thought to be related to women's smaller arterial luminal diameter.[20]

Sex Differences in Acute Coronary Syndrome

Numerous randomized trials have shown the benefit of an invasive strategy over conservative treatment in NSTEMI; however, the benefits for women in previous subgroup analyses has been less certain. A meta-analysis of eight large ACS trials that included 3075 women and 7075 men found that, similar to men, an invasive strategy was safe and effective in terms of the composite end point of death, MI, or rehospitalization (OR, 0.67; 95% CI, 0.50 to 0.88) in women who had positive biomarkers.[21] However, in women with negative biomarkers, an invasive strategy was associated with a trend toward higher rates of death and MI (OR, 1.35; 95% CI, 0.78 to 2.35), suggesting potential harm. The American College of Cardiology (ACC)/American Heart Association (AHA) now gives a Class IB recommendation for an initial conservative approach for low-risk women (i.e., those with negative biomarkers). A more recent study of 46,455 patients in the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry, which included 14,819 women—all of whom presented with NSTEMI and had positive biomarkers—showed a marked mortality reduction for both men and women treated with an invasive versus a noninvasive strategy (relative risk [RR], 0.46; 95% CI, 0.38 to 0.55).[22] However, a study of 184 women from the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial randomized to a routine invasive strategy versus a selective invasive strategy—defined as catheterization for patients with refractory ischemia, hemodynamic instability, or new ST elevations—showed no difference in the rates of death, MI, or stroke (hazard ratio [HR], 1.46; 95% CI, 0.73 to 2.94). A meta-analysis of 2692 women, which included this study group, showed no significant difference in the composite outcome of death or MI (OR, 1.18; 95% CI, 0.92 to 1.53) between the two treatment groups and demonstrated a trend toward higher mortality in those who received a routine invasive strategy (OR, 1.51; 95% CI, 1.00 to 2.29).[23] Of interest, women who present with NSTEMI or unstable angina are more likely to have elevated C-reactive protein (CRP) and brain natriuretic peptide (BNP), whereas men are more likely to have elevated creatine kinase MB (CK-MB) and troponin.[24] Surprisingly, sex differences are apparent in acute MI plaque morphology. Autopsies reveal more plaque erosion than plaque rupture in women after fatal MI compared with men (Fig. 9-1, *A* and *B*).[25] Also, women appear to have more distal microvascular embolization compared with men during fatal MI.[26]

The overall superiority of primary PCI over fibrinolytic therapy for women presenting with a STEMI has been demonstrated.[27] In fact, likely because of more comorbidities in women at presentation, the absolute benefit with primary PCI is greater for women than for men. An estimated 56 deaths are prevented for every 1000 women treated with primary PCI compared with 42 deaths per 1000 men. Sex-associated differences are also apparent in the amount of myocardial salvage after primary PCI for STEMI, with greater salvage in women than in men.[28] This may be attributed to sex-specific tolerance of hypoxia demonstrated in a number of basic science experiments. Sex-specific data regarding primary stenting versus primary balloon angioplasty in STEMI is also available. Women who presented with a STEMI benefitted from primary stenting with less reinfarction, TVR, and TLR. The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial randomized 2082 patients, of whom 27% were women, to BMS versus primary balloon

TABLE 9-4 Short-Term and Long-Term Percutaneous Coronary Intervention Outcomes in Patients With Myocardial Infarction, by Sex

PCI-MI Studies	Women/ Men (*N*)	Women (%)	Men (%)	Adjusted Rates Odds Ratio (95% CI)
Watanabe 2001				
In-hospital death	11,717/ 24,028	5.2	2.7	1.47 (1.23 to 1.75)
Vakili 2001				
In-hospital death	317/727	7.9	2.3	2.69 (1.4 to 5.2)
Mehili 2000				
30-day death 1-year death	502/1435	8.4 13.8	8.5 12.9	— 0.65 (0.49 to 0.87)
Lansky 2005				
30-day death 1-year death	562/1520	4.6 7.6	1.1 3.0	— 1.11 (0.53 to 2.36)
Antonucci 2001				
6-month death	230/789	12	7	1.25 (0.63 to 2.47)

CI, Confidence interval; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention.

angioplasty with or without a GP IIb/IIIa inhibitor and found superior efficacy and safety with primary stenting, with or without abciximab, compared with balloon angioplasty.[14a] In women, primary stenting resulted in a reduction in the 1-year composite of death, reinfarction, ischemia-driven TVR, or disabling stroke from 28.1% to 19.1% (P = .01) compared with percutaneous transluminal coronary angioplasty (PTCA) alone. Much controversy surrounds potential differences in mortality rates between women and men after STEMI (Table 9-4). A higher in-hospital mortality is apparent among women undergoing PCI for STEMI compared with men. This is in contrast to unstable angina and NSTEMI, in which no mortality difference is apparent when adjusting for other factors. A large study that used the Nationwide Inpatient Sample of 11,717 women and 24,028 men found a 5.2% in-hospital mortality rate in women compared with a 2.7% mortality rate in men. Even after adjusting for age, hypertension, institutional volume, and pulmonary disease, women had higher mortality (OR, 1.47; 95% CI, 1.23 to 1.75).[29] This has been replicated in a number of other studies.[30-32] However, no difference in mortality rates is apparent between the two groups at 30 days or 1 year (see Table 9-4). Of note, female sex is an independent risk factor for the development of cardiogenic shock as a complication of MI; however, no sex difference in mortality is apparent for patients with cardiogenic shock after adjustment for age. Thus the ACC/AHA STEMI guidelines recommend PCI or CABG for patients younger than 75 years who are in cardiogenic shock and have lesions amenable to revascularization regardless of sex.[6]

Much has been reported on sex differences in the diagnosis and treatment of ACS. Women with a higher Killip class present to the hospital later than men, and the initial presentation of coronary artery disease (CAD) in women is often sudden cardiac death (SCD) or acute MI. Women who present with an MI are less likely to undergo primary angioplasty within 90 minutes or to receive pharmacologic treatment on admission and are also less likely to be on accepted medical treatment upon discharge.[33,34] In 2005, the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) investigators published data on sex differences in patients with NSTEMI from a large registry of over 35,000 patients, of which 41% were women. They found that women were less likely to receive guideline-based therapies such as heparin (adjusted OR, 0.91; 95% CI, 0.86 to 0.97) at presentation. Moreover, women were less likely to undergo diagnostic left heart catheterization (adjusted OR, 0.86; 95% CI, 0.82 to 0.91) or PCI (adjusted OR, 0.91; 95% CI, 0.86 to 0.96).[35] Women were also less likely to be discharged on guideline-based medical therapies such as aspirin (adjusted OR, 0.91; 95% CI, 0.85 to 0.98), angiotensin converting enzyme (ACE) inhibitors (adjusted OR, 0.93; 95% CI, 0.88 to 0.98), and statins (adjusted OR, 0.92; 95% CI, 0.88 to 0.98). This is despite evidence that women derive the same benefit from these medications as men do. The CRUSADE registry confirms the unfortunate presence of continued treatment disparities between men and women. Another study that used the American College of Cardiology National Cardiovascular Data Registry (ACC-NCDR) registry looked at sex differences among patients with ACS (both NSTEMI and STEMI) and again showed disparities in treatment.[36] Of 199,690 patients, despite fewer high-risk criteria, the 55,691 women had greater in-hospital complications. For example, although the adjusted mortality among women and men was similar (OR, 0.97; 95% CI, 0.88 to 1.07; P = .52), women had higher rates of CHF (OR, 0.80; 95% CI, 0.69 to 0.92; P = .002), bleeding (OR, 0.55; 95% CI, 0.52 to 0.58; P < .01), and cardiogenic shock (OR, 0.82; 95% CI, 0.75 to 0.89; P < .01). Moreover, they found that women were less likely to receive aspirin (OR, 1.16; 95% CI, 1.13 to 1.20; P < .01) at admission and were less likely to be discharged on statins (OR, 1.10; 95% CI, 1.07 to 1.13; P < .01) or aspirin (OR, 1.17; 95% CI, 1.13 to 1.21; P < .01). Older age of female patients, symptom differences, and delay in presentation after acute MI have been suggested as possible explanations. Although these factors may explain initial treatment differences, they do not explain treatment disparities once the diagnosis has been made. These findings call for significant improvements in the care of ACS patients and highlight the importance of continued investigations into perceptual barriers that contribute to these differences.

Sex-Specific Causes of Acute Coronary Syndrome

Stress Cardiomyopathy

Stress cardiomyopathy, or *Takotsubo cardiomopathy,* results in often severe left ventricular dysfunction with a classical apical ballooning pattern. Commonly associated with sudden emotional or physical stress, patients present with signs and symptoms of MI without demonstrable epicardial CAD. The diagnosis of stress cardiomyopathy is based on "1) transient hypokinesis, akinesis, or dyskinesis in the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; and frequently, but not always, a stressful trigger; 2) the absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; 3) new electrocardiographic (ECG) abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and 4) the absence of pheochromocytoma and myocarditis."[37] Of stress cardiomyopathy cases, 80% to 100% are women in the sixth or seventh decade of life, but it has not yet been elucidated why the condition disproportionately affects postmenopausal women. Hormonal changes have been implicated, given that estrogen deficiency appears to attenuate the levels of cardioprotective substances in the body that in part regulate catecholamine surges. Estrogen deficiency may also increase the level of oxidative stress.[37]

The pathophysiology of stress cardiomyopathy is also unclear. It has been suggested that multivessel epicardial coronary spasm or spontaneously resolved plaque rupture results in stunned myocardium. However, the regional distribution of wall motion abnormality is often out of proportion to the level of cardiac enzyme elevation observed, and in the case of plaque rupture, it is frequently inconsistent with a single coronary vessel.[37] A catecholamine surge causing myocardial and neurogenic stunning is possible, although elevated catecholamine levels are often not seen in these patients.[37] Microvascular dysfunction has also been identified in a number of patients with this condition, but it is difficult to establish a causal relationship given that apical ballooning can result in microvascular dysfunction.[37] Given that left ventricular dysfunction frequently resolves spontaneously within several weeks and recurrence is exceedingly rare,[38,39] there is no standardized treatment for this condition. Some experts argue that beta-blockers are

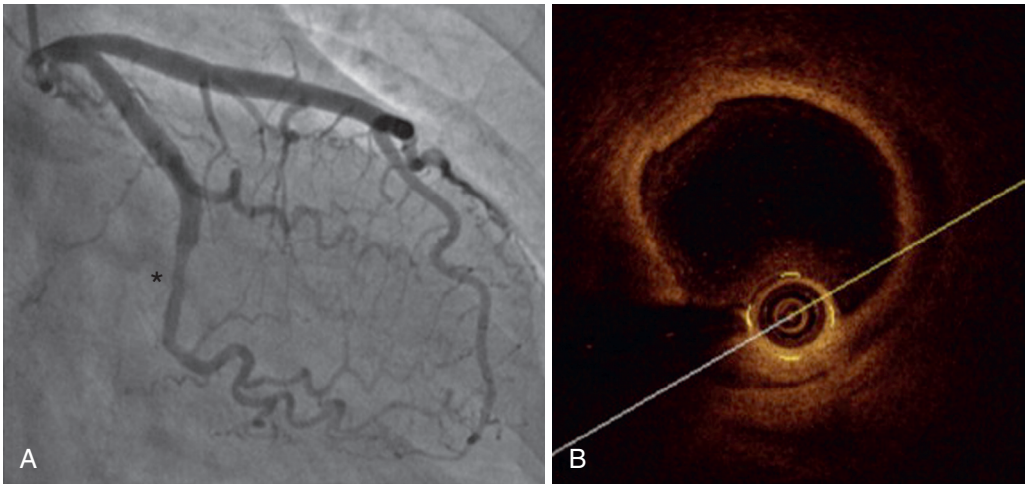


FIGURE 9-2 **A** and **B,** Coronary angiogram shows mild stenosis of the mid circumflex artery by spontaneous coronary artery dissection with intramural hematoma on optical coherence tomography. (From Saw J: Spontaneous coronary artery dissection. *Can J Cardiol* 29[9]:1027-1033, 2013. Image courtesy Dr. Deborah Kwon.)

contraindicated because of the resulting unopposed activation of alpha-adrenoreceptors. Also, no clear indication exists for other standard ACS therapies, such as aspirin and heparin, given the unclear mechanism of stress cardiomyopathy.

Spontaneous Coronary Artery Dissection

Spontaneous coronary artery dissection (SCAD) is an increasingly recognized cause of ACS identified predominantly in young (mean age, 30 to 45 years), healthy females. Dissection of the coronary intimal or medial layer or rupture of the vaso vasorum can lead to intramural hematoma formation, which can ultimately result in various degrees of coronary occlusion.[40,41] The mid to distal vessel is most often involved. The possibility of SCAD should be raised in patients who present with ACS with features of (1) age younger than 50 years, (2) absence of traditional cardiovascular risk factors, (3) little or no typical atherosclerotic changes, (4) peripartum state, (5) history of fibromuscular dysplasia or a connective tissue disorder, or (6) recent intensive exercise or emotional stress. Approximately half of the patients in one series presented with STEMI with the majority of the rest presenting with an NSTEMI.[41] Saw and colleagues[42] have classified SCAD into three types: *type 1* shows evident arterial wall staining; *type 2* shows diffuse stenosis of varying severity; and *type 3* mimics atherosclerosis. If the patient's presentation is clinically and angiographically consistent with type 1 SCAD, no further confirmatory test is necessary. If type 2 or type 3 SCAD is suspected, intravascular ultrasound (IVUS) or optical coherence tomography (OCT) can be used to better evaluate the vessel (Fig. 9-2).[40] Although OCT has greater spatial resolution, it is more costly and not as widely used as IVUS in the clinical setting. Although conservative management and CABG have resulted in minimal in-hospital morbidity, PCI has been complicated by technical failure in up to 35% of patients.[41] Experts currently recommend conservative management with standard ACS therapies. However, caution must be exercised with antithrombotic agents; although they can decrease thrombus burden, the risk of bleeding into the false lumen is increased. If patients experience recurrent or ongoing ischemia despite conservative management, revascularization or referral for CABG may become necessary. OCT or IVUS should be considered to ensure proper stent alignment and positioning. Although the mortality rate is relatively low (95% survival at 2 years),[40] the estimated risk of recurrent SCAD at 10 years is approximately 30%.[41] Of interest, a sizeable number of SCAD patients have coexisting fibromuscular dysplasia (FMD), a nonatherosclerotic, noninflammatory vascular condition that can affect any vascular bed in the body, although a predilection for the renal and carotid arteries is apparent (Fig. 9-3). FMD disproportionately affects women and is seen almost exclusively in the female subset of patients with SCAD.[43] Imaging of the carotid and renal arteries of SCAD patients has revealed a number of cases of FMD,[41,43] therefore if a diagnosis of SCAD is made, patients should also be evaluated for FMD.

FIGURE 9-3 Fibromuscular dysplasia of the renal arteries. (From Naderi S, Cho LS: Cardiovascular disease in women: prevention, symptoms, diagnosis, pathogenesis. *Cleve Clin J Med* 80[9]:577-587, 2013. Image courtesy Dr. Heather Gornik.)

Microvascular Angina

Microvascular angina is defined as chest pain and elevated cardiac biomarkers without angiographic evidence of significant atherosclerosis.[44] The condition is most commonly seen in perimenopausal and

postmenopausal women younger than those who classically present with CVD and is often characterized by lingering, dull chest pain after exertion. Given the ECG changes commonly seen, the condition is thought to be caused by ischemia of the microvascular bed.[45] Microvascular dysfunction caused by insulin resistance, abnormal vasoconstriction and impaired vasodilation of the microvascular bed, increased systemic inflammation, and abnormal pain response have all been cited as potentially contributing to the etiology of microvascular angina.[44] Estrogen deficiency may play a central role in the significantly increased burden of microvascular disease seen in women. Some studies suggest relief of symptoms in women who receive hormone therapy (HT), although concerns for adverse cardiovascular outcomes in women who receive HT has limited further investigation. Studies have also shown worse cardiovascular outcomes, higher angina-related hospitalization rates, and repeat heart catheterizations in women with microvascular angina.[46] The diagnosis must be made by indirect means because no safe and minimally invasive technique exists by which to directly observe the microvasculature given that current coronary angiography techniques cannot visualize vessels smaller than 0.5 mm.[47] Because the coronary microvasculature controls total coronary resistance and therefore regulates myocardial blood flow, measuring myocardial blood flow at maximum vasodilation, termed *coronary flow reserve* (CFR), can indirectly evaluate the degree of microvascular dysfunction.[48] CFR can be measured by invasive means in the catheterization lab after maximum hyperemia is induced by adenosine or another such vasodilatory agent.[49] It should be noted that CFR measurements performed in this invasive manner are greatly affected by hemodynamic changes and can have poor reproducibility.[48] In terms of noninvasive imaging, perfusion magnetic resonance imaging (MRI) or positron emission tomography (PET) is often performed (Fig. 9-4). Once a diagnosis has been made, lifestyle modification, antianginal agents, ACE inhibitors, and statins have been suggested for therapy.[47] Pain-management techniques are also suggested given the increased pain sensitivity observed in women with this condition. More recently, ranolazine has shown promise in small groups of patients with this condition.[50]

FIGURE 9-4 Magnetic resonance imaging (MRI) of a patient with microvascular disease. (From Naderi S, Cho LS: Cardiovascular disease in women: prevention, symptoms, diagnosis, pathogenesis. *Cleve Clin J Med* 80[9]:577-587, 2013. Image courtesy Dr. Deborah Kwon.)

SEX DIFFERENCES IN ADJUNCTIVE PHARMACOTHERAPY

Antiplatelet Therapy

Various forms of antiplatelet therapy have been recommended as first-line treatment of CAD in patients of both sexes. The differences in these adjunctive therapies are outlined here.

Aspirin

Aspirin remains the mainstay of antiplatelet therapy in patients with CAD. It acts by irreversibly inactivating cyclooxygenase (COX), which causes inhibition of platelet thromboxane A2 synthesis and ultimately leads to inhibition of thromboxane-mediated platelet aggregation. Although its role in primary prevention in women is controversial, the efficacy of aspirin in secondary prevention has been well established. An early prospective primary-prevention cohort study of 87,678 healthy women aged 34 to 65 years found that 325 mg of aspirin one to six times a week was associated with a significant reduction in MI ($P = .005$).[51] However, a randomized primary-prevention trial of 39,876 women who received 100 mg aspirin administered every other day found no cardiovascular risk reduction (RR, 0.91; 95% CI, 0.80 to 1.15).[52] Aspirin did, however, reduce the risk of ischemic stroke by 24%, and a subgroup analysis of women over the age of 65 showed a consistent cardiovascular risk reduction with aspirin. A meta-analysis of six randomized controlled trials of primary prevention in 51,342 women and 44,144 men demonstrated sex-specific benefits. In women, aspirin decreased the rate of ischemic stroke (OR, 0.76; 95% CI, 0.63 to 0.93; $P = .0008$) but showed no benefit in reducing MI. In contrast, men had a reduction in MI (OR, 0.68; 95% CI, 0.54 to 0.86; $P = .001$), but no significant reduction in the incidence of stroke was observed.[53] The treatment variability has been attributed to baseline clinical differences and to unique sex-specific responses to aspirin therapy. Both men and women showed similar platelet inhibition in the COX-1 direct pathway after aspirin therapy. In aggregation assays that were indirectly dependent on the COX-1 pathway, compared with men, women had a modest increase in platelet reactivity after aspirin therapy.[54]

Aspirin resistance appears to be more common in women than in men. A study of 326 patients with CVD assessed the prevalence and clinical significance of aspirin resistance by optical platelet aggregation.[55] Of these patients, 17 were *aspirin resistant,* defined as having a mean platelet aggregation of 70% or more with 10 µM adenosine diphosphate (ADP) and 20% or greater with 0.5 mg/mL arachidonic acid. Women were more likely to be aspirin resistant. The much larger Heart Outcome Prevention Evaluation (HOPE) trial assessed the relationship between aspirin resistance and the risk of adverse cardiovascular outcomes.[56] Patients in the study had a history of CAD, stroke, peripheral vascular disease, or diabetes in addition to at least one other cardiovascular risk factor. Aspirin resistance was determined by measuring urinary levels of 11-dehydro-thromboxane B2 (TXB2), a stable metabolite of thromboxane A2. Higher baseline urinary levels of 11-dehydro-TXB2 were associated with increased MI, stroke, and CVD mortality rates ($P = 01$). Female sex was independently associated with higher baseline levels of 11-dehydro-TXB2 level, indicating that women may be more aspirin resistant ($P = .0004$). Despite these data, aspirin for secondary prevention in women has been well established, making underutilization of aspirin in this group extremely concerning. In a large secondary prevention trial in women, only 83% of those with established CAD or CVD received aspirin therapy.[57] Even among patients with unstable angina, women were less likely to receive aspirin therapy. These findings are replicated in large registries and speak to the treatment gap that still exists in practice.[58] Despite advances with proven medical therapy after PCI, aspirin, ACE inhibitors, beta-blockers, and statins continue to be underutilized in all patients, particularly women.[58]

$P2Y_{12}$ Inhibitors

$P2Y_{12}$ inhibitors work by preventing activation of the $P2Y_{12}$ receptor, which promotes platelet aggregation. When given in addition to

aspirin, these agents reduce the rates of subacute stent thrombosis after stent implantation. The PCI-Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study enrolled 2658 ACS patients treated with PCI, of whom 30.2% were women, and assigned them to either long-term or short-term clopidogrel plus aspirin. They found that clopidogrel for up to 12 months was superior to aspirin alone.[59] A trend toward benefit was seen in women (RR, 0.77; 95% CI, 0.52 to 1.15) compared with the statistically significant benefit seen in men (RR, 0.65; 95% CI, 0.48 to 0.87). In the Clopidogrel for Reduction of Events During Observation (CREDO) trial, 2116 patients were enrolled, of whom 29% were women, and long-term treatment with clopidogrel for up to 12 months after elective PCI compared with short-term clopidogrel was associated with a 27% RR reduction in the primary end point of death, MI, or stroke.[60] In women, a 32% RR reduction in the primary end point was reported; however, it did not reach statistical significance (RR reduction, 32.1%; 95% CI, 58.9 to 12.1). No sex-specific data are available with regard to clopidogrel loading dose. In the Intracoronary Stenting and Antithrombotic Regimen Rapid Early Action for Coronary Treatment (ISAR-REACT) trial, which enrolled 2159 low-risk patients for PCI pretreated with 600 mg of clopidogrel and assigned to either abciximab or placebo, no additional benefit to GP IIb/IIIa inhibition was found.[61] In this study, women composed 24% of the population. Patients with ACS, insulin-dependent diabetes, and other high-risk criteria were excluded from this trial. Death, MI, and TVR at 30 days did not differ between the abciximab and placebo groups in either the entire population (4.0% vs. 4.0%, P = nonsignificant [NS]) or in the female subset (3.0% vs. 3.0%, P = NS).

Data for the new $P2Y_{12}$ inhibitors, such as prasugrel and ticagrelor, also suggest similar efficacy in both men and women. In the Platelet Inhibition and Patient Outcomes (PLATO) trial, women appeared to have a similar benefit as men when comparing ticagrelor to clopidogrel in terms of the primary composite end point of cardiovascular death, MI, and stroke in women (11.2% vs. 13.2% [adjusted HR, 0.88; 95% CI, 0.74 to 1.06]) and in men (9.4% vs. 11.1% [adjusted HR, 0.86; 95% CI, 0.76 to 0.97]). A benefit was also seen in terms of all-cause death in women (5.8% vs. 6.8% [adjusted HR, 0.90; 95% CI, 0.69 to 1.16)] and in men (4.0% vs. 5.7% [adjusted HR, 0.80; 95% CI, 0.67 to 0.96)] and definite stent thrombosis in women (1.2% vs. 1.4% [adjusted HR, 0.71; 95% CI, 0.36 to 1.38)] and in men (1.4% vs. 2.1% [adjusted HR, 0.63; 95% CI, 0.45 to 0.89]). No sex-specific difference was found in bleeding complications between women (adjusted HR, 1.01; 95% CI, 0.83 to 1.23) and men (adjusted HR, 1.10; 95% CI, 0.98 to 1.24).[62] In the Trial to Assess Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial, prasugrel was compared with clopidogrel in the management of patients who present with MI. A significant benefit of prasugrel over clopidogrel was seen in both men and women in terms of the combined primary end point of CV death, nonfatal MI, and nonfatal stroke.[63]

Glycoprotein IIb/IIIa Inhibitors

GP IIb/IIIa inhibitors prevent the interplatelet bridging mediated by fibrinogen. Many of the trials that show the efficacy of these drugs were performed prior to the development of the $P2Y_{12}$ agents.[18] With the advent of dual-antiplatelet therapy (DAPT) with aspirin and $P2Y_{12}$ inhibitors, the routine use of GP IIb/IIIa inhibitors in ACS has largely fallen out of favor given the excess bleeding risk and the lack of substantial benefit from triple-antiplatelet therapy. However, such therapies are still used in the modern era in certain high-risk patients. Even though GP IIb/IIIa inhibitors are associated with higher rates of both minor and major bleeding in women compared with men, the benefit derived is similar between the two groups.[18] The CRUSADE registry not only showed excess bleeding for women in the trial overall but also for women treated with a GP IIb/IIIa inhibitor (15.7% vs. 7.3%, P < .0001).[64] It also identified women as a vulnerable group more susceptible to excess dosing; therefore caution should be used when administering these agents to female patients.

Antithrombin Agents

Unfractionated Heparin

Unfractionated heparin (UFH) has long been used as the main anticoagulation therapy in PCI. In the early days of PCI, empiric heparin dosing was used. However, activated clotting time (ACT) levels after a fixed dose of UFH vary substantially because of differences in body size, concomitant use of other medications, and increased heparin resistance in ACS. Weight-based dosing is particularly essential in women given their higher risk of bleeding.[16] A weight-adjusted heparin dosing of 70 to 100 U/kg should be given to achieve an ACT of 250 to 300 seconds with the HemoTec device and 300 to 350 seconds with the Hemochron device.[65] The UFH bolus should be reduced to 50 to 70 U/kg when GP IIb/IIIa inhibitors are given, to achieve a target ACT of 200 seconds with either the HemoTec device or the Hemochron device.

Low-Molecular-Weight Heparin

The efficacy and safety of enoxaparin, a low-molecular-weight heparin (LMWH), in patients with an ACS undergoing PCI has been studied in two noninferiority trials.[66,67] The Aggrastat to Zocor (A-to-Z) study enrolled 3987 patients (29% women) and the Superior Yield of the New Strategy of Enoxaparin Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) study enrolled 9978 patients (34% women) and found no statistical benefit of enoxaparin over standard UFH in PCI. In the A-to-Z trial, no statistically significant difference was found in the primary composite end point of death, MI, or refractory ischemia in women treated with enoxaparin versus UFH.[66] In the SYNERGY trial, patients with ACS who were treated with an early invasive strategy were given either enoxaparin or UFH. At 30 days, no statistically significant difference in death or MI was found in women treated with enoxaparin versus UFH (13.5% vs. 12.9%, P = .59).[67] Some evidence suggests that LMWH causes more bleeding than UFH in women, but no difference is apparent in bleeding risk in men versus women treated with LMWH.

Direct Thrombin Inhibitors

The direct thrombin inhibitor bivalirudin has emerged as an alternative antithrombotic therapy during PCI. The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial enrolled 6010 patients, of whom 1537 were women, and demonstrated that bivalirudin with a provisional GP IIb/IIIa inhibitor was equivalent to heparin and GP IIb/IIIa inhibition with regard to MACE and was associated with less bleeding among patients undergoing PCI.[68] In a prospective analysis of sex, no difference was seen in the individual or composite end point of death, MI, or urgent revascularization at 30 days or 6 months between men and women with bivalirudin or heparin and a GP IIb/IIIa inhibitor.[17] No statistically significant difference was found in the composite of death, MI, or urgent revascularization at 30 days in women treated with heparin and a GP IIb/IIIa inhibitor versus bivalirudin (7.5% vs. 6.7%, P = .58). Major bleeding occurred in 5.9% of women in the heparin and GP IIb/IIIa inhibitor arm compared with 3.7% in the bivalirudin group (P = .04). Similarly, a decrease in minor bleeding (28.2% vs. 16.0%, P < .001) and access-site bleeding was reported with bivalirudin (4.1% vs. 1.6%, P = .003). Thus for female patients undergoing PCI, as in men, bivalirudin appears to provide lower bleeding events compared with heparin and a GP IIb/IIIa inhibitor.

RACE AND ETHNICITY

Currently, minorities make up 30% of the U.S. population, and this is projected to increase to 47.5% of the population by 2050. Studies regarding race and ethnicity in medicine are fraught with difficulties, but numerous studies suggest disparities in cardiovascular care and outcomes.

Disparities in Coronary Artery Disease

Heart disease is the leading cause of death for all racial and ethnic groups in the U.S. population. However, blacks have the highest heart

TABLE 9-5 Cardiovascular Disease in the United States: American Heart Association 2010 Heart and Stroke Statistics

	Total	White Male	White Female	Black Male	Black Female	Hispanic Male	Hispanic Female
Prevalence	81.1 M	38.1%	34.4%	44.6%	46.9%	28.5%	34.5%
Mortality	831 K	340 K	372 K	47.9 K	50.9 K	—	—

From Writing Group Members: Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation* 121:e46-e215, 2010.
M, Million; *K,* thousand.

TABLE 9-6 Short-Term and Long-Term Percutaneous Coronary Intervention Outcomes in Black Americans

Study	Total Patients (% Black)	Adjusted Event Rate Comparing Blacks With Whites (OR, 95% CI)
Maynard 2001		
In-hospital death	24,625 (11%)	0.97 (0.83 to 1.12)
2-year death		1.11 (1.05 to 1.17)
Leborgne 2004		
1-year death	10,561 (12%)	1.35 (1.06 to 1.71)
Slater 2003		
1-year death, MI, or CABG	4,618 (9.7%)	0.65 (0.36 to 1.14)
2-year death, MI, or CABG		1.47 (1.06 to 2.04)
Chen 2005		
1-year death or MI	8,832 (8.0%)	1.45 (1.14 to 1.84)

Writing Group Members: Heart disease and stroke statistics—2010 update: a report from the American Heart Association, *Circulation* 121:e46-e215, 2010.
CABG, Coronary artery bypass graft; *CI,* confidence interval; *MI,* myocardial infarction; *OR,* odds ratio.

disease–related mortality, with a rate that is 1.6 times that of their white counterparts (Table 9-5).[1] Furthermore, disease onset is 5 years earlier in blacks. Research indicates increasing rates of ischemic heart disease in other minority groups, namely Asian, Hispanic, and Native Americans. Despite the increased incidence of CAD among blacks, the presence of obstructive epicardial CAD on angiography is seen less often in blacks than in whites. Paradoxically, the prevalence of complications from atherosclerosis is greater in blacks despite a lower incidence of obstructive CAD. This is most likely due to increased rates of hypertension, diabetes, and smoking and not to inherent differences in the pathophysiology of CAD. Of note, data from the National Health and Nutrition Examination survey showed that blacks have a higher prevalence of peripheral arterial disease than their white counterparts (adjusted OR, 2.39; 95% CI, 1.11 to 5.12).[69] This finding was confirmed by the Genetic Epidemiology of Network Angiopathy (GENOA) study, which showed that this difference persisted in black men and women despite adjusting for risk factors (adjusted OR was 4.7 [95% CI, 1.4 to 16] for black men, and it was 2.2 [95% CI, 1.2 to 4.2] for black women).[70]

Characteristics of Racial and Ethnic Minorities Undergoing Intervention (Table 9-6)

Black patients undergoing PCI are younger, more likely to be female, and have more comorbidities—such as hypertension, diabetes, and chronic renal insufficiency—than their white counterparts. They are more likely to undergo urgent, rather than elective, PCI, although immediate procedural success and short-term rates of death and MI appear similar between black and white Americans.[71,72] However, some have reported lower long-term survival after PCI in blacks.[73] In a large PCI registry, adjusted mortality rate was increased among blacks at 2 years (OR, 1.87; 95% CI, 1.15 to 3.04),[74] findings consistent with another large, single-center PCI registry (OR, 1.45; 95% CI, 1.14 to 1.84).[71] These findings are likely multifactorial and are potentially due to a lack of access to quality health care for blacks. Studies have shown that in the United States blacks receive fewer preventive health services and less specialist care, and physicians treating blacks have had less rigorous clinical training.[75] Another contributing factor is the high prevalence of left ventricular hypertrophy (LVH) together with increased endothelin-1 levels in black Americans.[76] Endothelin-1, a potent vasoconstrictor, is stimulated by transforming growth factor beta (TGF-β), which is increased in blacks with hypertension. The combination of LVH and endothelial dysfunction in conjunction with CAD may contribute to greater mortality rates. It should be noted that despite the recent interest in the field, race-specific PCI analyses are still rare.

Acute Coronary Syndrome

Black patients who present with ACS in the United States are likely to be younger and to have hypertension, diabetes, heart failure, and renal insufficiency. They are also less likely to have insurance coverage or specialist care.[77] The investigators of CRUSADE, a large NSTEMI registry, found that black patients were more likely to receive older ACS treatments such as aspirin, beta-blockers, or ACE inhibitors but were significantly less likely to receive what was then considered newer ACS therapies such as GP IIb/IIIa inhibitors, clopidogrel, and statin therapy.[77] Also, blacks were less likely to receive cardiac catheterization, revascularization, or smoking-cessation counseling. In-hospital death and postadmission MI were similar between black and white patients in the United States (adjusted OR, 0.92; 95% CI, 0.81 to 1.05), consistent with findings from the National Registry of Myocardial Infarction (NRMI).[31] These data hold true when looking specifically at patients who present with a STEMI, and black Americans are less likely to undergo cardiac catheterization and revascularization following a STEMI.[78,79] The NRMI found that racial and ethnic minorities tended to be younger at presentation, and insurance status differed significantly among the groups studied.[78] They found that door-to-drug time and door-to-balloon time were significantly longer for minority patients. This finding persisted even after adjusting for age, sex, insurance status, clinical characteristics, time of arrival, time since symptom onset, and hospital characteristics. In the fully adjusted model, door-to-balloon time was 8.7 minutes longer in blacks compared with whites ($P < .001$) and 3.7 minutes longer for Hispanics compared with whites ($P = .002$).[78] Similarly, a fully adjusted model of door-to-drug time showed a 5.1-minute increase in blacks ($P < .001$), a 1.3-minute increase in Hispanic Americans ($P = .006$), and a 1.7-minute increase in Asian Americans ($P = .01$) compared with their white counterparts. Even though a substantial portion of the racial and ethnic disparities in time to treatment is accounted for by the hospital at which a patient is admitted, racial and ethnic treatment disparities persist despite adjusting for these factors. In a large fibrinolysis trial, the 30-day survival rates were similar between blacks and whites, but black Americans had a higher rate of in-hospital stroke (OR, 1.75; 95% CI, 1.19 to 2.59) and more major bleeding events (OR, 1.32; 95% CI, 1.13 to 1.55).[80] According to the NRMI data, in-hospital mortality rates for STEMI patients are similar between black Americans and their white counterparts.[31] However, at 5 years, the death rate was significantly higher among blacks despite their younger age (OR, 1.63; 95% CI, 1.41 to 1.90).[80] Several factors may explain the decreased rates of catheterization and revascularization in blacks, and it certainly suggests that access to care may play a role, with evidence that black Americans with ACS are more likely to be treated in low-volume hospitals.[81] Although some race-specific data are available regarding differential

antihypertensive medication response, to our knowledge, no such data exist on the efficacy of adjunctive PCI pharmacotherapy.

Social Aspects of Health Care Disparities

Disparities persist in health care because of complex social, political, physiologic, and genetic variation. Although it is important to note that patients from ethnic minority groups are more likely to be treated in low-volume hospitals and to refuse invasive procedures than their white counterparts, these factors do not fully account for the treatment disparities seen.[82] In reviewing over 100 studies, the National Institute of Medicine's 2001 report[83] found that patients from minority groups are less likely to receive the needed services, compared with their white counterparts, even after accounting for issues related to access to health care. Assuming each group had similar comorbidities and access to health care, the committee considered three sets of factors as likely contributors to these treatment differences:

- Data suggest that minorities seek care later than their white counterparts and that they may refuse recommended care. It is thought that this might be due to a number of factors that include the patient's inability to relate to the provider, mistrust and poor prior interactions with the health care system, misunderstanding of instructions, and a lack of knowledge of how to utilize health care services. This, however, does not fully explain racial and ethnic disparities and accounts for only a small proportion of the differences seen.
- Inherent stereotypes and discrimination exist in medicine, whether it is conscious or unconscious. A study of white and black American standardized patients revealed that cardiologists were more likely to refer white men and women and black men for cardiac catheterization than black women despite their exhibiting the same symptoms. In the report they concluded that even though a "myriad of sources contribute to these (treatment) disparities, some evidence suggests that bias, prejudice, and stereotyping on the part of the health care providers may contribute to differences in care."
- The organization and finances of the health care systems that minorities have access to have also been cited. For instance, a lack of interpretive services prevents many non–English speaking patients from adequately making decisions regarding their care. Fragmentation of health care with individuals receiving different tiers of care may also play a role. Although patients may have equal access to care, the quality of the care received may not be uniform.

To work toward eliminating disparities in care, the Institute of Medicine of the National Academies has recommended a comprehensive, multilevel strategy that includes training and educating health care providers, implementing policy and regulatory strategies that address health plans and health services, and promoting better use of clinical practice guidelines.

CONCLUSION

Much has been learned in the last few years regarding sex and racial differences in the presentation, management, and outcomes of patients with CAD. Much more remains to be learned regarding disparities in cardiovascular care, which requires ongoing research and education to bridge the divide.

REFERENCES

1. Writing group members: Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation* 121:e46–e215, 2010.
2. Hess CN, McCoy LA, Duggirala HJ, et al: Sex-based differences in outcomes after percutaneous coronary intervention for acute myocardial infarction: a report from TRANSLATE-ACS. *J Am Heart Assoc* 3:e000523, 2014.
3. Elsaesser A, Hamm CW: Acute coronary syndrome: the risk of being female. *Circulation* 109:565–567, 2004.
4. Jacobs AK: Coronary revascularization in women in 2003: sex revisited. *Circulation* 107:375–377, 2003.
5. Malenka DJ, Wennberg DE, Quinton HA, et al: Gender-related changes in the practice and outcomes of percutaneous coronary interventions in Northern New England from 1994 to 1999. *J Am Coll Cardiol* 40:2092–2101, 2002.
6. Smith SC, Jr, Feldman TE, Hirshfeld JW, Jr, et al: ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation* 113:e166–e286, 2006.
7. Gerber Y, Rihal CS, Sundt TM, 3rd, et al: Coronary revascularization in the community. A population-based study, 1990 to 2004. *J Am Coll Cardiol* 50:1223–1229, 2007.
8. Jacobs AK, Johnston JM, Haviland A, et al: Improved outcomes for women undergoing contemporary percutaneous coronary intervention: a report from the National Heart, Lung, and Blood Institute Dynamic registry. *J Am Coll Cardiol* 39:1608–1614, 2002.
9. Chiu JH, Bhatt DL, Ziada KM, et al: Impact of female sex on outcome after percutaneous coronary intervention. *Am Heart J* 148:998–1002, 2002.
10. Schulman KA, Berlin JA, Harless W, et al: The effect of race and sex on physicians' recommendations for cardiac catheterization. *N Engl J Med* 340:618–626, 1999.
11. Mehilli J, Kastrati A, Bollwein H, et al: Gender and restenosis after coronary artery stenting. *Eur Heart J* 24:1523–1530, 2003.
12. Ellis SG, Stone GW, Cox DA, et al: Long-term safety and efficacy with paclitaxel-eluting stents: 5-year final results of the TAXUS IV clinical trial (TAXUS IV-SR: Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent). *JACC Cardiovasc Interv* 2(12):1248–1259, 2009.
13. Moses JW, Leon MB, Popma JJ, et al: Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 349:1315–1323, 2003.
14. Solinas E, Nikolsky E, Lansky AJ, et al: Gender-specific outcomes after sirolimus-eluting stent implantation. *J Am Coll Cardiol* 50:2111–2116, 2007.

14a. Lansky AJ, Pietras C, Costa RA, et al: Gender differences in outcomes after primary angioplasty versus primary stenting with and without abciximab for acute myocardial infarction: results of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. *Circulation* 111:1611–1618, 2005.

15. Stefanini GG, Baber U, Windecker S, et al: Safety and efficacy of drug-eluting stents in women: a patient-level pooled analysis of randomised trials. *Lancet* 382:1879–1888, 2013.
16. Lansky AJ, Hochman JS, Ward PA, et al: Percutaneous coronary intervention and adjunctive pharmacotherapy in women: a statement for healthcare professionals from the American Heart Association. *Circulation* 111:940–953, 2005.
17. Chacko M, Lincoff AM, Wolski KE, et al: Ischemic and bleeding outcomes in women treated with bivalirudin during percutaneous coronary intervention: a subgroup analysis of the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial. *Am Heart J* 151:1032.e1–1032.e7, 2006.
18. Cho L, Topol EJ, Balog C, et al: Clinical benefit of glycoprotein IIb/IIIa blockade with Abciximab is independent of gender: pooled analysis from EPIC, EPILOG and EPISTENT trials. Evaluation of 7E3 for the Prevention of Ischemic Complications. Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with Abciximab GP IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stent. *J Am Coll Cardiol* 36:381–386, 2000.
19. Rao SV, Bernat I, Bertrand OF: Clinical update: remaining challenges and opportunities for improvement in percutaneous transradial coronary procedures. *Eur Heart J* 33:2521–2526, 2012.
20. Dregelid E, Jensen G, Daryapeyma A: Complications associated with the Angio-Seal arterial puncture closing device: intra-arterial deployment and occlusion by dissected plaque. *J Vasc Surg* 44:1357–1359, 2006.
21. O'Donoghue M, Boden WE, Braunwald E, et al: Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 300:71–80, 2008.
22. Alfredsson J, Lindback J, Wallentin L, Swahn E: Similar outcome with an invasive strategy in men and women with non-ST-elevation acute coronary syndromes: from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). *Eur Heart J* 32:3128–3136, 2011.
23. Swahn E, Alfredsson J, Afzal R, et al: Early invasive compared with a selective invasive strategy in women with non-ST-elevation acute coronary syndromes: a substudy of the OASIS 5 trial and a meta-analysis of previous randomized trials. *Eur Heart J* 33:51–60, 2012.
24. Wiviott SD, Cannon CP, Morrow DA, et al: Differential expression of cardiac biomarkers by gender in patients with unstable angina/non-ST-elevation myocardial infarction: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction 18) substudy. *Circulation* 109:580–586, 2004.
25. Arbustini E, Dal Bello B, Morbini P, et al: Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. *Heart* 82:269–272, 1999.
26. Kolodgie FD, Burke AP, Wight TN, Virmani R: The accumulation of specific types of proteoglycans in eroded plaques: a role in coronary thrombosis in the absence of rupture. *Curr Opin Lipidol* 15:575–582, 2004.
27. Tamis-Holland JE, Palazzo A, Stebbins AL, et al: Benefits of direct angioplasty for women and men with acute myocardial infarction: results of the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes Angioplasty (GUSTO II-B) Angioplasty Substudy. *Am Heart J* 147:133–1339, 2004.
28. Mehilli J, Ndrepepa G, Kastrati A, et al: Gender and myocardial salvage after reperfusion treatment in acute myocardial infarction. *J Am Coll Cardiol* 45:828–831, 2005.
29. Watanabe CT, Maynard C, Ritchie JL: Comparison of short-term outcomes following coronary artery stenting in men versus women. *Am J Cardiol* 88:848–852, 2001.
30. Vakili BA, Kaplan RC, Brown DL: Sex-based differences in early mortality of patients undergoing primary angioplasty for first acute myocardial infarction. *Circulation* 104:3034–3038, 2001.
31. Rogers WJ, Frederick PD, Stoehr E, et al: Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J* 156:1026–1034, 2008.
32. Benamer H, Tafflet M, Bataille S, et al: Female gender is an independent predictor of in-hospital mortality after STEMI in the era of primary PCI: insights from the greater Paris area PCI Registry. *EuroIntervention* 6:1073–1079, 2011.
33. Gan SC, Beaver SK, Houck PM, et al: Treatment of acute myocardial infarction and 30-day mortality among women and men. *N Engl J Med* 343:8–15, 2000.
34. Jneid H, Fonarow GC, Cannon CP, et al: Sex differences in medical care and early death after acute myocardial infarction. *Circulation* 118:2803–2810, 2008.
35. Blomkalns AL, Chen AY, Hochman JS, et al: Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. *J Am Coll Cardiol* 45:832–837, 2005.
36. Akhter N, Milford-Beland S, Roe MT, et al: Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *Am Heart J* 157:141–148, 2009.

37. Akashi YJ, Goldstein DS, Barbaro G, Ueyama T: Takotsubo cardiomyopathy: a new form of acute, reversible heart failure. *Circulation* 118:2754–2762, 2008.
38. Akashi YJ, Musha H, Kida K, et al: Reversible ventricular dysfunction takotsubo cardiomyopathy. *Eur J Heart Fail* 7:1171–1176, 2005.
39. Regnante RA, Zuzek RW, Weinsier SB, et al: Clinical characteristics and four-year outcomes of patients in the Rhode Island Takotsubo Cardiomyopathy Registry. *Am J Cardiol* 103:1015–1019, 2009.
40. Vrints CJ: Spontaneous coronary artery dissection. *Heart* 96:801–808, 2010.
41. Tweet MS, Hayes SN, Pitta SR, et al: Clinical features, management, and prognosis of spontaneous coronary artery dissection. *Circulation* 126:579–588, 2012.
42. Saw J, Poulter R, Fung A, et al: Spontaneous coronary artery dissection in patients with fibromuscular dysplasia: a case series. *Circ Cardiovasc Interv* 5:134–137, 2012.
43. Slovut DP, Olin JW: Fibromuscular dysplasia. *New Engl J Med* 350:1862–1871, 2004.
44. Singh M, Singh S, Arora R, Khosla S: Cardiac syndrome X: current concepts. *Int J Cardiol* 142:113–119, 2010.
45. Camici PG, Crea F: Coronary microvascular dysfunction. *New Engl J Med* 356:830–840, 2007.
46. Johnson BD, Shaw LJ, Buchthal SD, et al: Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation* 109:2993–2999, 2004.
47. Beltrame JF, Crea F, Camici P: Advances in coronary microvascular dysfunction. *Heart Lung Circ* 18:19–27, 2009.
48. Leung DY, Leung M: Non-invasive/invasive imaging: significance and assessment of coronary microvascular dysfunction. *Heart* 97:587–595, 2011.
49. Samim A, Nugent L, Mehta PK, et al: Treatment of angina and microvascular coronary dysfunction. *Curr Treat Options Cardiovasc Med* 12:355–364, 2010.
50. Mehta PK, Goykhman P, Thomson LE, et al: Ranolazine improves angina in women with evidence of myocardial ischemia but no obstructive coronary artery disease. *JACC Cardiovasc Imaging* 4:514–522, 2011.
51. Manson JE, Stampfer MJ, Colditz GA, et al: A prospective study of aspirin use and primary prevention of cardiovascular disease in women. *JAMA* 266:521–527, 1991.
52. Ridker PM, Cook NR, Lee IM, et al: A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 352:1293–1304, 2005.
53. Berger JS, Roncaglioni MC, Avanzini F, et al: Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA* 295:306–313, 2006.
54. Becker DM, Segal J, Vaidya D, et al: Sex differences in platelet reactivity and response to low-dose aspirin therapy. *JAMA* 295: 1420–1427, 2006.
55. Gum PA, Kottke-Marchant K, Poggio ED, et al: Profile and prevalence of aspirin resistance in patients with cardiovascular disease. *Am J Cardiol* 88:230–235, 2001.
56. Eikelboom JW, Hirsh J, Weitz JI, et al: Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. *Circulation* 105:1650–1655, 2002.
57. Vittinghoff E, Shlipak MG, Varosy PD, et al: Risk factors and secondary prevention in women with heart disease: the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 138:81–89, 2003.
58. Jani SM, Montoye C, Mehta R, et al: Sex differences in the application of evidence-based therapies for the treatment of acute myocardial infarction: the American College of Cardiology's Guidelines Applied in Practice projects in Michigan. *Arch Intern Med* 166:1164–1170, 2006.
59. Mehta SR, Yusuf S, Peters RJ, et al: Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 358:527–533, 2001.
60. Steinhubl SR, Berger PB, Mann JT, 3rd, et al: Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 288:2411–2420, 2002.
61. Kastrati A, Mehilli J, Schuhlen H, et al: A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med* 350:232–238, 2004.
62. Husted S, James SK, Bach RG, et al: The efficacy of ticagrelor is maintained in women with acute coronary syndromes participating in the prospective, randomized, PLATelet inhibition and patient Outcomes (PLATO) trial. *Eur Heart J* 35(23):1541–1550, 2014.
63. Antman EM, Wiviott SD, Murphy SA, et al: Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. *J Am Coll Cardiol* 51:2028–2033, 2008.
64. Alexander KP, Chen AY, Roe MT, et al: Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. *JAMA* 294:3108–3116, 2005.
65. Chew DP, Bhatt DL, Lincoff AM, et al: Defining the optimal activated clotting time during percutaneous coronary intervention: aggregate results from 6 randomized, controlled trials. *Circulation* 103:961–966, 2001.
66. Blazing MA, de Lemos JA, White HD, et al: Safety and efficacy of enoxaparin vs unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes who receive tirofiban and aspirin: a randomized controlled trial. *JAMA* 292:55–64, 2004.
67. Ferguson JJ, Califf RM, Antman EM, et al: Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. *JAMA* 292:45–54, 2004.
68. Lincoff AM, Bittl JA, Harrington RA, et al: Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 289:853–863, 2003.
69. Selvin E, Erlinger TP: Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. *Circulation* 110:738–743, 2004.
70. Kullo IJ, Bailey KR, Kardia SL, et al: Ethnic differences in peripheral arterial disease in the NHLBI Genetic Epidemiology Network of Arteriopathy (GENOA) study. *Vasc Med* 8:237–242, 2003.
71. Chen MS, Bhatt DL, Chew DP, et al: Outcomes in African Americans and whites after percutaneous coronary intervention. *Am J Med* 118:1019–1025, 2005.
72. Iqbal U, Pinnow EE, Lindsay J, Jr: Comparison of six-month outcomes after percutaneous coronary intervention for Whites versus African-Americans. *Am J Cardiol* 88:304–305, 2001.
73. Leborgne L, Cheneau E, Wolfram R, et al: Comparison of baseline characteristics and one-year outcomes between African-Americans and Caucasians undergoing percutaneous coronary intervention. *Am J Cardiol* 93:389–393, 2004.
74. Slater J, Selzer F, Dorbala S, et al: Ethnic differences in the presentation, treatment strategy, and outcomes of percutaneous coronary intervention (a report from the National Heart, Lung, and Blood Institute Dynamic Registry). *Am J Cardiol* 92:773–778, 2003.
75. Lillie-Blanton M, Maddox TM, Rushing O, Mensah GA: Disparities in cardiac care: rising to the challenge of Healthy People 2010. *J Am Coll Cardiol* 44:503–508, 2004.
76. Schiffrin EL: Role of endothelin-1 in hypertension and vascular disease. *Am J Hypertens* 14:83S–89S, 2001.
77. Sonel AF, Good CB, Mulgund J, et al: Racial variations in treatment and outcomes of black and white patients with high-risk non-ST-elevation acute coronary syndromes: insights from CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines?). *Circulation* 111:1225–1232, 2005.
78. Bradley EH, Herrin J, Wang Y, et al: Racial and ethnic differences in time to acute reperfusion therapy for patients hospitalized with myocardial infarction. *JAMA* 292:1563–1572, 2004.
79. Manhapra A, Canto JG, Vaccarino V, et al: Relation of age and race with hospital death after acute myocardial infarction. *Am Heart J* 148:92–98, 2004.
80. Mehta RH, Marks D, Califf RM, et al: Differences in the clinical features and outcomes in African Americans and whites with myocardial infarction. *Am J Med* 119:70.e1–70.e8, 2006.
81. Trivedi AN, Sequist TD, Ayanian JZ: Impact of hospital volume on racial disparities in cardiovascular procedure mortality. *J Am Coll Cardiol* 47:417–424, 2006.
82. Rosen AB, Tsai JS, Downs SM: Variations in risk attitude across race, gender, and education. *Med Decis Making* 23:511–517, 2003.
83. Smedley BD, Stith AY, Nelson AR, editors: *Unequal treatment: confronting racial and ethnic disparities in health care*, Washington, DC, 2001, National Academies Press.

10 Platelet Inhibitor Agents

MATTHEW J. PRICE | DOMINICK J. ANGIOLILLO

KEY POINTS

- Dual-antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor is the cornerstone of therapy after percutaneous coronary intervention (PCI).
- The thienopyridines—ticlopidine, clopidogrel, and prasugrel—are $P2Y_{12}$ inhibitors that are prodrugs and therefore require conversion into an active metabolite to exert their antiplatelet effect. This active metabolite irreversibly binds and antagonizes the $P2Y_{12}$ receptor for the life span of the platelet.
- Compared with clopidogrel, prasugrel reduces ischemic events in thienopyridine-naïve patients undergoing PCI but is associated with a higher risk of bleeding. Net clinical benefit is greatest in patients without a history of stroke or transient ischemic attack (TIA) who are older than 75 years of age and weigh over 60 kg. Compared with prasugrel administered after coronary angiography, pretreatment with prasugrel in invasively managed patients with non–ST-elevation acute coronary syndrome (NSTE-ACS) increases major bleeding, does not reduce ischemia, and should be avoided.
- Ticagrelor is a direct, reversibly acting nonthienopyridine $P2Y_{12}$ antagonist. In patients with acute coronary syndrome (ACS), including those treated with an invasive strategy, ticagrelor reduced ischemic events and cardiovascular mortality compared with clopidogrel. Although overall bleeding was not increased with ticagrelor, the risk of non–coronary artery bypass grafting (CABG)-related bleeding was increased.
- Substantial interindividual variability is evident in the antiplatelet effect of clopidogrel. High on-treatment platelet reactivity despite clopidogrel therapy can identify patients at risk for ischemic events after PCI. The clinical benefit of individualized antiplatelet strategies based on platelet function testing has yet to be demonstrated in randomized clinical trials.
- Several genetic polymorphisms reduce the enzymatic activity of CYP2C19, which is critical for the conversion of clopidogrel to its active metabolite. When treated with clopidogrel, carriers of these alleles with reduced function, especially those with two copies (poor metabolizers), are at higher risk of thrombotic events after PCI compared with patients with normal alleles. The CYP2C19 genotype does not influence the clinical efficacy of prasugrel or ticagrelor.
- The effects of thrombin, the most potent platelet activator, are mediated primarily through the protease-activated receptor 1 (PAR-1) receptor. The net clinical benefit of the PAR-1 antagonist, vorapaxar, is favorable in the setting of secondary prevention in patients with prior myocardial infarction (MI) in combination with standard antiplatelet therapy but is not approved for use in the setting of PCI because of a lack of ischemic efficacy and increased bleeding.
- In the modern era of pretreatment with $P2Y_{12}$ inhibitors, the benefit of glycoprotein (GP) IIb/IIIa inhibition appears to be restricted to high-risk patients with ACS who have elevated cardiac biomarkers.

BASIC PRINCIPLES OF ANTIPLATELET THERAPY

Platelets play a critical role in normal hemostasis and in the pathogenesis of atherothrombotic disease processes. Platelets provide an initial hemostatic plug at the site of vascular injury and promote pathophysiologic thrombosis, which in turn precipitates MI, stroke, and peripheral vascular occlusion; therefore antiplatelet agents are key in cardiovascular disease management. In particular, the main goal of antiplatelet treatment strategies is to reduce the risk of recurrent atherothrombotic events without excessive bleeding complications. However, because both pathologic and physiologic functions of platelets are due to the same mechanism, it is difficult to separate therapeutic benefits from potential harmful effects.

Platelet plug formation at sites of vascular injury occurs in three stages: (1) the initiation phase involves platelet adhesion; (2) the extension phase includes activation, additional recruitment, and aggregation; and (3) the perpetuation phase is characterized by platelet stimulation and stabilization of clot.[1] Circulating platelets are quiescent under normal circumstances and do not bind to the intact endothelium. However, endothelial damage leads to the exposure of circulating platelets to the subendothelial extracellular matrix (ECM) and triggers platelet recruitment and adhesion (Fig. 10-1).[2] In the initial phase of primary hemostasis, the tethering of platelets at sites of vascular injury is mediated by the GP Ib-IX-V receptor complex, which binds von Willebrand factor (vWF). Subendothelial collagen exposed by damaged vessels engages platelets via GP VI and GP Ia/IIa receptors. These interactions allow the arrest and activation of adherent platelets. In the *extension phase*, additional platelets are recruited and activated via soluble agonists. These platelet-activating factors include adenosine diphosphate (ADP), thromboxane A2 (TXA_2), epinephrine, serotonin, collagen, and thrombin. Signaling via ADP receptors contributes to platelet activation during both protective hemostasis and pathologic thrombosis. Two ADP receptors are expressed by platelets: $P2Y_1$ couples to $G\alpha q$ and contributes to initial aggregation, and $P2Y_{12}$ couples to $G\alpha_{12}$ and decreases cyclic adenosine monophosphate (cAMP), stabilizing the platelet aggregate.[3] $P2Y_{12}$ receptor signaling also stimulates surface expression of P-selectin and secretion of TXA_2, which is produced de novo and, like ADP, is released from adherent platelets. Generated from arachidonic acid through conversion by cyclooxygenase 1 (COX-1) and thromboxane synthase, TXA_2 binds platelet receptors TPα and TPβ; however, its effects in platelets are mediated primarily through TPα. ADP and TXA_2 are secreted from

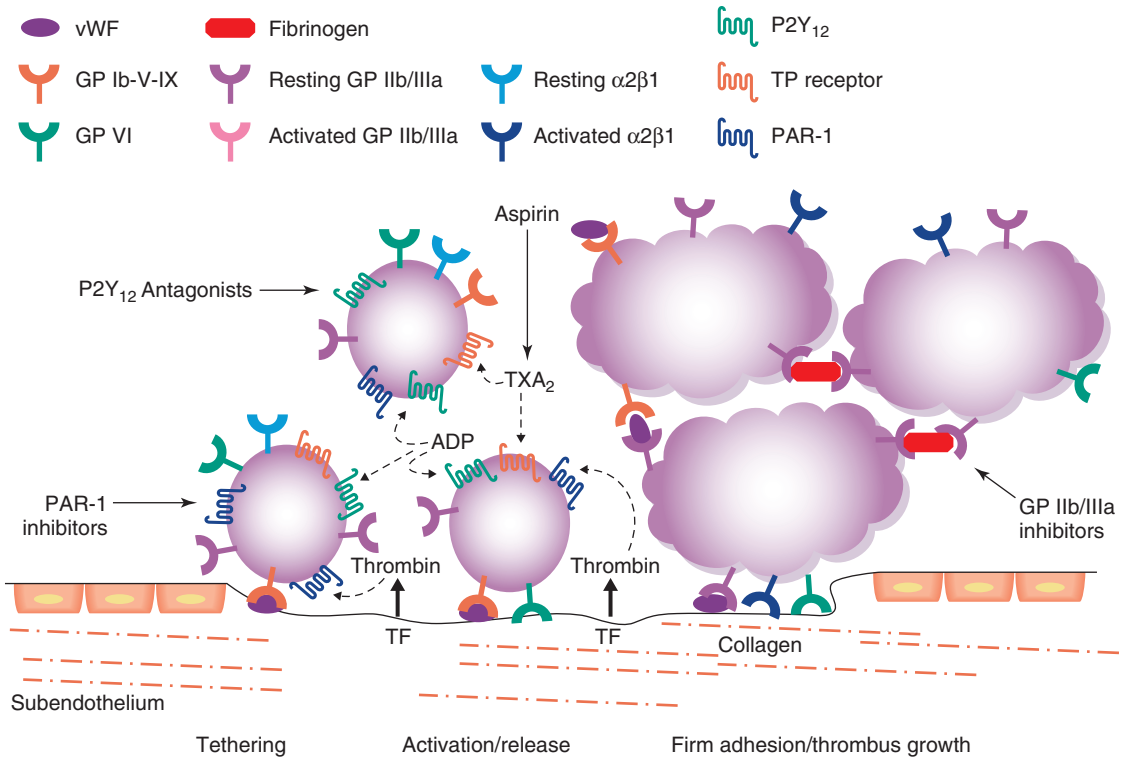


FIGURE 10-1 Platelet-mediated thrombosis. The interaction between von Willebrand factor (vWF) and the platelet receptor glycoprotein (GP) Ib-V-IX mediates platelet tethering to the subendothelium at the sites of injury. GP VI binds collagen with low affinity, which triggers intracellular signals that shift platelet integrins to a high-affinity state and induce the release of the secondary mediators adenosine diphosphate (ADP) and thromboxane A2 (TXA_2). In parallel, tissue factor (TF) locally triggers thrombin formation, which also contributes to platelet activation via binding to the platelet protease-activated receptor 1 (PAR-1). Ultimately, the integrin GP IIb/IIIa, which is the final common pathway mediating platelet aggregation, transforms from a resting to an activated phase, which allows it to bind fibrinogen with high affinity and leads to platelet aggregates. In the perpetuation phase, the platelet-rich thrombus and coagulation cascades reinforce one another, which contributes to thrombus growth and culminates in the generation of a stable platelet-fibrin–rich plug at the sites of injury. (Adapted from Varga-Szabo D, Pleines I, Nieswandt B: Cell adhesion mechanisms in platelets. *Arterioscler Thromb Vasc Biol* 28:403-412, 2008.)

adherent platelets, contribute to the recruitment of circulating platelets, and promote alterations in platelet shape and granule secretion; thus platelet activation is amplified and sustained during the extension phase. Thrombin, generated at the site of vascular injury, represents the most potent platelet activator[4] and contributes to the formation of the hemostatic plug and platelet thrombus growth. Thrombin also directly activates platelets through stimulation of the protease-activated receptors (PARs). Human platelets express two PARs for thrombin, PAR-1 and PAR-4. Thrombin facilitates the production of fibrin from fibrinogen and thus contributes to the formation and stabilization of the hemostatic plug.[4] The final common pathway is activation of the integrin GP IIb/IIIa, which allows platelets to bind fibrinogen with high affinity, leading to platelet aggregates.[5] In the *perpetuation phase,* the platelet-rich thrombus and coagulation cascades reinforce one another and culminate in the generation of a stable platelet-fibrin–rich plug at the sites of injury.

The mechanisms by which antiplatelet drugs interfere with platelet function involve targeting enzymes or receptors critical for synthesis or targeting the action of important mediators of these functional responses. Current and investigational oral antiplatelet therapies target key platelet-signaling pathways (Fig. 10-2). This chapter reviews the mechanisms of action, efficacy, and safety of antiplatelet agents that inhibit key platelet-signaling pathways and their components—including the TXA_2 pathway, the $P2Y_{12}$ and PAR-1 receptors, phosphodiesterase III, and the GP IIb/IIIa receptor—and focuses on their roles in PCI.

ASPIRIN

Mechanism of Action

Aspirin irreversibly inactivates the cyclooxygenase activity of prostaglandin H (PGH) synthase 1 and 2, also referred to as *COX-1* and *COX-2*. PGH synthase 1 and 2 convert arachidonic acid to PGH_2, which acts as a substrate for the generation of several prostanoids, including TXA_2 and prostacyclin (PGI_2). Aspirin enters the COX channel and acetylates the amino acid serine at positions 529 and 516 of COX-1 and COX-2, respectively, thereby preventing arachidonic acid access to the catalytic site of the enzyme through steric hindrance. Mature platelets express only COX-1 and are the primary sources of TXA_2, which is released by the platelet in response to a variety of agonists and induces platelet aggregation through the G protein–coupled TXA_2 receptor, TP. Other cells, including the vascular endothelium, express both COX-1 and COX-2. COX-1 is responsible for the production of cytoprotective prostaglandins PGE_2 and PGI_2 in the gastric mucosa, and COX-2 is the main source of vascular PGI_2. Unlike mature platelets, gastric mucosal cells can synthesize COX-1 and therefore recover the ability to produce prostaglandins within hours after aspirin exposure. Compared with COX-1, higher levels of aspirin are required to inhibit COX-2; therefore low-dose aspirin is sufficient to inhibit platelet TXA_2 production but insufficient to affect the generation of vascular PGI_2, which is a platelet inhibitor and vasodilator. In addition to its primary effect on platelet aggregation through

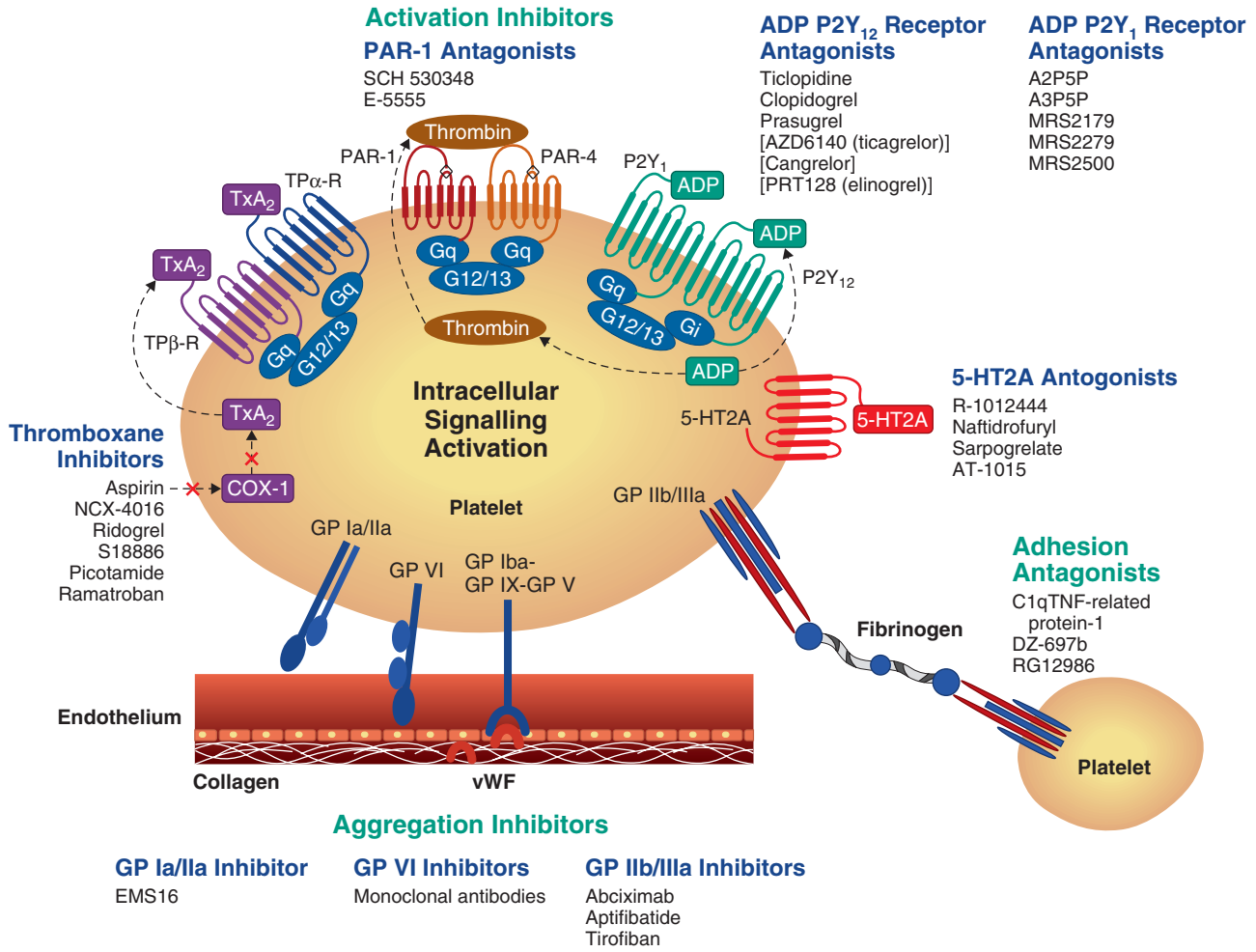


FIGURE 10-2 Sites of action of current and emerging antiplatelet agents. Platelet adherence to the endothelium occurs at the sites of vascular injury through the binding of glycoprotein (GP) receptors to exposed extracellular matrix proteins (collagen and von Willebrand factor [vWF]). Platelet activation occurs via complex intracellular signaling processes and causes the production and release of multiple agonists, including thromboxane A2 (TXA_2) and adenosine diphosphate (ADP) and also causes local production of thrombin. These factors bind to their respective G protein–coupled receptors, mediating paracrine and autocrine platelet activation. Further, they potentiate each other's actions ($P2Y_{12}$ signaling modulates thrombin generation). The major platelet integrin GP IIb/IIIa mediates the final common step of platelet activation by undergoing a conformational shape change and binding fibrinogen and vWF, leading to platelet aggregation. The net result of these interactions is thrombus formation mediated by platelet-platelet interactions with fibrin. Current and emerging therapies that inhibit platelet receptors, integrins, and proteins involved in platelet activation include thromboxane inhibitors, ADP receptor antagonists, GP IIb/IIIa inhibitors, and the novel PAR antagonists and adhesion antagonists. Reversibly acting agents are indicated by brackets. *5-HT2A,* 5-Hydroxytryptamine 2A receptor; *COX,* cyclooxygenase; *PAR,* protease-activated receptor; *TNF,* tumor necrosis factor. (From Angiolillo DJ, Capodanno D, Goto S: Platelet thrombin receptor antagonism and atherothrombosis. *Eur Heart J* 31:17-28, 2010.)

inhibition of the PGH synthase COX-1 activity, it has been suggested that aspirin also exerts antiplatelet effects via COX-1–independent pathways.[6]

Pharmacokinetics and Pharmacodynamics

Aspirin is rapidly absorbed in the stomach and small intestine and achieves peak plasma levels in 30 to 40 minutes. Esterases in the gastrointestinal mucosa and liver hydrolyze aspirin into salicylic acid, which then interacts with platelets in the portal circulation. The half-life is short, approximately 20 to 30 minutes, but the pharmacodynamic effect is prolonged given the permanent inactivation of platelet COX-1 activity. Low-dose aspirin requires several days to effectively suppress TXA_2 production; therefore a loading dose is needed to quickly achieve effective platelet inhibition in aspirin-naïve subjects; however, loading doses greater than 300 mg do not provide additional pharmacodynamic benefit at 2 hours after ingestion.

The American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) 2011 PCI guidelines state that patients not already taking daily long-term aspirin therapy should be administered 325 mg nonenteric aspirin before PCI (class I, level of evidence [LOE] B), and patients already on daily aspirin therapy should take 81 mg to 325 mg before PCI (class I, LOE B).

Aspirin Dose After Percutaneous Coronary Intervention

In healthy individuals, maintenance aspirin dosages as low as 30 mg daily are adequate to completely inhibit serum TXB_2 production, a

marker of platelet thromboxane production. Collaborative meta-analyses of the clinical benefit of long-term aspirin regimens in high-risk patients show that dosages greater than 75 to 150 mg daily are no more effective in reducing ischemic events but are associated with a greater risk of bleeding. However, patients undergoing PCI and receiving stents are not represented in these studies. The ACCF/AHA/SCAI 2011 PCI guidelines[7] state that after PCI, it is reasonable to use aspirin 81 mg per day in preference to higher maintenance doses (class IIa, LOE B).

The impact of different aspirin dosages on ischemia and bleeding in stented patients was examined in a post hoc observational analysis[8] of the PCI cohort of the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial. This analysis suggests that doses of aspirin below 200 mg might be optimal after PCI with a bare-metal stent (BMS). The study stratified the 2658 patients who underwent PCI for acute coronary syndrome in the CURE trial[9] into three groups: high-dose (≥200 mg), medium-dose (>100 mg to <200 mg), and low-dose aspirin (≤100 mg). No differences were found in the unadjusted or adjusted rates of death, MI, or stroke among the groups (high dose vs. low dose, adjusted hazard ratio [HR] 1.00; 95% confidence interval [CI]; 0.67 to 1.48; medium dose vs. low dose, adjusted HR 1.09; 95% CI, 0.73 to 1.60). Unadjusted and adjusted rates of major bleeding were significantly greater with high-dose aspirin compared with low-dose aspirin (adjusted HR 2.03; 95% CI, 1.15 to 3.57).

The Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT–OASIS 7)[10] examined the safety and efficacy of higher-dose aspirin (300 to 325 mg daily) compared with lower-dose aspirin (75 to 100 mg daily) in 25,086 patients with ACS treated with an invasive strategy. All patients received an aspirin loading dose of 300 mg or more the day of randomization, and patients were also randomized in a two-by-two factorial design to standard-dose or double-dose clopidogrel. In the overall cohort, the rate of cardiovascular death, MI, or stroke at 30 days was not different between higher-dose and lower-dose aspirin regimens (4.2% vs. 4.4%, HR 0.97; 95% CI, 0.86 to 1.09; $P = .61$). The incidence of major bleeding as defined by the trial was not different among groups (2.3% vs. 2.3%, HR 0.99; 95% CI, 0.84 to 1.17; $P = .9$). Minor bleeding was more frequent with higher-dose aspirin (5.0% vs. 4.4%, HR 1.13; 95% CI, 100 to 1.27; $P = .04$), as was gastrointestinal (GI) bleeding (0.4% vs. 0.2%, $P = .04$). The findings were similar among those patients who underwent PCI, approximately 42% of whom received a drug-eluting stent (DES), and no difference was found in the incidence of stent thrombosis within the PCI cohort. Therefore a treatment strategy of lower-dose aspirin in invasively managed patients with ACS for 30 days appears to provide ischemic outcomes similar to higher-dose aspirin with less minor bleeding and less GI bleeding. However, longer treatment durations have not been examined in a randomized fashion.

$P2Y_{12}$ INHIBITORS

Basic Principles

The platelet $P2Y_{12}$ receptor plays a central role in amplifying the effect of various stimuli on platelet activation, and it promotes thrombus growth and stability. It is an inhibitory G protein–coupled receptor (Gα12) activated by ADP, which is released from dense granules after platelet activation from a variety of stimuli. ADP binding to the $P2Y_{12}$ receptor leads to a series of intracellular signaling events that result in further granule release and amplification of platelet activation, conformational changes of the GP IIb/IIIa receptor, and stabilization of the platelet aggregate. $P2Y_{12}$ activation further amplifies other responses to platelet activation including P-selectin expression, microparticle formation, procoagulant changes in the surface membrane, and potentiation of shear stress–induced platelet aggregation. The intracellular effect of $P2Y_{12}$ receptor activation is mediated by signal transduction via a secondary messenger system that activates phosphoinositide 3-kinase (PI3K) and inhibits adenylyl cyclase. PI3K activation leads to GP IIb/IIIa receptor activation through activation of a serine-threonine protein kinase B (PKB/Akt) and *RAP1B* guanosine triphosphate (GTP) binding protein. Inhibition of adenylyl cyclase decreases intracellular levels of cAMP, a key cofactor for the phosphorylation of vasodilator-stimulated phosphoprotein (VASP). Dephosphorylated VASP helps promote the conformational change of the GP IIb/IIIa receptor to its active state. Therefore through its action on cAMP levels, $P2Y_{12}$ activation drives the dephosphorylation of VASP and in turn drives GP IIb/IIIa activation (Table 10-1).

Thienopyridines

The thienopyridines—ticlopidine, clopidogrel, and prasugrel—are prodrugs that require biotransformation into an active metabolite to exert their antiplatelet effect. The active metabolite irreversibly binds and antagonizes the $P2Y_{12}$ receptor for the platelet's life span (7 to 10 days). Differences in the rapidity and magnitude of platelet inhibition between the thienopyridines are predominantly the result of differences in prodrug metabolism that affect the efficiency of active metabolite formation. Because the interaction between the active metabolite and the $P2Y_{12}$ receptor is irreversible, a substantial waiting period for platelet functional recovery is required after thienopyridine exposure, which appears to be related to the magnitude of the initial inhibition.[11-13]

Ticlopidine

Ticlopidine was the first thienopyridine to be introduced into clinical practice. It has a slow onset of action, is poorly tolerated, and its use is associated with blood dyscrasias. The incidence of neutropenia has been reported to be 2.4%, peaking at 4 to 6 weeks after the start of therapy; the incidence of aplastic anemia is 1 in 4000 to 8000 patients; and the incidence of thrombotic thrombocytopenic purpura is approximately 1 in 2000 to 4000 patients. The onset of hematologic disorders is rare after 3 months of therapy; therefore hematologic monitoring is required before initiation and for the first 3 months of exposure. The Stent Anticoagulation Restenosis Study (STARS)[14] demonstrated that the combination of aspirin and ticlopidine significantly reduced the rate of death, angiographically evident stent thrombosis, MI, or revascularization at 30 days by 85% compared with aspirin alone and by 80% compared with the combination of aspirin and warfarin. Ticlopidine has been widely replaced by clopidogrel, given its better tolerability and lack of blood-monitoring requirements.

Clopidogrel

Metabolism

Clopidogrel is a prodrug that requires hepatic conversion into an active metabolite to exert its antiplatelet effect (Fig. 10-3). Approximately 85% of absorbed clopidogrel is hydrolyzed by human carboxylesterase[1] in the liver into an inactive carboxylic acid metabolite, so only a fraction of absorbed clopidogrel is available for conversion into the active metabolite by the cytochrome P450 (CYP) system. Hepatic biotransformation of absorbed clopidogrel into the active metabolite is thought to occur through a two-step process. The thiophene ring of clopidogrel is first oxidized to 2-oxo-clopidogrel, which is then hydrolyzed to a highly labile active metabolite (R-130964) that forms a disulfide bond with the $P2Y_{12}$ receptor as platelets pass through the liver. The first metabolic step involves the isoenzymes CYP2C19, CYP2B6, and CYP1A2; the second step involves the isoenzymes CYP2C19, CYP2B6, CYP3A4, CYP3A5, and CYP2C9. An alternative pathway for the oxidative biotransformation of clopidogrel that does not involve CYP2C19 has been suggested.[15] In this formulation, CYP-catalyzed oxidation of clopidogrel to 2-oxo-clopidogrel is mediated by CYP1A2, CYP2B6, and CYP3A, and conversion of 2-oxo-clopidogrel to the thiol active metabolite is mediated by the esterase paraoxonase 1 (PON-1). The catalytic activity of PON-1 is proposed to be the rate-determining step for the active metabolite formation of clopidogrel. However, this alternative pathway has not been independently validated; paraoxonase may catalyze the formation of a minor isomer of the active metabolite, rather than the major isomer, and several studies have shown no

TABLE 10-1 Key Randomized Clinical Trials of $P2Y_{12}$ Inhibitors in Patients Undergoing Invasive Management for Acute Coronary Syndrome, Percutaneous Coronary Intervention, or Both

Trial Name	*N*	Population Studied	Intervention	Control	Primary End Point	F/U	Treatment Effect†
Clopidogrel							
PCI-CURE*	2658	NSTE-ACS	Clopidogrel 300 mg LD, then 75 mg/day + ASA	Clopidogrel open-label for 28 days + ASA	CV death, MI, or revasc.	9 mo	RR 0.70 [0.50-0.97] *P* = .03
CREDO	2116	Stable CAD and unstable angina	Clopidogrel 300 mg pre-PCI, then 75 mg/day + ASA	Clopidogrel 75 mg/day for 28 days + ASA	CV death, MI, or stroke	1 yr	RRR 26.9% [3.9%-44.4%] *P* = .02
PCI-CLARITY*	1863	STEMI treated with fibrinolytics w/PCI 2 to 8 days later	Clopidogrel 300 mg before PCI, then 75 mg/day + ASA	Open-label clopidogrel starting at time of PCI + ASA	CV death, MI, or stroke	30 day	OR, 0.54 [0.35-0.85] *P* = .008
CURRENT–OASIS 7	25,807	NSTE-ACS and STEMI with intended PCI	Clopidogrel 600 mg before angiography, 150 mg/day for 6 days, then 75 mg/day + ASA	Clopidogrel 300 mg before angiography, then 75 mg/day + ASA	CV death, MI, or stroke	30 day	Overall cohort: HR 0.94 [0.83-1.06] *P* = .30 PCI cohort:* (*n* = 17,263) HR 0.86 [0.74-0.99] *P* = .04*
GRAVITAS	2214	Patients with high on-treatment reactivity to standard clopidogrel 12 to 24 hours after PCI	Clopidogrel 600 mg LD, then 150 mg/day + ASA	Clopidogrel 75 mg + ASA	CV death, nonfatal MI, stent thrombosis	6 mo	HR 1.01 [0.58-1.76] *P* = .97
Prasugrel							
TRITON–TIMI 38	13,608	NSTE-ACS and STEMI with planned PCI	Prasugrel 60-mg LD, then 10 mg/day MD + ASA	Clopidogrel 300-mg LD, then 75 mg/day MD + ASA	CV death, MI, or stroke	450 day	HR 0.81 [0.73-0.90] *P* < .001
ACCOAST	4003	NSTE-ACS planned for coronary angiography	Pretreatment with prasugrel 30-mg LD, additional 30-mg LD/10-mg MD if PCI performed	Pretreatment with placebo, 60-mg LD/10-mg MD if PCI performed	CV death MI, stroke, urgent revasc., or GP IIb/IIIa bailout at 7 days	30 day	HR 1.02 [0.84-1.25], *P* = .81
Ticagrelor							
PLATO Invasive	13,408 (PCI in 77%)	NSTE-ACS and STEMI, intended early invasive management	Ticagrelor 180-mg LD, then 90 mg bid + ASA	Clopidogrel 300- to 600-mg LD, then 75 mg/day + ASA	CV death, MI, or stroke	12 mo	HR 0.84 [0.75-0.94] *P* = .0025
ATLANTIC	1862	STEMI	180-mg LD in the ambulance, 90 mg bid thereafter + ASA	Placebo in the ambulance, 180-mg LD in the catheterization laboratory, 90 mg bid thereafter + ASA	Co-primary: Lack of ST-segment resolution; TIMI flow < 3 in infarct-related artery	In-hospital	ST-segment resolution: OR 0.93 [0.69-1.25], *P* = .63 TIMI flow: OR 0.97 [0.75-1.25], *P* = .82
				ASA + clopidogrel 600 mg post PCI	Death, MI, or revasc.	48 hr	OR 0.87 [0.71-1.07] *P* = .17
				ASA + clopidogrel 600 mg pre-PCI	Death, MI, or revasc.	48 hr	OR 1.05 [0.88-1.24] *P* = .59

ACCOAST, Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients With Non-ST Elevation Myocardial Infarction; ACS, acute coronary syndrome; *ATLANTIC,* Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST-Elevation Myocardial Infarction to Open the Coronary Artery; *ASA,* aspirin; *CAD,* cardiovascular disease; *CI,* confidence interval; *CLARITY,* Clopidogrel as Adjunctive Reperfusion Therapy; *CREDO,* Clopidogrel for the Reduction of Events During Observation; *CURE,* Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events; *CURRENT–OASIS 7,* Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes; *CV,* cardiovascular; *F/U,* duration of follow-up; *GP,* glycoprotein; *GRAVITAS,* Gauging Responsiveness With a VerifyNow Assay–Impact on Thrombosis and Safety; *HR,* hazard ratio; *LD,* loading dose; *MD,* maintenance dose; *MI,* myocardial infarction; *NSTE-ACS,* non–ST elevation acute coronary syndrome; *OR,* odds ratio; *PCI,* percutaneous coronary intervention; *PLATO,* Platelet Inhibition and Patient Outcomes; *revasc.,* revascularization; *RR,* risk reduction; *RRR,* relative risk reduction; *STEMI,* ST-elevation myocardial infarction; *TIMI,* thrombolysis in myocardial infarction; *TRITON–TIMI 38,* Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38.
*Postrandomization analysis of a larger clinical trial.
†Numbers in brackets represent 95% confidence intervals.

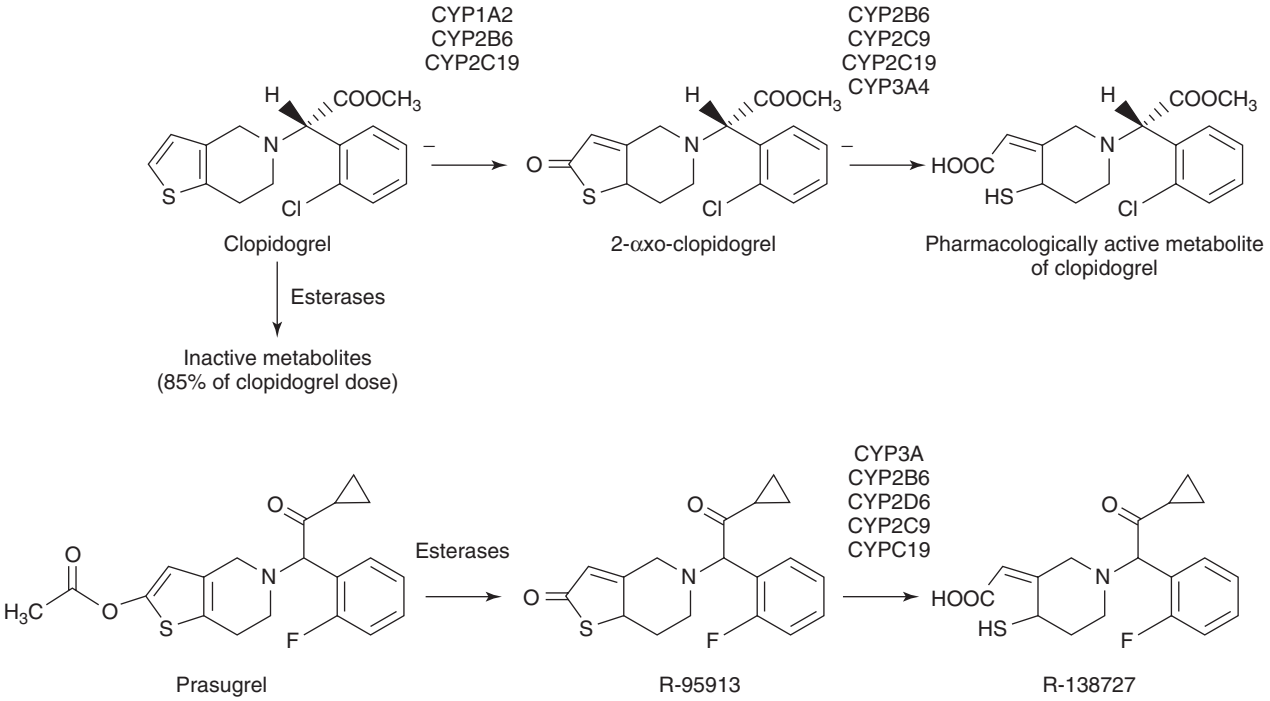


FIGURE 10-3 Comparative metabolism of clopidogrel and prasugrel. Both are prodrugs that require biotransformation into their respective active metabolites to exert an antiplatelet effect. Clopidogrel undergoes a two-step process mediated by CYP450 isoenzymes with involvement of CYP2C19 and CYP2B6 in both steps. A substantial portion of absorbed clopidogrel is shunted into a dead-end pathway by esterases. Prasugrel undergoes a one-step oxidation after the formation of a thiolactone intermediate. The greater inhibitory effect of prasugrel compared with clopidogrel is believed to be attributable to differences in the efficiency of active metabolite formation. (From Giusti B, Abbate R: Response to antiplatelet treatment: from genes to outcome. *Lancet* 376:1278-1281, 2010.)

influence of genetic polymorphisms of *PON1* on clopidogrel active metabolite levels or on clopidogrel's antiplatelet effects.[16]

Pharmacodynamics

A daily dose of clopidogrel 75 mg requires 3 to 7 days to reach steady-state platelet inhibition, whereas a loading dose (LD) provides a rapid onset of action. However, the clinical benefit of a 300-mg LD may not be seen for 6 hours to as long as 15 hours after administration.[17,18] Larger doses provide higher circulating levels of active metabolite, more rapid onset, and more intense inhibition.[19,20] Peak inhibition after a 600-mg LD occurs at 4 to 6 hours after exposure.[19,21] A 900-mg LD may or may not provide more rapid and additional suppression of platelet function compared with a 600-mg dose because the intestinal absorption of clopidogrel may be limited at doses greater than 600 mg.[19,20] A maintenance dose regimen of 150 mg daily is associated with greater inhibition than a dose of 75 mg daily.[22,23] Variability is wide among individuals in regard to the antiplatelet effect of clopidogrel after either a loading dose or a maintenance dose. Higher doses of clopidogrel reduce, but do not eliminate, this variability. The pharmacodynamic response to clopidogrel has been associated with CYP2C19 genotype, age, diabetes mellitus, body mass index, sex, ACS presentation, active smoking, renal dysfunction, pretreatment reactivity, and concomitant therapy with calcium channel blockers or proton pump inhibitors.[24-27] However, clinical characteristics and the CYP2C19 genotype only partly explain the variability in on-treatment reactivity.[16,25,28] The level of ADP-induced platelet reactivity measured by several ex vivo platelet function tests have been associated with clinical outcomes in clopidogrel-treated patients undergoing PCI.[29,30]

Clinical Studies

NON–ST-ELEVATION ACUTE CORONARY SYNDROME. The longer-term ischemic benefit of clopidogrel in patients who present with ACS was established by the CURE trial, which randomized 12,562 patients with NSTE-ACS to aspirin and clopidogrel (300-mg LD followed by 75 mg daily) or aspirin alone for 3 to 12 months.[31] The composite end point of cardiovascular death, nonfatal MI, or stroke occurred in 9.3% of patients in the clopidogrel group and in 11.4% of patients in the placebo group ($P < .001$). Clopidogrel therapy was associated with an increased rate of major bleeding as defined by the trial (3.7% vs. 2.7%, $P = .001$). In the population of patients enrolled in CURE who underwent PCI (17% of the overall cohort, 82% of whom received a BMS), pretreatment with clopidogrel for a median of 6 days reduced the rate of cardiovascular death, MI, or urgent target-vessel revascularization within 30 days from 6.4% to 4.5% ($P = .03$).

ST-ELEVATION MYOCARDIAL INFARCTION. The Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction (CLARITY–TIMI 28) trial[32] randomized 3491 patients 75 years of age and younger who received aspirin and fibrinolytic therapy within 12 hours of an ST-elevation MI (STEMI) to clopidogrel 300 mg followed by 75 mg daily or placebo. All patients underwent mandated angiography 2 to 8 days later. Clopidogrel significantly reduced the rates of occluded infarct–related artery, death, or recurrent MI before angiography (15.0% vs. 21.7%, $P < .001$) without increasing TIMI-defined major bleeding, minor bleeding, or intracranial hemorrhage. A prespecified analysis of patients who underwent PCI demonstrated that clopidogrel significantly reduced ischemic events from randomization through 30 days, from PCI through 30 days, and from randomization to PCI.[33] This trial supports the use of clopidogrel in patients 75 years and younger who present with STEMI and are treated with aspirin and fibrinolysis.

Pretreatment for Percutaneous Coronary Intervention

The rationale for clopidogrel pretreatment is based on the slow onset of a substantial pharmacodynamic effect even after a clopidogrel loading dose. The Clopidogrel for the Reduction of Events During

Observation (CREDO) trial randomized 2116 patients with stable coronary artery disease (CAD), unstable angina, or recent ACS to a clopidogrel 300 mg loading dose or placebo 3 to 24 hours before PCI. All patients received clopidogrel 75 mg daily for 28 days thereafter; patients in the control arm did not receive a loading dose. Pretreatment did not significantly reduce the primary composite end point of death, MI, and urgent target revascularization at 28 days (6.8% vs. 8.3%, $P = .23$). Post hoc analysis suggested that longer durations of pretreatment were associated with improved outcomes, but little benefit was achieved when the treatment duration was less than 12 hours.[18] A prospectively planned analysis of the 1863 patients in CLARITY–TIMI 28 who underwent PCI after mandated angiography showed that pretreatment for a median duration of 3 days in patients with STEMI treated with aspirin and fibrinolysis significantly reduced the incidence of cardiovascular death, MI, or stroke following PCI (3.6% vs. 6.2%, $P = .008$) and from randomization through 30 days (7.5% vs. 12.0%, $P = .001$).[33] Unfortunately, the use of a 300-mg loading dose in CREDO, PCI-CURE, and the Effect of Clopidogrel Pretreatment Before Percutaneous Coronary Intervention in Patients With ST-Elevation Myocardial Infarction Treated With Fibrinolytics (PCI-CLARITY) studies and the prolonged duration of pretreatment in PCI-CURE and PCI-CLARITY limit their applicability to current practice patterns for both elective and urgent PCI. The ischemic benefit of a shorter pretreatment duration of high-dose clopidogrel before PCI has not been examined in a large, randomized, placebo-controlled trial. Post hoc analysis of the Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment (ISAR-REACT) trial, which compared abciximab with placebo in elective PCI patients treated with clopidogrel 600 mg for at least 2 hours before intervention, showed no incremental benefit from durations of pretreatment greater than 2 to 3 hours.[34] The PRAGUE-8[35] study randomized 1028 patients undergoing coronary angiography and potential ad hoc PCI for stable angina to either clopidogrel 600 mg more than 6 hours before angiography or clopidogrel 600 mg in the catheterization laboratory only in the case of PCI. No differences were found in the rate of death, MI, stroke, or reintervention among groups at 7 days, not in the entire population or in the subgroup undergoing PCI (0.8% vs. 1.0%, $P = .7$; 1.3% vs. 2.8%, $P = .4$, respectively), but bleeding was increased in the pretreatment group (3.5% vs. 1.4%, $P = .025$). The findings of this small trial support a strategy of "on the table" clopidogrel loading before ad hoc PCI in elective patients, although the findings must be interpreted within the context of the relatively small sample size and very low event rates. The findings are supported by another smaller trial, Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA) PRELOAD, which randomized 409 patients (39% with ACS) to a 600-mg clopidogrel loading dose 4 to 8 hours before PCI or a 600-mg LD given in the catheterization laboratory after coronary angiography and before PCI.[36] The rates of major adverse cardiovascular events (MACEs) at 30 days were similar between groups and occurred in 10.8% of patients pretreated, compared with 8.8% in the patients receiving clopidogrel, in the laboratory ($P = .7$). No differences in the rates of bleeding were reported.

Dosing Strategies

Pharmacodynamic studies have demonstrated that higher clopidogrel loading doses and maintenance doses provide more rapid onset of action and greater levels of inhibition compared with a 300-mg loading dose and a 75-mg maintenance dose, respectively.[19-21,37] Two large randomized studies, CURRENT–OASIS 7 and GRAVITAS (Gauging Responsiveness With a VerifyNow Assay–Impact on Thrombosis and Safety), have examined the efficacy and safety of higher-dose clopidogrel in patients managed invasively or undergoing PCI.

The CURRENT–OASIS 7 trial[38] examined the ischemic benefit of a higher-dose strategy in 25,086 patients with NSTE-ACS and ST-elevation ACS undergoing an early invasive strategy, of whom 17,263 underwent PCI. Before angiography, patients were randomized to receive either a 600-mg loading dose, followed by 150 mg daily for 6 days and 75 mg daily thereafter, or a 300-mg LD followed by 75 mg daily thereafter. Patients were also randomized to high-dose aspirin or low-dose aspirin in a two-by-two factorial design. The primary end point—a composite of cardiovascular death, MI, or stroke at 30 days—was no different with double-dose clopidogrel or standard-dose clopidogrel (4.2% vs. 4.4%, $P = .30$). Major bleeding, as defined by the trial, was significantly greater in the patients randomized to double-dose clopidogrel (2.5% vs. 2.0%, HR 1.24; 95% CI, 1.05 to 1.46; $P = .01$); however, no differences were noted in fatal bleeding, CABG-related bleeding, or TIMI-criteria major bleeding. Within the subgroup of patients who underwent PCI, high-dose clopidogrel was associated with a 13% relative risk reduction in the primary end point (3.9% vs. 4.5%, $P = .04$).[39] However, the interaction test between patients who underwent PCI and those who did not failed to reach the prespecified threshold for statistical significance; therefore the possibility that the results of the PCI subgroup are a chance finding cannot be excluded.[38]

The GRAVITAS trial[40] tested whether an additional clopidogrel loading dose followed by a 6-month course of clopidogrel 150 mg daily would reduce thrombotic events compared with clopidogrel 75 mg daily in patients who had undergone PCI with a DES and displayed high on-treatment reactivity according to ex vivo platelet function testing 12 to 24 hours after the intervention. Unlike the population examined by the CURRENT–OASIS 7 trial, the predominant indication for PCI in the enrolled population was stable CAD or low-risk unstable angina (UA). No difference was reported in the rate of cardiovascular death, nonfatal MI, or stent thrombosis at 6 months between groups (2.3% vs. 2.3%, $P = .9$). The incidence of severe or moderate bleeding per the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) criteria was not increased with the high-dose regimen (1.4% vs. 2.3%, $P = .10$). The higher-dose clopidogrel regimen had a significant but only modest effect on platelet inhibition in patients with high on-treatment reactivity to standard dosing, which may partly explain the similar outcomes of the two groups.

Duration of Therapy

The small but incremental risk of late thrombosis with DES use has raised uncertainty about the optimal duration of DAPT after PCI. Observational studies have shown that discontinuation of antiplatelet therapy after DES placement has been associated with late and very late stent thrombosis, but the interpretation of these studies is limited by study design and the presence of potentially unmeasured confounders. Randomized trials from the BMS era demonstrate the benefit of prolonged aspirin and clopidogrel over the first year after PCI.[17,41] Patients who have undergone PCI could possibly receive benefits from very long-term clopidogrel because of a reduction in atherosclerosis-mediated events rather than stent-mediated events.

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial compared aspirin and clopidogrel with aspirin alone over a median treatment duration of 28 months in 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors.[42] Although no difference was apparent in the rate of cardiovascular death, MI, or stroke between treatment groups in the overall cohort, a post hoc analysis showed that aspirin and clopidogrel appeared to provide a significant 17% relative risk reduction in the rate of the composite ischemic end point in patients with a prior MI, ischemic stroke, or symptomatic peripheral arterial disease (PAD).[43] In contrast, a randomized study of 2701 patients who underwent DES placement and were free of major adverse cardiovascular or cerebrovascular events (MACCEs) at 1 year observed no significant ischemic benefit for extended aspirin and clopidogrel therapy compared with aspirin alone.[44] These findings will be confirmed or rebutted by the Dual Antiplatelet Therapy (DAPT) trial (ClinicalTrials.gov identifier NCT00977938), which will randomize more than 20,000 patients treated with either a DES or BMS who are event free 12 months after the procedure to receive either aspirin and a thienopyridine or aspirin and placebo for an additional 18 months. Current ACC/AHA/SCAI guidelines state that all patients who receive a DES should be given

clopidogrel 75 mg daily for at least 12 months if they are not at high risk of bleeding; for patients who receive a BMS, clopidogrel should be given for a minimum of 1 month, ideally up to 12 months, unless the patient is at increased risk of bleeding, in which case it should be given for a minimum of 2 weeks.[7] In the setting of ACS, for post-PCI patients who receive a stent (BMS or DES), a daily maintenance dose should be given for at least 12 months and for up to 15 months unless the risk of bleeding outweighs the anticipated net benefit afforded by a thienopyridine, and continuation beyond 15 months may be considered in patients undergoing DES placement.[45]

DAPT was the first randomized, clinical trial to be adequately powered to test the safety and efficacy of prolonged dual-antiplatelet therapy on stent-related outcomes in patients treated with a DES.[46] A total of 9961 patients who had undergone DES placement and were MACE free at 12 months after the procedure and receiving DAPT with a thienopyridine and aspirin were randomly assigned to either continue the thienopyridine for an additional 18 months or to receive placebo; all patients continued to receive aspirin. Among the enrolled patients, 60% had been treated with a next-generation DES (47% everolimus-eluting and 13% zotarolimus-eluting stents). Continued DAPT significantly reduced the rate of the coprimary end point of definite or probable stent thrombosis (1.4% vs. 0.4%, HR 0.29; 95% CI, 0.17 to 0.48; $P < .001$), as well as definite stent thrombosis (1.2% vs. 0.3%, HR 0.26; 95% CI, 0.14 to 0.45; $P < .001$; Fig. 10-4). The treatment effect of continued DAPT on stent thrombosis was consistent across DES types (P interaction [P_{int}] = .79). The rate of MI was also significantly reduced by continued DAPT (4.1% vs. 2.1%, HR 0.47; 95% CI, 0.37 to 0.61; $P < .001$); MIs not related to stent thrombosis accounted for about 55% of this treatment effect. The second coprimary end point, a composite of MACCEs, was significantly reduced with continued DAPT (5.9% vs. 3.4%, HR 0.71; 95% CI, 0.59 to 0.85; $P < .001$). An increase in noncardiovascular mortality was observed (1.0% vs. 0.5%, HR 2.23; 95% CI, 1.32 to 3.78; $P = .002$), which the investigators suggest may have been because of the presence of a disproportionate number of patients with prior cancer in the placebo arm. A subsequent, large meta-analysis of randomized trials that assigned patients to extended thienopyridine use (>6 mo), which included the DAPT trial, did not demonstrate any effect of thienopyridine treatment on noncardiovascular mortality.[47] Whereas continued thienopyridine therapy from 12 through 30 months after DES implantation reduced both stent-related and non–stent-related ischemic events in the DAPT trial, this was balanced by an increased risk in the primary safety end point, moderate or severe GUSTO bleeding (1.6% vs. 2.5%, $P = .001$). However, moderate bleeding events drove this difference, and no increase in fatal bleeding was reported. Therefore the findings of the DAPT trial support continued thienopyridine treatment beyond 12 months in patients who receive a DES, irrespective of stent type, in those who are not at high risk for bleeding.

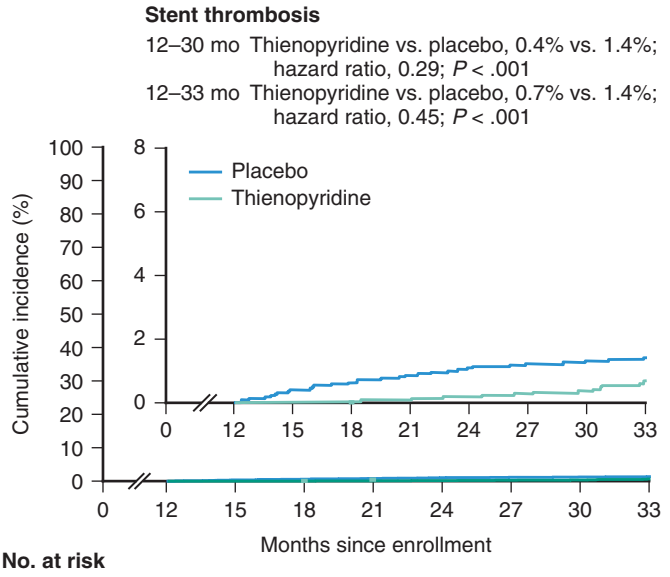


FIGURE 10-4 Cumulative incidence of definite or probable stent thrombosis in the Dual Antiplatelet Therapy Trial. At 12 months after drug-eluting stent implantation, continued aspirin and thienopyridine for an additional 18 months significantly reduced the rate of stent thrombosis compared with aspirin alone. (From the DAPT Study Investigators: Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 371[23]:2155-2166, 2014.)

The Role of CYP2C19

The antiplatelet effect of clopidogrel is dependent on the generation of an active metabolite through the hepatic CYP450 system. Patients who are carriers for genetic polymorphisms that reduce the catalytic activity of CYP2C19 have lower clopidogrel active metabolite levels and diminished platelet inhibition with treatment. Approximately 5% to 12% of the variability in ADP-induced platelet reactivity appears to be explained by carriage of the reduced function CYP2C19*2 allele.[25,28] The sensitivity of active metabolite generation to changes in the catalytic activity of CYP2C19 may be attributed to the important contribution of this enzyme to both steps in clopidogrel biotransformation. Decreased CYP2C19 function could lead to a bottleneck at the level of hepatic activation, thereby shunting the prodrug into the pathway that leads to an inactive carboxylic acid metabolite.

Predicted Metabolic Phenotype

Patients can be classified on the basis of the predicted metabolic phenotype of the CYP2C19 genotype. The single-nucleotide polymorphisms that affect enzyme activity are described using the established "star allele" nomenclature. The CYP2C19*1 allele denotes the lack of known polymorphisms and therefore is considered to be a wild type. CYP2C19*2 is the most common reduced-function allele, with an allelic frequency of approximately 13% in whites, 18% in blacks, and 30% in Asians. CYP2C19*3 is the second most common reduced-function allele; it has an allelic frequency of approximately 10% in Asians but is rare in other ethnicities. Much less common reduced-function alleles include *4, *5, *6, *7, *8, and *10. In addition, the *17 variant is associated with increased gene transcription and increased catalytic activity of the enzyme. The combination of two alleles (genotype) can be used to predict the metabolic phenotype of a particular individual (Table 10-2). Metabolic phenotype is associated with the pharmacokinetics and pharmacodynamics of clopidogrel. In a study of healthy volunteers, ultra-rapid metabolizers had the highest exposure to active metabolite and the greatest platelet inhibition, and poor metabolizers had the lowest exposure and least platelet inhibition with both loading and maintenance doses.[48] The frequency of poor metabolizers is approximately 2% in the white population.

TABLE 10-2 Classification of Predicted Metabolic Phenotype According to CYP2C19 Genotype

CYP2C19 Genotype	Predicted Phenotype
*17/*17	Ultra-rapid metabolizer
*1/*17	Ultra-rapid metabolizer
*1/*1	Extensive metabolizer
*1/*2–*8	Intermediate metabolizer
*17/*2–*8	Intermediate metabolizer/unknown
*2–*8/*2–*8	Poor metabolizer

CYP2C19 and Clinical Outcomes

A collaborative meta-analysis of nine studies involving 9685 patients, 91% of whom had a PCI, reported a significantly increased risk of the composite end point of cardiovascular death, MI, or ischemic stroke in carriers of at least one reduced-function CYP2C19 allele (HR 1.57; 95% CI, 1.13 to 2.16; $P = .006$) and in patients with two reduced-function CYP2C19 alleles (HR 1.76; 95% CI, 1.24 to 2.50; $P = .002$). Carriers of at least one reduced-function CYP2C19 allele had an increased risk of stent thrombosis (HR 2.81; 95% CI, 1.81 to 4.37; $P < .0001$); this risk was especially strong in patients with two reduced-function alleles (HR 3.97; 95% CI, 1.75 to 9.02; $P = .001$). The influence of CYP2C19 genotype on outcomes is less apparent in populations treated with clopidogrel for indications other than PCI. In the genetic substudy of the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE A), a randomized comparison of aspirin and clopidogrel compared with aspirin alone for the prevention of thromboembolic events in atrial fibrillation (AF), the primary outcome was similar in carriers and noncarriers of the CYP2C19*2 reduced-function alleles. Similarly, in the CURE trial, in which only 14% of patients who presented with ACS underwent PCI, no difference was reported in ischemic outcomes according to CYP2C19 genotype.[49]

U.S. Food and Drug Administration's Boxed Warning

The U.S. Food and Drug Administration (FDA) mandated a warning in the clopidogrel package insert in the fall of 2009 that highlights the impact of CYP2C19 on the exposure to clopidogrel active metabolite, platelet inhibition, and clinical outcomes. This warning emphasizes that the effectiveness of clopidogrel is dependent on bioactivation by CYP2C19 and that poor metabolizers generate less active metabolite and have less platelet inhibition with the recommended dosage of clopidogrel (i.e., 300-mg loading and 75-mg daily maintenance doses). Furthermore, the warning states that compared with patients with normal CYP2C19 function, cardiovascular event rates are higher in poor metabolizers with ACS and those who are undergoing PCI when treated with recommended doses of clopidogrel. The warning goes on to state that tests are available to identify a patient's CYP2C19 genotype, that these tests can be used as an aid in determining therapeutic strategy, and that alternative treatment or treatment strategies should be considered in patients identified as poor metabolizers of CYP2C19. A subsequent ACCF/AHA Clopidogrel Clinical Alert stated that the evidence base was insufficient to recommend routine genetic testing, but testing to determine whether a patient is a poor metabolizer may be considered before starting clopidogrel therapy in patients believed to be at moderate or high risk for poor outcomes, for example, those undergoing elective high-risk PCI. The alert also noted that if genotyping identifies a poor metabolizer, other antiplatelet therapies, particularly prasugrel for coronary patients, should be considered, taking into account the balance of potential ischemic benefit with the known increased risk of bleeding.[50]

Other Genetic Polymorphisms

PON1. An alternative model for the bioactivation of clopidogrel posits a central role for the paraoxonase-1 enzyme (PON-1) in hydrolyzing 2-oxo-clopidogrel into the thiol active metabolite. A genetic variant that lowers the activity of PON-1 (Q192R) and may reduce the efficiency of clopidogrel bioactivation has been identified. Carriage of two *PON1* loss-of-function alleles was associated with definite stent thrombosis in a prospective cohort of 1982 patients with ACS (HR 10.20; 95% CI, 4.39 to 71.43; $P < .001$).[15] However, subsequent studies have raised the possibility that paraoxonase-1 is involved in the formation of a minor thiol metabolite isomer,[51,52] rather than the major clopidogrel active metabolite, and an association between *PON1* genotype and on-treatment platelet reactivity or clinical outcomes after PCI has not been confirmed in several other clinical studies.[16,53-55]

ABCB1. P-glycoprotein is an adenosine triphosphate (ATP)–dependent efflux pump encoded by the *ABCB1* gene. It is expressed in the intestinal epithelial cells, and its increased expression or function can influence the bioavailability of drugs that are its substrate. Healthy subjects homozygous for the 3435 C->T polymorphism have a decreased pharmacodynamic effect of clopidogrel.[56] The results of clinical outcomes studies are inconsistent. A genetic substudy of the Trial to Assess Improvement in the Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI 38) study reported that *ABCB1* 3435 TT homozygotes had a significantly increased risk of adverse cardiovascular events during treatment with clopidogrel after PCI for ACS, whereas event rates were highest in *ABCB1* 3435 CC homozygotes in the genetic substudy of the Platelet Inhibition and Patient Outcomes (PLATO) trial.[56,57]

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are extensively metabolized by CYP2C19 and CYP3A4. The different PPIs inhibit CYP2C19 activity to varying degrees. Omeprazole, lansoprazole, and esomeprazole demonstrate more potent inhibition by ex vivo assays, and lesser inhibition is observed with pantoprazole and rabeprazole. PPIs interfere with the pharmacodynamic effect of clopidogrel. In the Omeprazole Clopidogrel Aspirin (OCLA) study, 124 patients who had undergone coronary stent implantation received aspirin and clopidogrel (300 mg in a loading dose followed by 75 mg daily) and were randomized to either omeprazole 20 mg daily or placebo for 7 days.[58] Omeprazole significantly decreased the inhibitory effect of clopidogrel as assessed by VASP phosphorylation analysis. Administering the two drugs 12 hours apart does not mitigate the clopidogrel-PPI interaction.[59] A pharmacodynamic interaction does not appear to occur with pantoprazole.[59,60] Large retrospective cohort and population-based studies have reported an association between concomitant PPI and clopidogrel use with an increased risk of recurrent cardiovascular events, including MI.[61,62] Although these analyses adjust for baseline differences among treatment groups, unmeasured confounders may, in part, explain these observations because patients treated with PPIs after PCI have substantially more comorbidities than those not treated with PPIs. Post hoc analysis of the TRITON–TIMI 38 randomized trial found no association between PPI use and the risk of cardiovascular death, MI, or stroke in patients treated with clopdiogrel.[63]

The Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT)[64] was a multicenter, randomized, phase III study of the safety and efficacy of a fixed-dose combination of clopidogrel 75 mg or omeprazole 20 mg in patients at high risk for GI bleeding who required aspirin and clopidogrel therapy for at least 12 months. The primary end point was the time to first occurrence of an upper GI clinical event; the primary cardiovascular end point was a composite of cardiovascular death, nonfatal MI, coronary revascularization, or ischemic stroke. The study was not powered a priori for the cardiovascular end point, and it was halted prematurely for lack of funding. A total of 3873 patients were randomized, of whom approximately 42% had a history of ACS. At 180 days, the rate of the composite GI end point was significantly lower in the combination clopidogrel-omeprazole group compared with the group who received clopidogrel alone (1.1% vs. 2.9%, HR 0.34; 95% CI, 0.18 to 0.63; $P < .001$), and no difference was apparent in the incidence of cardiovascular events (4.9% vs. 5.7%, HR 0.99; 95% CI, 0.68 to 1.44; $P = .96$). The cardiovascular end point was driven predominantly by the need for coronary revascularization (generally not a platelet-driven phenomenon); cardiovascular death or MI occurred in only 23 patients in the omeprazole group and in 20 patients in the placebo group. Given the possibility of a 44% increased hazard for cardiovascular events in the low-risk group that was studied, the COGENT results may not rule out a clinically meaningful difference in cardiovascular events with the use of omeprazole in patients administered clopidogrel for its labeled indications.[65] The findings of a meta-analysis of 13 studies involving 48,674 clopidogrel-treated patients suggested that the clinical impact of concomitant PPI use might be significant only in patients with high baseline cardiovascular risk.[66] An ACCF/American College of Gastroenterology/AHA

2010 expert consensus document on the concomitant use of PPIs and thienopyridines states that clinical decisions regarding concomitant use of PPIs and thienopyridines must balance overall risks and benefits, considering both cardiovascular and GI complications.[67] Patients with ACS and prior upper GI bleeding are at substantial cardiovascular risk, so DAPT with concomitant use of a PPI may provide the optimal balance of risk and benefit. Among stable patients undergoing coronary revascularization, a history of GI bleeding should inform the choice of revascularization method; if a coronary stent is selected to treat such patients, the risk-benefit trade-off may favor concomitant use of DAPT plus a PPI.

Prasugrel

Metabolism

Prasugrel is a thienopyridine, like ticlopidine and clopidogrel, but its biotransformation into the active metabolite is substantially more efficient (see Fig. 10-3). Hydrolysis by human carboxylesterase 2 during absorption forms a thiolactone precursor, which is then oxidized in a single CYP-dependent step to the active metabolite. CYP3A4/5 and CYP2B6 are major contributors to this process, whereas CYP2C19 and CYP2C9 play a minor role; oxidation by intestinal CYP3A also occurs.[68] The biotransformation of prasugrel is more efficient than that of clopidogrel because of the lack of a competing metabolic pathway to an inactive metabolite. The greater magnitude of inhibition of platelet aggregation (IPA) achieved by prasugrel 60 mg compared with clopidogrel 600 mg is caused by differences in active metabolite exposure.[69] The area under the concentration-time curve of the prasugrel active metabolite is dose proportionate between 10 and 60 mg. Genetic polymorphisms that reduce the catalytic activity of CYP2C19 have no effect on active metabolite formation, the achieved level of platelet inhibition, or clinical outcomes in patients with ACS treated with PCI.[68,70]

Pharmacodynamics

Compared with clopidogrel, a prasugrel 60-mg loading dose followed by 10 mg daily provides a more rapid onset of action, significantly greater $P2Y_{12}$ inhibition, and less interindividual variability in the extent of inhibition. Prasugrel 60 mg achieves greater than twice the mean IPA at 4 hours after administration compared with a clopidogrel 300-mg loading dose in patients with stable coronary artery disease (ADP 5 mmol/L, 74% vs. 37%; ADP 20 mmol/L, 68% vs. 30%), and the stronger effect on IPA can be detected as early as 15 to 30 minutes after administration.[71] Prasugrel 10 mg daily provides a greater level of IPA compared with clopidogrel 75 mg daily (ADP 5 mmol/L, 59% vs. 31%; ADP 20 mmol/L, 58% vs. 31%).[71] A randomized pharmacodynamic study demonstrated that a prasugrel 60-mg load followed by 10 mg daily also provides a greater level of platelet inhibition than clopidogrel 600 mg followed by 150 mg daily.[72] The variability in inhibition among individuals is substantially less with prasugrel 10 or 60 mg compared with clopidogrel. However, prasugrel maintenance doses of less than 10 mg daily are associated with greater degrees of interindividual variability in the extent of inhibition.[71]

Clinical Studies

The clinical efficacy and safety of prasugrel in ACS were examined in TRITON–TIMI 38.[73] In this phase III, randomized, active-control, time-to-event trial, 13,608 patients with moderate- to high-risk ACS undergoing treatment with PCI were assigned a prasugrel 60-mg loading dose followed by 10 mg daily or a clopidogrel 300-mg LD followed by 75 mg daily for 6 to 15 months. The primary efficacy end point was a composite of death from cardiovascular causes, nonfatal MI, or stroke. To be eligible, patients were required to be naïve to thienopyridine therapy. Randomization to the study drug occurred after diagnostic coronary angiography and determination that PCI was to be performed except in the case of STEMI, when randomization was allowed before the assessment of coronary anatomy. Over a median duration of therapy of 14.5 months, the primary composite end point occurred in 12.1% of the patients receiving clopidogrel and in 9.9% of patients receiving prasugrel ($P < .001$). The treatment effect of prasugrel was driven primarily by a reduction in the rate of nonfatal MI. The benefit of prasugrel was similar in patients with NSTE-ACS (HR 0.82; 95% CI, 0.73 to 0.93; $P = .002$) or STEMI (HR 0.79; 95% CI, 0.65 to 0.97; $P = .02$). The rate of definite or probable stent thrombosis was also significantly reduced with prasugrel (1.13% vs. 2.35%, HR 0.48; 95% CI, 0.36 to 0.64; $P < .001$). Key elements of the TRITON–TIMI 38 study design that may have impacted the findings were the timing of study drug administration and the clopidogrel dosing strategy to which prasugrel was compared (clopidogrel 300-mg loading dose at the time of PCI). Prespecified landmark analyses for efficacy were performed from randomization to day 3 and from day 3 to the end of the trial to separate the events that could be attributed to the loading dose of the study drug. These analyses demonstrated that in addition to an early benefit, prasugrel provided a significant reduction in the rates of MI and stent thrombosis after 3 days, supporting the hypothesis that prasugrel is superior to clopidogrel during the chronic phase of management after PCI (nonfatal MI: HR 0.69; 95% CI, 0.58 to 0.83; $P < .001$; stent thrombosis: HR 0.45; 95% CI, 0.32 to 0.64; $P < .001$).[74] Further, a landmark analysis[75] also showed that prasugrel reduced stent thrombosis both early (≤30 days, 0.64% vs. 1.56%, $P < .001$) and late (>30 days, 0.49% vs. 0.82%, $P = .03$). Although prasugrel provided a significant benefit with regard to ischemic outcomes, a significant hazard for major bleeding was also observed (HR 1.32; 95% CI, 1.03 to 1.68; $P = .03$), including fatal bleeding. A determination of net clinical outcome (combination of ischemic and bleeding events) may be helpful to assess the overall benefit of prasugrel for a particular patient, assuming that the components of this composite—death from any cause, nonfatal MI, stroke, and major non–CABG-related bleeding—can be considered of equivalent importance to the physician and the patient. In TRITON–TIMI 38, patients with a prior history of stroke or transient ischemic attack (TIA) experienced net harm from prasugrel because of a lack of ischemic benefit and a strong trend toward excessive major bleeding, including intracranial hemorrhage, and patients 75 years of age and older who weighed less than 60 kg experienced no net clinical benefit because of modest ischemic benefit balanced by an increased risk of bleeding; therefore prasugrel is contraindicated in patients with a history of stroke or TIA. It can be considered in patients 75 years of age and older who have an increased ischemic risk (e.g., diabetes or prior MI) in whom the potential ischemic benefit may outweigh any increased risk of major bleeding, and a maintenance dose adjustment to 5 mg may be considered in patients who weigh less than 60 kg because pharmacokinetic modeling suggests that active metabolite exposure with this dose is similar to the 10-mg dose in heavier patients.

In TRITON–TIMI 38, subjects with prior exposure to a thienopyridine were excluded, and patients with NSTE-ACS received study drug (prasugrel LD or placebo) only after coronary anatomy was documented by angiography. The safety and efficacy of pretreatment with prasugrel prior to PCI were explored in the Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) trial.[75a] In this trial, 4033 patients with NSTE-ACS and elevated troponin who were scheduled for coronary angiography were randomly assigned to either pretreatment with prasugrel in a 30-mg LD or placebo. If PCI was indicated at the time of angiography, an additional prasugrel 30-mg LD was administered to the pretreatment group, and a prasugrel 60-mg LD was administered to the control group. Approximately one quarter of the enrolled patients were at high risk (Global Registry of Acute Coronary Events [GRACE] score ≥140), and the time between pretreatment and coronary angiography was slightly greater than 4 hours. The primary end point—cardiovascular death, MI, stroke, urgent revascularization, or GP IIb/IIIa bailout at 7 days—was no different between study groups, whereas TIMI major bleeding was significantly increased in the pretreatment group (at day 7, HR 1.90; 95% CI, 1.19 to 3.02; $P = .006$]). Therefore the results of the ACCOAST trial do not support pretreatment with prasugrel in the setting of NSTE-ACS.

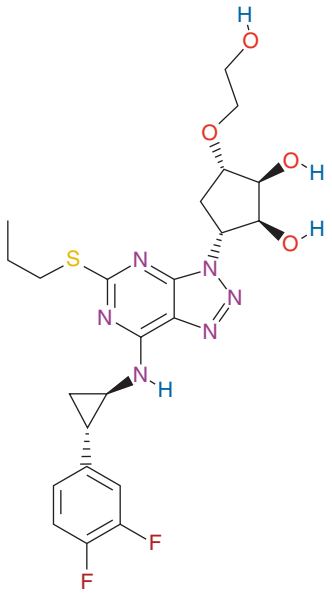


FIGURE 10-5 Chemical structure of ticagrelor.

Nonthienopyridines

Ticagrelor

Ticagrelor, a cyclopentyltriazolopyrimidine, is a reversibly binding oral $P2Y_{12}$ receptor antagonist (Fig. 10-5). It interacts with the $P2Y_{12}$ receptor at a ligand binding site separate from that for ADP or the thienopyridines and therefore antagonizes ADP-mediated $P2Y_{12}$ receptor activation noncompetitively.[76] In addition to $P2Y_{12}$ receptor antagonism, ticagrelor inhibits the adenosine transporter ENT-1 (type 1 equilibrative nucleoside transporter), thereby inhibiting cellular uptake of adenosine and increasing its concentration and biologic activity.[77]

Pharmacology and Metabolism

Unlike the thienopyridines, ticagrelor does not require metabolic conversion to an active form to antagonize the $P2Y_{12}$ receptor. Peak plasma concentration is attained at a median of 90 minutes after administration. The parent compound is metabolized primarily by CYP3A isoenzymes into a metabolite that has a similar potency in inhibiting the $P2Y_{12}$ receptor; this metabolite is present at approximately 40% of the parent concentration. Elimination of ticagrelor is mainly through hepatic metabolism, and the primary route of elimination of the active metabolite is likely through biliary excretion. CYP3A inhibitors such as ketoconazole or diltiazem increase plasma concentrations of ticagrelor, and ticagrelor increases the exposure to drugs that are CYP3A substrates, such as simvastatin. The CYP2C19 genotype has no effect on ticagrelor pharmacodynamics.[78] The mean half-lives of ticagrelor and its active metabolite are 7.2 hours and 8.5 hours, respectively.

Pharmacodynamics

Compared with clopidogrel, ticagrelor has a rapid onset of action, achieves more intensive $P2Y_{12}$ inhibition, and has a relatively faster offset of antiplatelet effect.[79] A ticagrelor 180-mg LD provides an IPA with ADP 20 mmol/L of 41% at 30 minutes and 88% at 2 hours after administration compared with 8% and 41% after a clopidogrel 600-mg LD, respectively. Maintenance-dose ticagrelor 90 mg twice daily provides an IPA with ADP 20 mmol/L of approximately 75% compared with 50% with clopidogrel 75 mg daily. The extent of inhibition is similar 24 hours after discontinuation of either clopidogrel or ticagrelor because of faster offset with ticagrelor, and the IPA for ticagrelor on day 3 after the last dose is comparable with that for clopidogrel at day 5.

Clinical Studies

The PLATO trial randomized 18,624 patients with ACS with or without ST elevation to either ticagrelor or clopidogrel.[80] The primary efficacy end point was a composite of death from cardiovascular causes, MI, or stroke; the major safety end point was major bleeding as defined by the trial, which was more inclusive than TIMI-defined major bleeding. Initial patient management could be conservative or invasive, and patient randomization was stratified by the intent for early invasive management as indicated by the investigator. Unlike TRITON–TIMI 38, PLATO included both thienopyridine-naïve patients and thienopyridine-treated patients. At 12 months, ticagrelor led to a significant reduction in the primary composite end point compared with clopidogrel (9.8% vs. 11.7%, HR 0.84; 95% CI, 0.77 to 0.92; $P < .001$). A similar relative reduction in the primary end point was observed in the 13,408 patients treated with a planned invasive strategy, 44% of whom had received clopidogrel before randomization and allocation to the study drug.[81] Ticagrelor significantly reduced cardiovascular mortality by an absolute risk reduction of 1.1% and reduced all-cause mortality by 1.4%; however, the statistical validity of this latter finding may be questioned because this end point was analyzed in a hierarchical fashion after the rate of stroke, which was not statistically significant between study arms. No increase in all-cause major bleeding was reported with ticagrelor. The rate of fatal intracerebral hemorrhage was significantly greater with ticagrelor therapy, but this was balanced by a higher rate of nonintracranial fatal bleeding with clopidogrel, resulting in an overall similar rate of fatal bleeding with the two therapies. Non–CABG-related TIMI major bleeding was significantly more frequent with ticagrelor (HR 1.25; 95% CI, 1.03 to 1.53; $P = .03$). In subgroup analyses according to region, ticagrelor did not provide an ischemic benefit in the North American cohort (HR 1.25; 95% CI, 0.93 to 1.67; $P_{int} = .045$). A potential explanation for this interaction was an observed attenuation of the treatment effect of ticagrelor with high-dose aspirin, which was more commonly used in North America.[82] To that end, the U.S. prescribing information for ticagrelor states that maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and should be avoided.

The timing of ticagrelor therapy in STEMI patients was further examined in the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST-Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial, in which a total of 1862 STEMI patients were randomly assigned to receive a ticagrelor LD either upstream in the ambulance or in the hospital within the cardiac catheterization laboratory. The time from randomization to coronary angiography was rapid (48 min), and the mean duration of pretreatment for the in-ambulance group was 31 minutes. In-ambulance ticagrelor did not reduce the incidence of either of the coprimary end points (absence of ST-segment resolution and less than TIMI grade 3 flow in the infarct-related artery), nor did it affect the rates of major adverse cardiovascular events (MACEs) or bleeding. The rate of early stent thrombosis was significantly lower with upstream treatment, but this finding must be considered exploratory and hypothesis generating because the results of the overall trial were negative.

Adverse Effects

Ticagrelor has been associated with dyspnea, hyperuricemia, and ventricular pauses, possibly attributable to interference with adenosine degradation and inhibition of erythrocyte adenosine reuptake. The reversible interaction with the $P2Y_{12}$ receptor of sensory neurons may also contribute to the perception of breathlessness,[83] although this is speculative. Holter monitoring in a subgroup of patients in the PLATO trial demonstrated that ticagrelor led to an infrequent but greater rate of ventricular pauses of 3 or more seconds in the first week of therapy but did not result in significantly increased syncope or pacemaker implantation compared with clopidogrel. An increased rate of the complaint of dyspnea has been consistently observed in phase II and III studies. In the Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 Versus Clopidogrel in Non–ST-Segment Elevation Myocardial Infarction (DISPERSE-2),[84] 10.5% of patients who received

ticagrelor 90 mg twice daily reported dyspnea, compared with 6.4% of patients who received clopidogrel ($P = .07$). In PLATO, dyspnea was reported in 13.5% of ticagrelor-treated patients compared with 7.8% of clopidogrel-treated patients ($P < .001$). In a randomized, double-blind phase II study that actively monitored the complaint of dyspnea in 123 patients with stable coronary artery disease, 38.6%, 9.3%, and 8.3% of patients in the ticagrelor, clopidogrel, and placebo groups reported dyspnea, respectively ($P < .001$). Most cases of dyspnea occurred within 1 week of starting ticagrelor and were not associated with adverse changes in cardiac or pulmonary function.[85]

Cangrelor

PHARMACOLOGY AND METABOLISM. Cangrelor is a nonthienopyridine adenosine triphosphate (ATP) analogue.[86] It is administered intravenously and is a rapid and direct-acting reversible inhibitor of the $P2Y_{12}$ receptor that has a half-life of approximately 3 minutes (Fig. 10-6). Cangrelor is metabolized through dephosphorylation by ecto-endonucleatase (CD39) to form a nucleoside (AR-C69712XX), which is the major circulating metabolite. AR-C69712XX is further metabolized into several products and is primarily eliminated in the urine (58%) and to a lesser degree in the feces (35%). The pharmacokinetic/pharmacodynamic relationship for the parent compound and metabolites are unchanged in renal impairment. In healthy volunteers, a 30-μg/kg bolus followed by a 4-μg/kg/minute infusion provided extensive IPA by 2 minutes after the bolus dose, and 80% of subjects returned to near-baseline platelet activity within 60 minutes.[87] In a phase II study of patients undergoing elective PCI, a dose of 4 μg/kg/minute achieved greater than 95% IPA within 15 minutes of administration.[88]

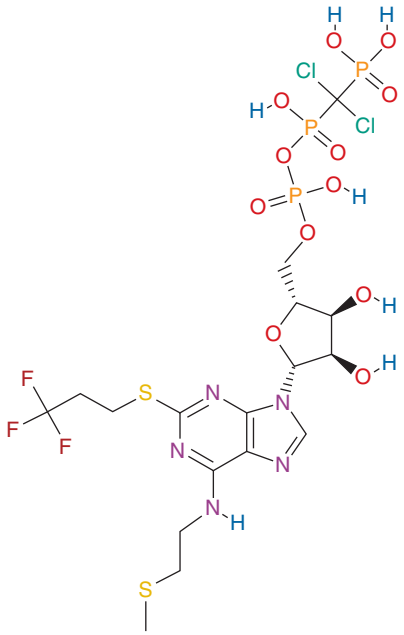


FIGURE 10-6 Chemical structure of cangrelor.

CLINICAL STUDIES. Three randomized clinical trials have assessed the safety and efficacy of cangrelor during urgent and nonurgent PCI (Table 10-3). The Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION)-PCI and CHAMPION-PLATFORM trials compared cangrelor with clopidogrel administered before or after PCI, respectively.[89,90] Cangrelor was not superior to clopidogrel in either trial with respect to the primary end point of death from any cause, MI, or ischemia-driven revascularization at 48 hours. The median times from hospital admission to PCI in CHAMPION-PCI and CHAMPION-PLATFORM were only 6.3 and 7.9 hours, respectively, which may have affected the ability to detect a periprocedural MI in those NSTE-ACS patients with elevated biomarkers at presentation; this is because increased biomarker levels may reflect the initial thrombotic event rather than being a result of the procedure. When the universal definition of MI was applied to a post hoc, pooled analysis of the CHAMPION-PCI and CHAMPION-PLATFORM trials, a significant reduction was reported in the primary end point of death, MI, and ischemia-driven revascularization with cangrelor (odds ratio [OR] 0.82; 95% CI, 0.68 to 0.99; $P = .037$).[91]

The CHAMPION-PHOENIX trial randomly assigned 11,145 patients with stable CAD or ACS undergoing PCI to receive either a bolus and infusion of cangrelor followed by transition to clopidogrel or a clopidogrel 300- or 600-mg LD at the time of PCI (see Table 10-3).[50] The primary end point was a composite of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours. The definition of periprocedural MI involved an assessment of patients' baseline biomarker status, and if abnormal, additional clinical evidence of ischemia. Stent thrombosis included both intraprocedural stent thrombosis and definite stent thrombosis according to the Academic Research Consortium (ARC) definition. An independent and blinded angiographic core laboratory evaluated all procedures to determine any procedural complications. Cangrelor significantly reduced the primary efficacy end point (4.7% vs 5.9%, OR 0.78; 95% CI, 0.66 to 0.93; $P = .005$), driven by reductions in stent thrombosis and MI. The treatment effect of cangrelor was consistent across the subgroups of stable CAD, NSTE-ACS, STEMI, and whether the patient received clopidogrel in a 300-mg or 600-mg LD. With respect to safety, the rates of the primary safety end point—GUSTO severe bleeding—were not significantly different among the groups.

TABLE 10-3 The Phase III Clinical Trials of Cangrelor

Trial	*N*	Prior Thienopyridine Exposure	Comparator	End Point	Duration	Outcome*
CHAMPION-PCI	8,877	Prior exposure allowed	Clopidogrel 600 mg within 30 min prior to PCI	Death, MI, or IDR	48 hr	OR 0.87 [0.71-1.07] $P = .17$
CHAMPION-PLATFORM	5,362	Naïve patients only	Clopidogrel 600 mg at end of PCI	Death, MI, or IDR	48 hr	OR 1.05 [0.88-1.24] $P = .59$
CHAMPION-PHOENIX	10,942	Naïve patients only	Clopidogrel 300 or 600 mg, dose and timing per operator	Death, MI (universal definition), IDR, or ST	48 hr	OR 0.78 [0.66-0.93] $P = .005$

Adapted from Walsh JA 3rd, Price MJ: Cangrelor for treatment of arterial thrombosis, *Expert Opin Pharmacother* 15:565-572, 2014.
*Figures in brackets represent 95% confidence intervals.
CHAMPION, Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition; *CI,* confidence interval; *IDR,* ischemia driven revascularization; *MI,* myocardial infarction; *OR,* odds ratio; *PCI,* percutaneous coronary intervention; *ST,* stent thrombosis.

ADVERSE EFFECTS. Pooled analysis of patient-level data from the CHAMPION trials[92] demonstrated that cangrelor bolus and infusion during PCI does not increase GUSTO severe or TIMI major bleeding rates, nor does it increase the need for any blood transfusion. However, cangrelor was associated with increased bleeding according to more sensitive indices such as Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) major bleeding (4.2% vs 2.8%, $P < .0001$) and led to a greater rate of less severe bleeding events (GUSTO mild and TIMI minor bleeding). The rate of ACUITY major bleeding, excluding hematomas greater than 5 cm, was significantly more frequent with cangrelor, but the absolute difference was small (1.3% vs. 1.0%, $P = .007$). Cangrelor was associated with a higher rate of dyspnea compared with placebo (1.1% vs. 0.4%, $P < .0001$), which led to drug cessation in 0.1% of cases.

In sum, cangrelor is a novel, intravenous (IV) ATP analogue that has been evaluated in several phase III studies involving over 25,000 patients undergoing PCI for stable CAD or ACS. The drug is well tolerated, although transient dyspnea may rarely occur. Cangrelor reduces ischemic events compared with conventional clopidogrel therapy in thienopyridine-naïve patients undergoing PCI, driven by reductions in MI according to the universal definition and in stent thrombosis, with rates similar to placebo of major bleeding and blood transfusions but at the cost of more minor bleeding events.[86] At present, cangrelor is not approved for use in the United States.

Thrombin Receptor Antagonists

Basic Principles

Thrombin exerts a multitude of effects on thrombosis, hemostasis, and inflammation. Generated at sites of vascular injury, it is the effector protease of the coagulation cascade, converting circulating fibrinogen to fibrin monomer, which polymerizes to form fibrin, the fibrous matrix of thrombus. Thrombin promotes edema by increasing the permeability of the vascular endothelium, induces vasoconstriction in the absence of the endothelium through its action on smooth muscle cells, and stimulates prostaglandin and cytokine production by endothelial cells. Thrombin is also the most potent agonist for platelet activation and provokes shape change, granule secretion, synthesis and release of TXA_2, mobilization of P-selectin and CD40 to the platelet surface, and activation of the GP IIb/IIIa receptor.[4] The cellular effects of thrombin are mediated primarily by the activation of protease-activated receptors (PARs). The two platelet thrombin receptors in humans are PAR-1 and PAR-4, but PAR-1 is more important, mediating platelet activation at low thrombin concentrations, whereas PAR-4 mediates platelet activation only at high thrombin concentrations. PARs are unique in that each receptor carries its own ligand that is active only after cleavage. Thrombin binds the N-terminus of the PAR-1 receptor with high affinity at an extracellular, hirudin-like site and then cleaves the receptor between residues Arg 41 and Ser 42; this unmasks a new N-terminus beginning with the sequence *SFLLRN* (serine, phenylalanine, leucine, leucine, arginine, asparagine). This N-terminus functions as a tethered ligand that docks intramolecularly with the body of the receptor and activates it. The inability of PAR-4 to activate platelets at low thrombin concentrations is likely caused by the absence of an extracellular hirudin-like domain. The PAR-1 receptor is an attractive candidate for targeted inhibition in patients with cardiovascular disease. PAR-mediated signaling appears to be a more important contributor to thrombosis compared with hemostasis. In addition, platelet PAR antagonism maintains the fibrin-generating and protein-C functions of thrombin and does not appear to interfere with other platelet-signaling pathways such as those mediated by collagen and ADP (Fig. 10-7). Therefore unlike other platelet receptor inhibitors, PAR-1 antagonists have been suggested to have a wider therapeutic window between ischemia reduction and bleeding risk. Although many PAR-1 antagonists have been developed and investigated in early phase clinical testing, only vorapaxar has been approved for clinical use.

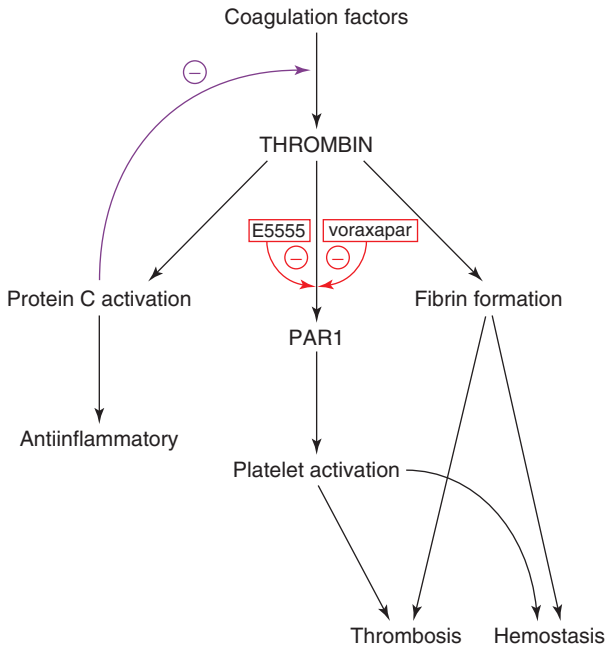


FIGURE 10-7 Rationale for protease-activated receptor (PAR) inhibition in the treatment of cardiovascular disease. Thrombin acts as a platelet agonist through its activation of the platelet PAR-1 and PAR-4 receptors; it is the main effector protease of the coagulation cascade and triggers fibrin formation, and within the environment of the normal endothelium, it activates protein C to terminate its own production. Fibrin(ogen) appears to be more important than thrombin-induced platelet activation for hemostasis. PAR-1 is the primary mediator of thrombin-induced platelet activation, and PAR-1 antagonists may have a wide therapeutic window for platelet-dependent processes—such as acute coronary syndrome and stent thrombosis—by leaving the fibrin generation and protein-C functions of thrombin intact. Vorapaxar and atopaxar are PAR-1 inhibitors currently under clinical investigation. (From Angiolillo DJ, Capodanno D, Goto S: Platelet thrombin receptor antagonism and atherothrombosis. *Eur Heart J* 31:17-28, 2010.)

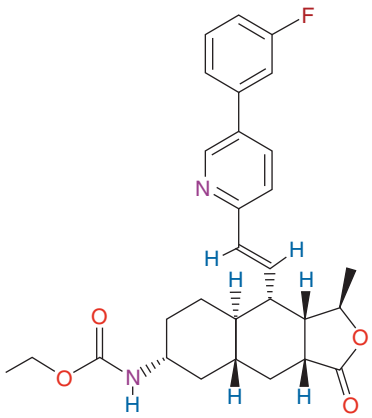


FIGURE 10-8 Chemical structure of vorapaxar.

Vorapaxar

Vorapaxar is a synthetic tricyclic 3-phenylpyridine analogue of himbacine (Fig. 10-8). It is a high-affinity, orally active, low-molecular-weight, nonpeptide competitive PAR-1 antagonist that is slowly eliminated, with a half-life of approximately 5 to 11 days. Recovery of

platelet function to 50% or more of baseline occurred at 4 weeks after treatment discontinuation in healthy volunteers.

After the promising findings from early phase clinical investigations, vorapaxar was tested in two large-scale phase III clinical trials: Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) and Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction (TRA 2P–TIMI 50).[93,94] After a safety review in January 2011, the Data and Safety Monitoring Board recommended halting the TRACER trial and discontinuing the drug in the ongoing TRA 2P trial in patients with prior stroke, in whom there was an observed excess of intracranial hemorrhage with vorapaxar.

TRACER tested the safety and efficacy of vorapaxar in combination with standard antiplatelet therapy in patients with NSTE-ACS. A total of 12,944 patients were randomly assigned to receive either vorapaxar (40-mg LD followed by 2.5 mg daily) or placebo in addition to standard antiplatelet therapy. Concomitant clopidogrel therapy was administered in 92%, and aspirin was administered in 99% of the enrolled patients.[93] The primary end point was a composite of death from cardiovascular causes, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization. In the patients assigned to vorapaxar, a nonsignificant decrease was found in the primary efficacy end point at 2 years (18.5% vs. 19.9%, HR 0.92; 95% CI, 0.85 to 1.01; $P = .07$) at the cost of a significant (35%) increase in the rate of GUSTO moderate or severe bleeding (7.2% vs. 5.2%, HR 1.35; 95% CI, 1.16 to 1.58; $P < .001$) and a threefold increase in the rate of intracranial bleeding (0.6% vs 0.2%, HR 3.39; 95% CI, 1.78 to 6.45; $P < .001$).

The TRA 2P–TIMI 50 trial evaluated the role of vorapaxar in the secondary prevention of cardiovascular events in patients with known atherothrombotic disease (i.e., history of prior MI, ischemic stroke, or PAD).[94] A total of 26,449 patients were randomly assigned to receive either vorapaxar 2.5 mg daily or placebo in addition to standard-of-care therapy, including aspirin and/or a thienopyridine. Concomitant aspirin was administered in 94% of enrolled patients, and clopidogrel was given in a majority of the patients with a qualifying diagnosis of MI. After a median follow-up of 30 months, vorapaxar significantly reduced the primary end point (a composite of death from cardiovascular causes, MI, or stroke) compared with placebo (HR 0.87; 95% CI, 0.80 to 0.94; $P < .001$), driven by a 17% reduction in the rate of MI. However, vorapaxar increased the rate of GUSTO moderate or severe bleeding (HR 1.66; 95% CI, 1.43 to 1.93; $P < .001$), as well as intracranial bleeding (HR 1.94; 95% CI, 1.39 to 2.70; $P < .001$). In the subgroup of patients with prior stroke, vorapaxar was associated with higher rates of major bleeding and intracranial hemorrhage without any improvement in ischemic outcomes. The benefit of vorapaxar over placebo in reducing the primary end point was enhanced in the large subgroup of patients with prior MI (HR 0.80; 95% CI, 0.72 to 0.89; $P < .0001$) and was consistent across timing and types of MI.[95] Despite an increase in total bleeding (HR 1.61; 95% CI, 1.31 to 1.97; $P < .0001$), intracranial and fatal bleeding were not significantly higher in the vorapaxar group among patients with prior MI, and an overall benefit was seen in net clinical outcome.

The FDA approved vorapaxar for clinical use in 2014. In specific, vorapaxar at a dose of 2.5 mg once daily is indicated for the reduction of thrombotic cardiovascular events in patients with a history of MI or with PAD, and it must be used in addition to antiplatelet therapy (aspirin and/or clopidogrel) as per the standard of care. Vorapaxar is contraindicated in patients with a history of stroke, TIA, or intracranial hemorrhage and in those with active pathologic bleeding.

Phosphodiesterase Inhibitors

Cilostazol

Cilostazol, a selective phosphodiesterase type 3 (PDE-3) inhibitor, increases cAMP levels in multiple cell lines—including platelets, endothelial cells, and smooth muscle cells—and results in both vasodilatory and antiplatelet effects. It was approved by the FDA in 1998 for the treatment of symptoms of intermittent claudication. Pharmacodynamic studies have shown that the addition of cilostazol to aspirin and clopidogrel (triple-antiplatelet therapy) results in greater ADP-induced platelet inhibition compared with aspirin and clopidogrel alone.[96] Adjunctive cilostazol therapy in addition to aspirin and clopidogrel has been associated with a reduced risk of stent thrombosis, restenosis, and MACEs without increased bleeding complications in patients undergoing PCI, including those treated with a DES.[97,98] These benefits have been more marked in complex settings such as in patients with diabetes mellitus and long lesions. The clinical studies of cilostazol in the PCI setting have been conducted primarily in Asia. The most common side effects of cilostazol include headache, tachycardia, palpitations, soft stools, and diarrhea, and these may lead to drug discontinuation in up to 15% of cases. Cilostazol should be avoided in patients with congestive heart failure of any severity, with or without preserved left ventricular systolic function, because of an increased mortality risk with PDE inhibitors.

Glycoprotein IIb/IIIa Inhibitors

The GP IIb/IIIa receptor is an integrin, a heterodimer consisting of noncovalently associated alpha and beta subunits, which mediate the final common pathway of platelet aggregation. In specific, the GP IIb/IIIa receptor consists of the αIIb and β_3 subunits. By competing with fibrinogen and vWF for GP IIb/IIIa binding, GP IIb/IIIa antagonists interfere with platelet cross-linking and platelet-derived thrombus formation (Fig. 10-9). Because the GP IIb/IIIa receptor represents the final common pathway leading to platelet aggregation, these agents are very effective in inhibiting platelets. Investigations of oral GP IIb/IIIa inhibitors have been stopped because of their lack of benefit and increased mortality in patients with ACS and in those undergoing PCI. The reasons for these negative outcomes remain elusive. Currently, only parenteral GP IIb/IIIa inhibitors are approved for clinical use and are recommended only in the setting of patients with ACS who are undergoing PCI. Although GP IIb/IIIa inhibitors have reduced MACEs (death, MI, and urgent revascularization) by 35% to 50% in patients undergoing PCI, their broad use has been limited because of their association with an increased risk of bleeding.[99]

Pharmacology

Three parenteral GP IIb/IIIa antagonists have been approved for clinical use: abciximab, eptifibatide, and tirofiban (Table 10-4).

Abicximab

Abciximab is a large chimeric monoclonal antibody with a high binding affinity that results in a prolonged pharmacologic effect. In particular, it is a monoclonal antibody that is a fragment antigen binding (Fab) fragment of a chimeric human–mouse genetic reconstruction of 7E3. The Fc portion of the antibody was removed to decrease immunogenicity, and the Fab portion was attached to the constant regions of a human immunoglobulin (Ig). Abciximab binding is specific for the β_3-subunit and explains its ability to bind other β_3-receptors such as vitronectin ($\alpha V\beta_3$). Unlike the small-molecule GP IIb/III inhibitors eptifibatide and tirofiban, abciximab interacts with the GP IIb/IIIa receptor at sites distinct from the ligand-binding RGD sequence site and exerts its inhibitory effect noncompetitively. Its plasma half-life is biphasic, with an initial half-life of less than 10 minutes and a second-phase half-life of approximately 30 minutes. However, because of its high affinity for the GP IIb/IIIa receptor, it has a biologic half-life of 12 to 24 hours; and because of its slow clearance from the body, it has a functional half-life of up to 7 days. Platelet-associated abciximab can be detected for more than 14 days after the infusion has been stopped. The recommended dose for abciximab is a 0.25 mg/kg bolus followed by an IV infusion with 0.125 µg/kg/minute for 12 hours. No renal adjustments are required.

Epitifibatide

Unlike abciximab, the small-molecule agents eptifibatide and tirofiban do not induce an immune response and have a lower affinity for the

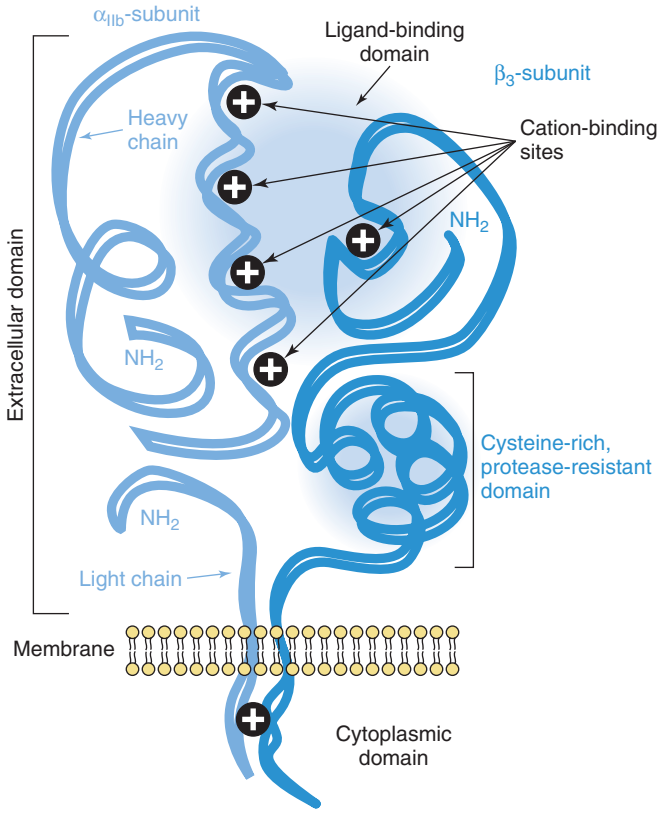


FIGURE 10-9 Structure of the glycoprotein (GP) IIb/IIIa receptor. The GP IIb/IIIa receptor is an integrin, a heterodimer consisting of noncovalently associated alpha and beta subunits that mediate the final common pathway of platelet aggregation. The GP IIb/IIIa receptor consists of the αIIb and β3 subunits. The α-subunit is a 136-kD molecule with light and heavy chains; the light chain contains a short cytoplasmic tail, a transmembrane region, and a short extracellular domain, whereas the heavy chain is entirely extracellular. The β-subunit is an 84.5-kD molecule with a short intracellular tail, a transmembrane region, and a large extracellular domain. Platelet activation leads to a conformational change in the GP IIb/IIIa receptor, which markedly increases its affinity for its ligands through its binding sites. On the GP IIb/IIIa receptor are two main binding sites: One recognizes the amino acid sequence arginine–glycine–aspartic acid (Arg-Gly-Asp, or *RGD*) found on multiple ligands (fibronectin, von Willebrand factor [vWF], and vitronectin) but most important on fibrinogen, the major GP IIb/IIIa ligand, in which the *RGD* sequence occurs twice. The other peptide sequence is the lysine–glutamine–alanine–glycine–aspartic acid–valine (Lys-Gln-Ala-Gly-Asp-Val [*KQAGDV*]) sequence, which is only located at the carboxyl terminus of the γ-chain of fibrinogen. (From Topol EJ, Byzova TV, Plow EF: Platelet GP IIB/IIIa blockers. *Lancet* 353:227-231, 1999.)

TABLE 10-4 Characteristics of the Glycoprotein IIb/IIIa Inhibitors

	Abciximab	Eptifibatide	Tirofiban
Molecule	Fab 7E3	Synthetic peptide	Nonpeptide mimetic
Molecular weight	~50,000	~800	~500
Stoichiometry (drug to GP IIb/IIIa)	~1.5 : 1	≫100 : 1	≫100 : 1
Binding	Noncompetitive	Competitive	Competitive
Half-life	Plasma: 10 to 15 hr Biologic: 12 to 24 hr	Plasma: 2 to 2.5 hr Biologic = plasma	Plasma: 2 to 2.5 hr Biologic = plasma
PCI dosing	Bolus: 0.25 mg/kg (10 to 60 min) Infusion: 0.125 μg/kg/min (12 hr)	Bolus: 180 μg/kg (10 min) + 180 μg/kg Infusion: 2 μg/kg/min (24 to 48 hr)	Bolus: 25 μg/kg (30 min) Infusion: 0.10 μg/kg/min (48 hr)
Renal adjustment	No	Bolus: 180 μg/kg Infusion: 1 μg/kg/min (24 to 48 hr)	Bolus: 12.5 μg/kg (30 min) Infusion: 0.10 μg/kg/min (48 hr)

Fab, Fragment antigen binding; *GP,* glycoprotein; *PCI,* percutaneous coronary intervention.

GP IIb/IIIa receptor. Eptifibatide is a reversibly interacting and highly selective heptapeptide with a rapid onset and a short plasma half-life of 2 to 2.5 hours. Its molecular design is based on barbourin, a member of the disintegrin family, which contains a novel Lys-Gly-Asp (KGD) sequence, making it highly specific for the GP IIb/IIIa receptor. In the setting of PCI, a double-bolus and infusion regimen is recommended (180 μg/kg, followed by a second, 180 μg/kg bolus, followed by 2 μg/kg/min for a minimum of 12 hr); peak plasma levels are established shortly after the bolus dose, and a slightly lower concentration is subsequently maintained throughout the infusion period. Because eptifibatide is mostly eliminated through renal mechanisms, a lower infusion dose (1 μg/kg/min) is recommended in patients with creatinine clearance less than 50 mL/minute. Recovery of platelet aggregation occurs within 4 hours of completion of the infusion.

Tirofiban

Tirofiban is a tyrosine-derived non–peptide inhibitor that mimics the *RGD* sequence and is highly specific for the GP IIb/IIIa receptor. Tirofiban is associated with a rapid onset and a short duration of action, with a plasma half-life of approximately 2 hours. Like eptifibatide, substantial recovery of platelet aggregation is present within 4 hours of completion of infusion. Tirofiban was previously administered as a 10 μg/kg bolus followed by infusion 0.15 μg/kg/minute for 18 to 24 hours. Several studies have documented that this treatment regimen achieves suboptimal levels of platelet inhibition for up to 4 to 6 hours, which likely accounted for its inferior clinical results in the PCI setting. For this reason, a high-dose bolus regimen (25 μg/kg) that achieves more optimal platelet inhibition has been tested and has shown antiplatelet efficacy comparable to the other GP IIb/IIIa inhibitors. The FDA has approved a high-bolus-dose tirofiban regimen, as well as a shorter duration of infusion, for patients undergoing PCI. Because tirofiban is mostly eliminated through renal mechanisms, dosage adjustment is required for patients with renal insufficiency.

Thrombocytopenia

Patients treated with GP IIb/IIIa inhibitors have a higher incidence of thrombocytopenia. Severe thrombocytopenia is more commonly associated with abciximab and requires immediate cessation of therapy. The mechanism of thrombocytopenia is unknown; however, regardless of its etiology, thrombocytopenia in patients undergoing PCI is associated with more ischemic events, bleeding complications, and transfusions. The platelet count typically falls within hours of GP IIb/IIIa administration. Readministration of abciximab, but not eptifibatide and tirofiban, is associated with a slightly increased risk of thrombocytopenia.

Pivotal Clinical Trials With Glycoprotein IIb/IIIa Inhibitors

Before the era of pretreatment with high loading doses of clopidogrel, the safety and efficacy of GP IIb/IIIa inhibition was tested in several clinical studies that included patients with ACS and those with stable CAD. The landmark trial that demonstrated the efficacy of GP IIb/IIIa inhibition in the PCI setting was the Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications (EPIC).[100] In this study, high-risk patients undergoing balloon angioplasty were randomized to abciximab bolus and infusion, abciximab bolus alone, or placebo. The group treated with abciximab bolus and infusion had a 35% lower rate of death, MI, or unplanned urgent revascularization at 30 days compared with the placebo group. No significant benefit with abciximab bolus alone was observed, suggesting that a shorter duration of platelet inhibition was insufficient to favorably affect clinical outcomes. Major bleeding complications occurred in a very high proportion of patients treated with abciximab. A series of procedural modifications—including front-wall arterial puncture, reducing arterial sheath size (from 8 to 6 Fr), reducing heparin dosing (target activated clotting time [ACT] of 200 to 250 seconds rather than >300 seconds), early sheath removal, and abandoning the use of routine venous sheaths—markedly reduced major bleeding complications (~1% to 1.5% in later trials). After the EPIC trial, the Evaluation of Percutaneous Transluminal Coronary Angioplasty (PTCA) to Improve Long-Term Outcome With Abciximab GP IIb/IIIa Blockade (EPILOG)[101] was conducted in patients undergoing balloon angioplasty who were at a lower risk than the patients in EPIC. In EPILOG, abciximab was given with lower doses of weight-adjusted heparin and with weight-adjusted infusions of abciximab. This study was stopped prematurely because of a significant reduction in the incidence of death or MI in patients treated with abciximab and in the setting of acceptable bleeding rates. Similar results were reported in the Evaluation of Platelet GP IIb/IIIa Inhibition in Stenting (EPISTENT),[102] which was the first randomized trial to examine the use of GP IIb/IIIa inhibitors—in this case, abciximab—among patients undergoing stent placement. The Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT)[103] trial conducted in patients undergoing coronary stenting using eptifibatide was also terminated early because of the superior efficacy of eptifibatide. Major bleeding was rare but occurred more frequently in eptifibatide-treated patients compared with placebo-treated patients. On the basis of these trials, GP IIb/IIIa inhibitors became a cornerstone in the treatment of patients undergoing PCI because of their ability to improve short- and long-term outcomes, mostly by reducing the occurrence of periprocedural MI. Subsequently, however, it was shown that a GP IIb/IIIa inhibitor may no longer benefit patients if they had been pretreated with high-dose clopidogrel, particularly those with stable CAD or in the absence of elevated cardiac enzymes. The first Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment (ISAR-REACT) trial[104] showed that in 2159 low- to intermediate-risk patients undergoing elective PCI, all of whom had been pretreated for at least 2 hours with a 600-mg loading dose of clopidogrel, no benefit of abciximab therapy was found, compared with placebo, with respect to the incidence of death, MI, and urgent target-vessel revascularization at 30 days (P = .8). The findings were similar in the Intracoronary Stenting and Antithrombotic Regimen—Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics? (ISAR-SWEET) trial,[105] the first dedicated randomized trial to evaluate GP IIb/IIIa blockade in patients with diabetes scheduled for elective PCI. Overall, these studies suggest that GP IIb/IIIa inhibitors offer no clinical benefit in low- to intermediate-risk patients scheduled for PCI, including those with diabetes, if they have been pretreated with clopidogrel. The ISAR-REACT 2 trial[106] assessed the incremental benefit of GP IIb/IIIa inhibitors for patients with ACS in the current era of treatment with a high loading dose of clopidogrel before PCI. This trial randomized 2022 patients with ACS pretreated with clopidogrel 600 mg for at least 2 hours to either abciximab or placebo in the catheterization laboratory at the time of PCI. Abciximab significantly reduced the incidence of the primary end point of death, MI, or target-vessel revascularization at 30 days, but the benefit of abciximab treatment was limited only to those patients who presented with elevated troponin. Overall, these findings, and those from retrospective analyses of other studies, suggest that in the modern era of interventional cardiology using high clopidogrel dosing regimens, GP IIb/IIIa inhibition should be reserved only for high-risk patients with ACS and elevated cardiac biomarkers.

Timing of Glycoprotein IIb/IIIa Administration

Two different timing strategies for the administration of GP IIb/IIIa inhibitors have been used in the large, randomized GP IIb/IIIa trials: before angiography (*upstream treatment*) or in the cardiac catheterization laboratory in patients about to undergo PCI (*provisional treatment*). These two strategies were compared in the Early Glycoprotein IIb/IIIa Inhibition in Non–ST Segment Elevation Acute Coronary Syndrome (EARLY-ACS) trial,[107] which randomized 9492 invasively managed patients with NSTE-ACS to either routine upstream eptifibatide or placebo infusion and provisional eptifibatide after angiography. No differences were found between the groups in the primary end point, and patients in the early eptifibatide group had significantly higher rates of bleeding and transfusion. These findings do not support the routine use of upstream GP IIb/IIIa inhibition compared with ad hoc GP IIb/IIIa inhibition in patients with ACS undergoing PCI.

Glycoprotein IIb/IIIa Inhibitors in Primary Percutaneous Coronary Intervention

The use of GP IIb/IIIa inhibitors, in particular abciximab, in STEMI patients undergoing primary PCI is supported by a meta-analysis of 11 randomized trials that involved a total 27,115 patients. In this meta-analysis, the administration of abciximab was associated with a significant reduction in the rate of reinfarction, as well as mortality rates, at 30 days.[108] However, most of the studies included in the meta-analysis were conducted in patients who had not been pretreated with clopidogrel. In the Third Bavarian Reperfusion Alternatives Evaluation (BRAVE 3), 800 patients with acute STEMI within 24 hours from symptom onset, all of whom were treated with clopidogrel 600 mg, were randomly assigned to receive either upstream abciximab or placebo.[109] Abciximab was not associated with a reduction in the primary end point, infarct size, or ischemic end points at 30 days, which argued against the routine use of upstream abciximab in clopidogrel-pretreated patients undergoing primary PCI. Strategies of facilitated PCI have been developed on the basis of the premise that time to reperfusion is a critical determinant of outcome. A series of small pilot investigations with GP IIb/IIIa inhibitors that measured surrogate markers of ischemic benefit, such as angiographic flow or ST-segment resolution, showed promising results. This series set the basis for larger studies to clarify the safety and efficacy of different regimens of facilitated PCI using GP IIb/IIIa inhibitors alone or in combination with a reduced-dose fibrinolytic. In the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial,[110] 2452 patients with STEMI who presented within 6 hours after symptom onset were randomized to receive PCI facilitated with early abciximab and half-dose reteplase (*combination facilitated*), PCI with early abciximab alone (*abciximab facilitated*), or primary PCI with abciximab at the time of the procedure. The primary end point—composite of death from all causes, ventricular fibrillation occurring more than 48 hours after randomization, cardiogenic shock, and congestive heart failure during the first 90 days after randomization—occurred in 9.8%, 10.5%, and 10.7% of the patients in the combination-facilitated, abciximab-facilitated, and primary PCI groups, respectively (P = .55) without significant differences in mortality. These results do not support the use of a facilitated pharmacologic strategy for reperfusion, with either abciximab alone or abciximab plus reduced-dose reteplase, in anticipation of urgent PCI for patients who present early with STEMI.[110]

Although the GP IIb/IIIa inhibitors are approved for IV use, several studies have assessed the efficacy of intracoronary (IC) administration

in patients with STEMI undergoing primary PCI. A meta-analysis of small-sample studies[110a] suggests a benefit of IC use of GP IIb/IIIa inhibitors; however, this finding was not supported by the large Abciximab Intracoronary Versus Intravenous Drug Application in ST-Elevation Myocardial Infarction (AIDA-STEMI) trial.[111] In this trial, a total of 2065 patients with STEMI undergoing primary PCI were randomly assigned to an IC or IV abciximab bolus during the PCI procedure, followed by an IV infusion. No difference was found between groups in the primary end point of all-cause mortality, recurrent infarction, or new congestive heart failure at 90 days, nor were there significant differences in the secondary end points of early ST-segment resolution, TIMI flow grade, or enzymatic infarct size. In the Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction (INFUSE-AMI)[112] trial, IC abciximab delivered through a specialized drug-delivery catheter reduced infarct size compared with no abciximab in 452 patients with large, anterior MIs undergoing primary PCI with bivalirudin anticoagulation.

Triple-Antithrombotic Therapy: Considerations for the Patient With Atrial Fibrillation Undergoing Percutaneous Coronary Infarction

Atrial fibrillation (AF) represents the most common cardiac arrhythmia, and chronic oral anticoagulation (OAC) is strongly recommended to prevent cerebrovascular events among patients with high thromboembolic risk.[113] Notably, because the prevalence of both AF and CAD increase with age, these conditions frequently coexist: nearly 30% of patients with AF have concomitant CAD. Management of these patients has become an emerging clinical problem with the ever-growing elderly population. In particular, many of these patients may undergo PCI and may therefore require concomitant use of dual-antiplatelet therapy (DAPT), including aspirin and a $P2Y_{12}$ receptor inhibitor in addition to OAC, also known as *triple-antithrombotic therapy* (TAT). However, the use of TAT comes at the expense of an increased risk of bleeding complications. Data are limited on the optimal antithrombotic treatment regimen for these patients, and the conundrum of the optimal antithrombotic treatment regimen for patients with AF undergoing PCI is further exacerbated by the introduction into clinical practice of the novel oral anticoagulants (NOACs). Although the NOACs have shown favorable safety and efficacy profiles in patients with AF, data are limited on how to combine these agents with standard antiplatelet treatment regimens. To date most information on clinical outcomes derive from studies using vitamin K antagonists. Guidelines recommend treating patients with low-dose aspirin (81 mg) and clopidogrel (75 mg) and maintaining an international normalized ratio (INR) in the lower therapeutic range (2.0 to 2.5) to minimize bleeding complications. The novel $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor are not recommended in this setting because this would increase the risk of bleeding complications, and they have not been studied in the setting of concomitant anticoagulation. In the Use of Clopidogrel With or Without Aspirin in Patients Taking Oral Anticoagulant Therapy and Undergoing Percutaneous Coronary Intervention (WOEST) study,[114] patients undergoing PCI were randomly assigned to triple therapy or clopidogrel monotherapy and a vitamin K antagonist. The dual-therapy regimen was associated with significantly lower bleeding events and improved ischemic outcomes compared with the triple-therapy regimen. However, few patients in this trial were treated for complex multivessel disease, and larger studies are warranted to support these findings. Several large-scale randomized clinical trials are planned or are ongoing and include the use of NOACs to better define the optimal antithrombotic treatment regimen in AF patients undergoing PCI. Expert consensus documents have been developed to provide guidance to physicians on how to best manage these patients; these are summarized in Table 10-5.[115,116] In summary, the management of AF patients undergoing PCI should take into consideration the thrombotic and bleeding risks of an individual patient.

Platelet Function Testing

The pharmacodynamic effect of an antiplatelet agent can be defined by the *response* before and after exposure (i.e., the IPA) or by the absolute level of platelet reactivity on therapy, termed *on-treatment reactivity* (Table 10-6). On-treatment reactivity has been proposed as a better measure of thrombotic risk because of the variability in platelet reactivity before treatment.[29] The results of several ex vivo platelet function tests have been associated with clinical outcomes after PCI in clopidogrel-treated patients (Table 10-7). Diagnostic cutoffs to identify at-risk patients using the various tests have been proposed using receiver-operator characteristic (ROC) curve analysis.[29] In a large, multicenter, observational study of more than 8500 patients undergoing PCI with drug-eluting stents, patients with high on-treatment platelet reactivity despite clopidogrel therapy had a significantly greater 1-year risk of the primary end point of definite or probable stent thrombosis (adjusted HR 2.49; 95% CI, 1.43 to 4.1) and the secondary end point of MI (HR 1.42; 95% CI, 1.09 to 1.86), whereas the adjusted risk of clinically relevant bleeding was significantly decreased (HR 0.73; 95% CI, 0.61 to 0.89).[117]

The results of two small randomized trials suggested that intensified antiplatelet therapy with additional clopidogrel or adjunctive GP IIb/IIIa receptor antagonist therapy in patients with high on-clopidogrel reactivity, may reduce periprocedural ischemic events.[118,119] Two larger randomized trials have tested the hypothesis that adjustment of antiplatelet therapy around the time of PCI based on platelet function testing may reduce ischemic events.

GRAVITAS

The Gauging Responsiveness With a VerifyNow Assay—Impact on Thrombosis and Safety (GRAVITAS) trial was a multicenter, double-blinded, active control trial that randomly assigned 2214 patients with high on-treatment reactivity after PCI to either high-dose clopidogrel (additional 600-mg LD followed by a 150-mg daily maintenance dose [MD]) or standard-dose clopidogrel (75-mg MD).[120] Few patients enrolled in the trial had non–ST-elevation MI (NSTEMI) or STEMI. At 6 months, the rate of death from cardiovascular causes, MI, or stent thrombosis did not differ between the groups (2.3% vs. 2.3%, HR 1.01; 95% CI, 0.58 to 1.76; $P = .97$). High-dose therapy was not associated with increased GUSTO severe or moderate bleeding compared with standard-dose therapy (1.4% vs. 2.3%, HR 0.59; 95% CI, 0.31 to 1.11; $P = .10$). Lower-than-expected event rates reduced the power of the study to detect differences in outcomes between the study groups. Therefore a strategy of a clopidogrel 150-mg MD did not appear to provide therapeutic benefit in patients noted to have high on-treatment reactivity to standard dosing after PCI, particularly in patients with stable angina or ischemia. On pharmacodynamic analysis, the high-dose regimen provided only a 22% absolute reduction in the rate of high on-treatment reactivity. In a post hoc analysis, those patients who achieved lower levels of on-treatment reactivity after PCI or over follow-up ($P2Y_{12}$ reaction units [PRUs] <208) had a significantly lower adjusted risk of cardiovascular events.[121] Only a minority of patients who received a clopidogrel 150-mg MD achieved this threshold for reactivity, suggesting that an insufficient antiplatelet effect of the study intervention may in part have contributed to the lack of clinical efficacy observed in the overall trial.[122]

ARCTIC

The Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption Versus Continuation One Year After Stenting (ARCTIC) trial[123] was a randomized, multicenter, open-label trial that tested whether the incorporation of platelet function testing into antiplatelet therapy decision making would be superior to conventional management without platelet function testing in reducing ischemic events in patients undergoing PCI. Patients in the platelet function testing arm were assessed for both clopidogrel and aspirin responsiveness prior to PCI and again 2 to 4 weeks after the procedure. The choice of

TABLE 10-5 Practical Considerations on Antithrombotic Management for Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

Categories	Considerations
Periprocedural management	1. Avoid unnecessary PCI. 2. Consider radial access to reduce periprocedural bleeding. 3. Select the appropriate stent. a) BMS is preferred to first-generation DES (sirolimus- or paclitaxel-eluting stents). b) Second-generation DES (zotarolimus- or everolimus-eluting stents) is preferred to first-generation DES. 4. Intraprocedural anticoagulation a) In patient with high thromboembolic risk, temporary discontinuation of warfarin followed by bridging therapy (UFH, LMWH, or direct thrombin inhibitor) is recommended. b) Uninterrupted OAC therapy could replace heparin bridging, except in those undergoing coronary procedures with a high risk of perforation (e.g., chronic total occlusion). c) Consider bivalirudin in patients at high risk of bleeding. d) Additional UFH on top of chronic OAC treatment with therapeutic INR levels (2 to 3) is not necessary and can trigger bleeding complications. e) Try to avoid glycoprotein IIb/IIIa inhibitors.
GENERAL PRINCIPLES IN SELECTING ANTITHROMBOTIC AGENTS	
Antiplatelet agents	1. Low-dose aspirin (<100 mg/day) and clopidogrel (75 mg/day) are the standard of care. 2. Prasugrel or ticagrelor are not recommended on top of OAC.
Anticoagulants	1. OAC with warfarin (targeting an INR between 2.0 and 2.5) remains the standard of care. 2. NOACs are not recommended.
LONG-TERM ANTITHROMBOTIC STRATEGIES	
In the Setting of Elective PCI	
North American perspectives	1. Low risk of both stent thrombosis and bleeding: TAT 1 or more months after placement of BMS or 6 or more months after placement of DES, followed by OAC plus single antiplatelet agent (aspirin or clopidogrel) up to 12 months, and then OAC only thereafter. 2. High risk of stent thrombosis, low risk of bleeding: TAT 6 or more months after placement of BMS or 12 months after placement of DES, followed by OAC plus single antiplatelet agent (aspirin or clopidogrel), and then OAC only thereafter. 3. High risk of bleeding (regardless of the risk of stent thrombosis): TAT 1 or more months after placement of BMS, followed by OAC plus single antiplatelet agent up to 12 months, and then OAC only thereafter.
European perspectives	1. Patients with low/intermediate risk of bleeding (HAS-BLED <3): BMS–TAT (low-intensity OAC with INR 2.0 to 2.5, low-dose aspirin, and clopidogrel 75 mg qd) for more than 1 month with gastric protection, followed by OAC (INR 2.0 to 3.0) thereafter. 2. Patients with high risk of bleeding (HAS-BLED ≥3): BMS–TAT (same as 1) for 2 to 4 weeks, followed by OAC thereafter. 3. Patients receiving DES: Duration of TAT (aspirin, OAC [INR 2.0 to 2.5] and clopidogrel) according to stent types (paclitaxel-eluting stents ≥6 mo, limus-eluting stents ≥3 mo), followed by OAC and aspirin up to 12 months, then OAC (INR 2.0 to 3.0) thereafter.
In the Setting of ACS	
Common guidelines	12 months of DAPT after an ACS event irrespective of treatment (either medical or PCI with BMS or DES).
North American perspectives	Patients with high risk of thrombotic events, low risk of bleeding: DAPT for 12 months.
European perspectives	1. Patients with low or intermediate bleeding risk: TAT for 6 or more months, followed by DAT with low-intensity OAC (INR 2.0 to 2.5) and single-antiplatelet therapy (clopidogrel or low-dose aspirin) up to 12 months, and then OAC thereafter. 2. Patients with a high risk of bleeding: TAT for 4 weeks, drop aspirin (or clopidogrel) for up to 12 months, and continue OAC (INR 2.0 to 3.0) thereafter. 3. Patients undergoing PCI: BMS is strongly recommended; GP IIb/IIIa inhibitors need to be reserved for bail-out in those with INR greater than 2.0.
Gastrointestinal protection	Concomitant use of a PPI on top of OAC is recommended (except for those who have CYP2C19 interaction with clopidogrel, such as with omeprazole and esomeprazole).
Management of bleeding	1. Treatment for the patient with a high INR should be focused on reversing the anticoagulation effect (stop OAC immediately and administer vitamin K intravenously and fresh-frozen plasma or prothrombin complex concentrate). 2. No reversing agents are used for $P2Y_{12}$ receptor inhibitors (clopidogrel, prasugrel, or ticagrelor). 3. Reversing agent (antidote) for NOACs are under investigation. 4. Use platelet concentrate (no proven data).

Adapted from Faxon DP, Eikelboom JW, Berger PB, et al: Antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting: a North American perspective: executive summary. *Circ Cardiovasc Interv* 4(5):522-534, 2011; and Lip GY, Huber K, Andreotti F, et al: Antithrombotic management of atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing coronary stenting: executive summary—a Consensus Document of the European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 31(11):1311-1318, 2010.

ACS, Acute coronary syndrome; *BMS,* bare-metal stent; *CYP2C19,* cytochrome P450 2C19; *DAPT,* dual-antiplatelet therapy; *DAT,* dual-antithrombotic therapy; *DES,* drug-eluting stent; *GP,* glycoprotein; *INR,* international normalized ratio; *HAS-BLED* (score), hypertension, abnormal liver/renal function, stroke history, bleeding predisposition, labile INRs, elderly (age >65 yr), drugs/alcohol usage; *LMWH,* low-molecular-weight heparin; *NOAC,* novel oral anticoagulant; *OAC,* oral anticoagulation; *PCI,* percutaneous coronary intervention; *PPI,* proton pump inhibitor; *UFH,* unfractionated heparin; *TAT,* triple-antithrombotic therapy.

antiplatelet therapy in either the platelet function testing or conventional management arms was according to operator discretion, although general recommendations were provided for adjustment in the platelet function testing group. Approximately three-quarters of the enrolled patients presented with stable angina or ischemia. Among the patients with high on-treatment reactivity in whom the operators chose to adjust therapy, the most frequent interventions were administration of GP IIb/IIIa inhibitors at the time of the procedure and a clopidogrel 150-mg MD after the procedure. At 1-year follow-up, the rate of the primary end point—death, MI, stroke or TIA, urgent

TABLE 10-6 Terminology Commonly Used to Describe the Antiplatelet Effect of $P2Y_{12}$ Inhibitors

Term	Sampling Requirements	Definition
High on-treatment reactivity High residual platelet reactivity High posttreatment reactivity	Single blood sample after $P2Y_{12}$ inhibitor exposure or on maintenance therapy	Platelet reactivity while on $P2Y_{12}$ inhibitor therapy (e.g., percent aggregation, PRU, PRI percent, AU·min) above a particular threshold
Nonresponsiveness	Blood sample before and after $P2Y_{12}$ inhibitor exposure	Change in platelet reactivity before and after $P2Y_{12}$ inhibitor exposure below a particular threshold

AU, Aggregation unit; *PRI,* platelet reactivity index; *PRU,* $P2Y_{12}$ reaction units.

TABLE 10-7 Methods to Measure the Effect of $P2Y_{12}$ Antagonists on Platelet Function

Assay	Methodology	Units of Measurement/Expression of Results
LTA	Transmission of light through platelet-rich sample compared with platelet-poor sample after exposure to ADP	• *Maximal aggregation* (%)—Measurement of on-treatment reactivity • *Final (late) aggregation* (%)—Aggregation 5 to 6 minutes after induction of ADP; measurement of on-treatment reactivity • *IPA* (%)—Relative change in aggregation before and after exposure • Δ *Platelet aggregation* (%)—Absolute change in aggregation before and after exposure)
VASP	Phosphorylation status of VASP measured by flow cytometry after incubation with ADP, PGE_1, or both	• *Platelet reactivity index* (%)—ratio of PGE_1-stimulated VASP phosphorylation to ADP– + PGE_1–stimulated VASP phosphorylation (i.e., a measure of the reduction of phosphorylated VASP induced by ADP)
VerifyNow	Agglutination of fibrinogen-coated beads by platelets in the presence of ADP (20 mmol) and PGE_1	• *$P2Y_{12}$ reaction units (PRUs)*—measurement of on-treatment reactivity • *%*—One minus the ratio of ADP-induced aggregation with iso-TRAP–induced aggregation; surrogate measure of IPA
Multiplate analyzer (MEA)	Change in electrical conductance between a pair of electrodes as platelets adhere after exposure to ADP	• *AU*—Measurement of on-treatment reactivity
Plateletworks	Ratio of single platelet counts by cell counter after stimulation with ADP versus baseline (no ADP)	• *%*—Measurement of on-treatment reactivity

Each test listed has been associated with clinical outcomes in clopidogrel-treated patients in at least one study.
ADP, Adenosine diphosphate; *AU,* aggregation unit; *IPA,* inhibition of platelet aggregation; *LTA,* light transmittance aggregometry; *MEA,* multiple electrode aggregometry; *PRI,* platelet reactivity index; *TRAP,* thrombin-receptor activating peptide; *VASP,* vasodilator-stimulated phosphoprotein phosphorylation analysis.

coronary revascularization, or stent thrombosis—did not differ between treatment groups (34.6% vs. 31.1%, HR 1.13; 95% CI, 0.98 to 1.29), driven by troponin-defined periprocedural MI (single troponin 3× the upper limit of normal [ULN] measured 6 hours after PCI). The rates of stent thrombosis were low and were similar between groups (0.7% vs. 1.0%, HR 1.34; 95% CI, 0.56 to 3.18).

Synthesizing the Randomized Trials Incorporating Platelet Function Testing

Several tentative conclusions can be drawn from these trials. First, a clopidogrel 150-mg daily MD does not provide a sufficient pharmacodynamic effect in many patients with high on-treatment platelet reactivity after PCI.[124] Second, although high on-treatment reactivity is associated with cardiovascular outcomes after nonurgent PCI,[117] the absolute rate of postdischarge events is low irrespective of on-treatment reactivity, and routine intensification of antiplatelet therapy according to platelet function does not provide clinical benefit in this patient population. Third, patients who present with ACS—who have greater rates of recurrent thrombotic events—were not well represented in either GRAVITAS or ARCTIC, and the role of platelet function testing in this patient population has not been fully addressed.[125]

CONCLUSION

Dual-antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor antagonist improves outcomes in patients undergoing coronary stent implantation. There is now an ever-increasing array of options for platelet inhibitor therapy during and after PCI, including newer thienopyridines, oral and IV nonthienopyridines, and triple therapy with oral PAR-1 antagonists, cilostazol, or IV GP IIb/IIIa inhibitors. Genotyping and platelet function testing may provide further insight into the optimal treatment strategy for PCI patients. A comprehensive understanding of the mechanistic underpinnings and trial data for each of these agents and approaches is essential for best clinical practice.

REFERENCES

1. Davi G, Patrono C: Platelet activation and atherothrombosis. *N Engl J Med* 357:2482–2494, 2007.
2. Varga-Szabo D, Pleines I, Nieswandt B: Cell adhesion mechanisms in platelets. *Arterioscler Thromb Vasc Biol* 28:403–412, 2008.
3. Dorsam RT, Kunapuli SP: Central role of the P2Y12 receptor in platelet activation. *J Clin Invest* 113:340–345, 2004.
4. Angiolillo DJ, Capodanno D, Goto S: Platelet thrombin receptor antagonism and atherothrombosis. *Eur Heart J* 31(1):17–28, 2010.
5. Angiolillo DJ, Ueno M, Goto S: Basic principles of platelet biology and clinical implications. *Circ J* 74:597–607, 2010.
6. Gurbel PA, Bliden KP, DiChiara J, et al: Evaluation of dose-related effects of aspirin on platelet function: results from the Aspirin-Induced Platelet Effect (ASPECT) study. *Circulation* 115:3156–3164, 2007.
7. King SB, 3rd, Smith SC, Jr, Hirshfeld JW, Jr, et al: 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association task force on practice guidelines: 2007 writing group to review new evidence and update the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention, writing on behalf of the 2005 writing committee. *Circulation* 117:261–295, 2008.
8. Jolly SS, Pogue J, Haladyn K, et al: Effects of aspirin dose on ischaemic events and bleeding after percutaneous coronary intervention: insights from the PCI-cure study. *Eur Heart J* 30:900–907, 2009.
9. Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Trial Investigators: Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation* 108(14):1682–1687, 2003.
10. CURRENT-OASIS 7 Investigators: Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med* 363(10):930–942, 2010.
11. Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to revise the 2002 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction): Developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: Endorsed by the American Association of Cardiovascular and Pulmonary

Rehabilitation and the Society for Academic Emergency Medicine. *Circulation* 116:e148–e304, 2007.
12. Price MJ, Teirstein PS: Dynamics of platelet functional recovery following a clopidogrel loading dose in healthy volunteers. *Am J Cardiol* 102:790–795, 2008.
13. Price MJ, Walder JS, Baker BA, et al: Recovery of platelet function after discontinuation of prasugrel or clopidogrel maintenance dosing in aspirin-treated patients with stable coronary disease: the recovery trial. *J Am Coll Cardiol* 59:2338–2343, 2012.
14. Leon MB, Baim DS, Popma JJ, et al: A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med* 339:1665–1671, 1998.
15. Bouman HJ, Schömig E, van Werkum JW, et al: Paraoxonase-1 is a major determinant of clopidogrel efficacy. *Nat Med* 17(1): 110–116, 2010.
16. GIFT Investigators: Influence of genetic polymorphisms on the effect of high- and standard-dose clopidogrel after percutaneous coronary intervention: the GIFT (Genotype Information and Functional Testing) study. *J Am Coll Cardiol* 59:1928–1937, 2012.
17. Steinhubl SR, Berger PB, Mann JT, 3rd, et al: Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 288:2411–2420, 2002.
18. Steinhubl SR, Berger PB, Brennan DM, et al: Optimal timing for the initiation of pre-treatment with 300 mg clopidogrel before percutaneous coronary intervention. *J Am Coll Cardiol* 47:939–943, 2006.
19. Montalescot G, Sideris G, Meuleman C, et al: A randomized comparison of high clopidogrel loading doses in patients with non-ST-elevation acute coronary syndromes: the ALBION (Assessment of the best Loading dose of clopidogrel to Blunt platelet activation, Inflammation, and Ongoing Necrosis) trial. *J Am Coll Cardiol* 48:931–938, 2006.
20. von Beckerath N, Taubert D, Pogatsa-Murray G, et al: Absorption, metabolization, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel: results of the ISAR-choice (Intracoronary Stenting and Antithrombotic Regimen: Choose between 3 high oral doses for immediate clopidogrel effect) trial. *Circulation* 112:2946–2950, 2005.
21. Price MJ, Coleman JL, Steinhubl SR, et al: Onset and offset of platelet inhibition after high-dose clopidogrel loading and standard daily therapy measured by a point-of-care assay in healthy volunteers. *Am J Cardiol* 98:681–684, 2006.
22. Aleil B, Jacquemin L, De Poli F, et al: Clopidogrel 150 mg/day to overcome low responsiveness in patients undergoing elective percutaneous coronary intervention. *JACC Cardiovasc Interv* 1(6):631–638, 2008.
23. Angiolillo DJ, Bernardo E, Palazuelos J, et al: Functional impact of high clopidogrel maintenance dosing in patients undergoing elective percutaneous coronary interventions. Results of a randomized study. *Thromb Haemost* 99:161–168, 2008.
24. Gurbel PA, Bliden KP, Hiatt BL, et al: Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* 107:2908–2913, 2003.
25. Hochholzer W, Trenk D, Fromm MF, et al: Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. *J Am Coll Cardiol* 55:2427–2434, 2010.
26. Siller-Matula JM, Lang I, Christ G, et al: Calcium-channel blockers reduce the antiplatelet effect of clopidogrel. *J Am Coll Cardiol* 52:1557–1563, 2008.
27. Price MJ, Nayak KR, Barker CM, et al: Predictors of heightened platelet reactivity despite dual-antiplatelet therapy in patients undergoing percutaneous coronary intervention. *Am J Cardiol* 103:1339–1343, 2009.
28. Shuldiner AR, O'Connell JR, Bliden KP, et al: Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA* 302:849–857, 2009.
29. Bonello L, Tantry US, Marcucci R, et al, Working Group on High On-Treatment Platelet Reactivity: Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. *J Am Coll Cardiol* 56:919–933, 2010.
30. Stone GW, Witzenbichler B, Weisz G, et al: Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet* 382:614–623, 2013.
31. Yusuf S, Zhao F, Mehta SR, et al: Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 345:494–502, 2001.
32. Sabatine MS, Cannon CP, Gibson CM, et al: Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 352:1179–1189, 2005.
33. Sabatine MS, Cannon CP, Gibson CM, et al: Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA* 294:1224–1232, 2005.
34. Kandzari DE, Berger PB, Kastrati A, et al: Influence of treatment duration with a 600-mg dose of clopidogrel before percutaneous coronary revascularization. *J Am Coll Cardiol* 44:2133–2136, 2004.
35. PRAGUE-8 Trial Investigators: Clopidogrel pre-treatment in stable angina: for all patients >6 h before elective coronary angiography or only for angiographically selected patients a few minutes before PCI? A randomized multicentre trial PRAGUE-8. *Eur Heart J* 29:1495–1503, 2008.
36. Di Sciascio G, Patti G, Pasceri V, et al: Effectiveness of in-laboratory high-dose clopidogrel loading versus routine preload in patients undergoing percutaneous coronary intervention: results of the ARMYDA-5 PRELOAD (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) randomized trial. *J Am Coll Cardiol* 56:550–557, 2010.
37. von Beckerath N, Kastrati A, Wieczorek A, et al: A double-blind, randomized study on platelet aggregation in patients treated with a daily dose of 150 or 75 mg of clopidogrel for 30 days. *Eur Heart J* 28:1814–1819, 2007.
38. Mehta SR, Bassand JP, Chrolavicius S, et al: Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med* 363:930–942, 2010.
39. Mehta SR, Tanguay JF, Eikelboom JW, et al: Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet* 376:1233–1243, 2010.
40. Price MJ, Berger PB, Teirstein PS, et al: Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 305:1097–1105, 2011.
41. Mehta SR, Yusuf S, Peters RJ, et al: Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 358:527–533, 2001.
42. Bhatt DL, Fox KA, Hacke W, et al: Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 354:1706–1717, 2006.
43. Bhatt DL, Flather MD, Hacke W, et al: Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol* 49:1982–1988, 2007.
44. Park SJ, Park DW, Kim YH, et al: Duration of dual antiplatelet therapy after implantation of drug-eluting stents. *N Engl J Med* 362:1374–1382, 2010.
45. Kushner FG, Hand M, Smith SC, Jr, et al: 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation* 120:2271–2306, 2009.
46. DAPT Study Investigators: Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 371(23): 2155–2166, 2014.
47. Elmariah S, Mauri L, Doros G, et al: Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis. *Lancet* 385(9970):792–798, 2015. doi: 10.1016/S0140-6736(14)62052-3.
48. Mega JL, Close SL, Wiviott SD, et al: Cytochrome P450 polymorphisms and response to clopidogrel. *N Engl J Med* 360:354–362, 2009.
49. Pare G, Mehta SR, Yusuf S, et al: Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. *N Engl J Med* 363:1704–1714, 2010.
50. Holmes DR, Jr, Dehmer GJ, Kaul S, et al: ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation task force on clinical expert consensus documents and the American Heart Association endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 56:321–341, 2010.
51. Dansette PM, Rosi J, Bertho G, Mansuy D: Cytochromes P450 catalyze both steps of the major pathway of clopidogrel bioactivation, whereas paraoxonase catalyzes the formation of a minor thiol metabolite isomer. *Chem Res Toxicol* 25:348–356, 2012.
52. Kim MJ, Jeong ES, Park JS, et al: Multiple cytochrome P450 isoforms are involved in the generation of a pharmacologically active thiol metabolite, whereas paraoxonase 1 and carboxylesterase 1 catalyze the formation of a thiol metabolite isomer from ticlopidine. *Drug Metab Dispos* 42:141–152, 2014.
53. Sibbing D, Koch W, Massberg S, et al: No association of paraoxonase-1 Q192R genotypes with platelet response to clopidogrel and risk of stent thrombosis after coronary stenting. *Eur Heart J* 32:1605–1613, 2011.
54. Trenk D, Hochholzer W, Fromm MF, et al: Paraoxonase-1 Q192R polymorphism and antiplatelet effects of clopidogrel in patients undergoing elective coronary stent placement. *Circ Cardiovasc Genet* 4:429–436, 2011.
55. PON1 Meta-Analysis Group: Influence of the paraoxonase-1 Q192R genetic variant on clopidogrel responsiveness and recurrent cardiovascular events: a systematic review and meta-analysis. *J Thromb Haemost* 10:1242–1251, 2012.
56. Mega JL, Close SL, Wiviott SD, et al: Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. *Lancet* 376:1312–1319, 2010.
57. Wallentin L, James S, Storey RF, et al: Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet* 376(9749):1320–1328, 2010.
58. Gilard M, Arnaud B, Cornily JC, et al: Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol* 51:256–260, 2008.
59. Angiolillo DJ, Gibson CM, Cheng S, et al: Differential effects of omeprazole and pantoprazole on the pharmacodynamics and pharmacokinetics of clopidogrel in healthy subjects: randomized, placebo-controlled, crossover comparison studies. *Clin Pharmacol Ther* 89:65–74, 2011.
60. Cuisset T, Frere C, Quilici J, et al: Comparison of omeprazole and pantoprazole influence on a high 150-mg clopidogrel maintenance dose: the PACA (Proton Pump inhibitors and Clopidogrel Association) prospective randomized study. *J Am Coll Cardiol* 54:1149–1153, 2009.
61. Ho PM, Maddox TM, Wang L, et al: Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 301:937–944, 2009.
62. Juurlink DN, Gomes T, Ko DT, et al: A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 180(7):713–718, 2009.
63. O'Donoghue ML, Braunwald E, Antman EM, et al: Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet* 374:989–997, 2009.
64. Bhatt DL, Cryer BL, Contant CF, et al: Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 363:1909–1917, 2010.
65. Southworth MR, Temple R: Interaction of clopidogrel and omeprazole. *N Engl J Med* 363(20):1901–1917, 1977.
66. Hulot JS, Collet JP, Silvain J, et al: Cardiovascular risk in clopidogrel-treated patients according to cytochrome P450 2C19*2 loss-of-function allele or proton pump inhibitor coadministration: a systematic meta-analysis. *J Am Coll Cardiol* 56:134–143, 2010.
67. Abraham NS, Hlatky MA, Antman EM, et al: ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. *J Am Coll Cardiol* 56:2051–2066, 2010.
68. Varenhorst C, James S, Erlinge D, et al: Genetic variation of CYP2C19 affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease. *Eur Heart J* 30:1744–1752, 2009.
69. Brandt JT, Payne CD, Wiviott SD, et al: A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J* 153(66):e9–e16, 2007.
70. Mega JL, Close SL, Wiviott SD, et al: Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. *Circulation* 119:2553–2560, 2009.
71. Jernberg T, Payne CD, Winters KJ, et al: Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. *Eur Heart J* 27: 1166–1173, 2006.
72. Wiviott SD, Trenk D, Frelinger AL, et al: Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation* 116:2923–2932, 2007.
73. Wiviott SD, Braunwald E, McCabe CH, et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 357:2001–2015, 2007.
74. Antman EM, Wiviott SD, Murphy SA, et al: Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet iNhibition with prasugrel-Thrombolysis In Myocardial Infarction) analysis. *J Am Coll Cardiol* 51:2028–2033, 2008.
75. Wiviott SD, Braunwald E, McCabe CH, et al: Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. *Lancet* 371:1353–1363, 2008.
75a. Montalescot G, Bolognese L, Dudek D, et al: Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med* 369:999–1010, 2013.
76. Van Giezen J, Nilsson L, Berntsson P, et al: Ticagrelor binds to human P2Y(12) independently from ADP but antagonizes ADP-induced receptor signaling and platelet aggregation. *J Thromb Haemost* 7:1556–1565, 2009.
77. Cattaneo M, Schulz R, Nylander S: Adenosine-mediated effects of ticagrelor: evidence and potential clinical relevance. *J Am Coll Cardiol* 63:2503–2509, 2014.

78. Tantry US, Bliden KP, Wei C, et al: First analysis of the relation between CYP2C19 genotype and pharmacodynamics in patients treated with ticagrelor versus clopidogrel: the ONSET/OFFSET and RESPOND genotype studies. *Circ Cardiovasc Genet* 3:556–566, 2010.
79. Gurbel PA, Bliden KP, Butler K, et al: Randomized double-blind assessment of the onset and offset of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary disease: the ONSET/OFFSET study. *Circulation* 120(25):2577–2585, 2009.
80. Wallentin L, Becker RC, Budaj A, et al: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 361:1045–1057, 2009.
81. Cannon CP, Harrington RA, James S, et al: Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet* 375:283–293, 2010.
82. PLATO Investigators: Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation* 124:544–554, 2011.
83. Cattaneo M, Faioni EM: Why does ticagrelor induce dyspnea? *Thromb Haemost* 108:1031–1036, 2012.
84. Cannon CP, Husted S, Harrington RA, et al: Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol* 50:1844–1851, 2007.
85. ONSET/OFFSET Investigators: Incidence of dyspnea and assessment of cardiac and pulmonary function in patients with stable coronary artery disease receiving ticagrelor, clopidogrel, or placebo in the ONSET/OFFSET study. *J Am Coll Cardiol* 56:185–193, 2010.
86. Walsh JA, 3rd, Price MJ: Cangrelor for treatment of arterial thrombosis. *Expert Opin Pharmacother* 15:565–572, 2014.
87. Akers WS, Oh JJ, Oestreich JH, et al: Pharmacokinetics and pharmacodynamics of a bolus and infusion of cangrelor: a direct, parenteral P2Y12 receptor antagonist. *J Clin Pharmacol* 50:27–35, 2010.
88. Greenbaum AB, Grines CL, Bittl JA, et al: Initial experience with an intravenous P2Y12 platelet receptor antagonist in patients undergoing percutaneous coronary intervention: results from a 2-part, phase II, multicenter, randomized, placebo- and active-controlled trial. *Am Heart J* 151:689 e1–689 e10, 2006.
89. Harrington RA, Stone GW, McNulty S, et al: Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med* 361:2318–2329, 2009.
90. Bhatt DL, Lincoff AM, Gibson CM, et al: Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med* 361:2330–2341, 2009.
91. White HD, Chew DP, Dauerman HL, et al: Reduced immediate ischemic events with cangrelor in PCI: a pooled analysis of the CHAMPION trials using the universal definition of myocardial infarction. *Am Heart J* 163:182–190 e4, 2012.
92. CHAMPION Investigators: Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. *Lancet* 382:1981–1992, 2013.
93. TRACER Investigators: Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. *N Engl J Med* 366(1):20–33, 2012.
94. TRA 2P-TIMI 50 Steering Committee and Investigators: Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med* 366:1404–1413, 2012.
95. TRA 2°P-TIMI 50 Steering Committee Investigators: Vorapaxar for secondary prevention of thrombotic events for patients with previous myocardial infarction: a prespecified subgroup analysis of the TRA 2°P-TIMI 50 trial. *Lancet* 380(9850):1317–1324, 2012.
96. Angiolillo DJ, Capranzano P, Goto S, et al: A randomized study assessing the impact of cilostazol on platelet function profiles in patients with diabetes mellitus and coronary artery disease on dual antiplatelet therapy: results of the OPTIMUS-2 study. *Eur Heart J* 29:2202–2211, 2008.
97. Lee SW, Park SW, Kim YH, et al: Drug-eluting stenting followed by cilostazol treatment reduces late restenosis in patients with diabetes mellitus the DECLARE-DIABETES Trial (A Randomized Comparison of Triple Antiplatelet Therapy With Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Diabetic Patients). *J Am Coll Cardiol* 51:1181–1187, 2008.
98. Chen KY, Rha SW, Li YJ, et al: Triple versus dual antiplatelet therapy in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Circulation* 119:3207–3214, 2009.
99. Boersma E, Harrington RA, Moliterno DJ, et al: Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 359:189–198, 2002.
100. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC investigation. *N Engl J Med* 330:956–961, 1994.
101. The EPILOG investigators: Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 336:1689–1696, 1997.
102. EPISTENT Investigators: Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet* 352:87–92, 1998.
103. ESPRIT Investigators: Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrilin Therapy. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet* 356:2037–2044, 2000.
104. Kastrati A, Mehilli J, Schuhlen H, et al: A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med* 350:232–238, 2004.
105. Mehilli J, Kastrati A, Schuhlen H, et al: Randomized clinical trial of abciximab in diabetic patients undergoing elective percutaneous coronary interventions after treatment with a high loading dose of clopidogrel. *Circulation* 110:3627–3635, 2004.
106. Kastrati A, Mehilli J, Neumann FJ, et al: Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA* 295:1531–1538, 2006.
107. Giugliano RP, White JA, Bode C, et al: Early versus delayed, provisional eptifibatide in acute coronary syndromes. *N Engl J Med* 360:2176–2190, 2009.
108. De Luca G, Suryapranata H, Stone GW, et al: Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *JAMA* 293:1759–1765, 2005.
109. Mehilli J, Kastrati A, Schulz S, et al: Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. *Circulation* 119:1933–1940, 2009.
110. Ellis SG, Tendera M, de Belder MA, et al: Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med* 358:2205–2217, 2008.

110a. Shimada YJ, Nakra NC, Fox JT, Kanei Y: Meta-analysis of prospective randomized controlled trials comparing intracoronary versus intravenous abciximab in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol* 109(5):624–628, 2012.

111. Thiele H, Wöhrle J, Hambrecht R, et al: Intracoronary versus intravenous bolus abciximab during primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction: a randomised trial. *Lancet* 379(9819):923–931, 2012.
112. INFUSE-AMI Investigators: Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. *JAMA* 307(17):1817–1826, 2012.
113. Capodanno D, Angiolillo DJ: Management of antiplatelet and anticoagulant therapy in patients with atrial fibrillation in the setting of acute coronary syndromes or percutaneous coronary interventions. *Circ Cardiovasc Interv* 7(1):113–124, 2014.
114. WOEST Study Investigators: Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 381(9872):1107–1115, 2013.
115. Faxon DP, Eikelboom JW, Berger PB, et al: Antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting: a North American perspective: executive summary. *Circ Cardiovasc Interv* 4(5):522–534, 2011.
116. Lip GY, Huber K, Andreotti F, et al: Consensus document of European Society of Cardiology Working Group on Thrombosis. Antithrombotic management of atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing coronary stenting: executive summary—a consensus document of the European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 31(11):1311–1318, 2010.
117. Stone GW, Witzenbichler B, Weisz G, et al: Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet* 382:614–623, 2013.
118. Bonello L, Camoin-Jau L, Arques S, et al: Adjusted clopidogrel loading doses according to vasodilator-stimulated phosphoprotein phosphorylation index decrease rate of major adverse cardiovascular events in patients with clopidogrel resistance: a multicenter randomized prospective study. *J Am Coll Cardiol* 51:1404–1411, 2008.
119. Valgimigli M, Campo G, de Cesare N, et al: Intensifying platelet inhibition with tirofiban in poor responders to aspirin, clopidogrel, or both agents undergoing elective coronary intervention: results from the double-blind, prospective, randomized Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel study. *Circulation* 119:3215–3222, 2009.
120. Price MJ, Berger PB, Teirstein PS, et al: Standard- vs. high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 205(11):1097–1105, 2011.
121. Price MJ, Angiolillo DJ, Teirstein PS, et al: Platelet reactivity and cardiovascular outcomes after percutaneous coronary intervention: a time-dependent analysis of the gauging responsiveness with a VerifyNow P2Y12 assay: impact on thrombosis and safety (GRAVITAS) trial. *Circulation* 124:1132–1137, 2011.
122. Homan DJ, Price MJ: The role of clopidogrel in the management of ischemic heart disease. *Curr Opin Cardiol* 28:381–388, 2013.
123. ARCTIC Investigators: Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med* 367:2100–2109, 2012.
124. Price MJ, Berger PB, Teirstein PS, et al: Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 305:1097–1105, 2011.
125. Price MJ: Platelet reactivity after coronary stenting. *Lancet* 382:583–584, 2013.

11 Anticoagulation in Percutaneous Coronary Intervention

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KEY POINTS

- Unfractionated heparin (UFH), enoxaparin, fondaparinux, and bivalirudin are the anticoagulants with established efficacy in contemporary percutaneous coronary intervention (PCI) practice.
- Platelets and coagulation play a synergistic role in the generation of thrombus. Improved antithrombin approaches reduce the dependence on antiplatelet therapy for achieving suppression of ischemic events.
- Although the impact of ischemic events on late mortality is well appreciated, a robust link between bleeding events and late mortality is evident. These factors bear careful consideration when weighing efficacy and safety considerations among antithrombotic therapies.
- A large collection of clinical trial data now exists that compares the different anticoagulants in various clinical settings, from elective PCI through to ST-elevation myocardial infarction (STEMI); however, substantial heterogeneity exists in the trial protocols and inclusion criteria, and these require careful consideration when choosing among agents.
- Multiple factors need to be considered when selecting an agent, such as indication for PCI, patient bleeding risk, renal function, concomitant use of the newer antiplatelet $P2Y_{12}$ agents and glycoprotein (GP) IIb/IIIa inhibitors, familiarity with the anticoagulant, hospital protocol, and current European Society of Cardiology and American College of Cardiology guidelines.

The last two decades have witnessed the introduction of a number of new pharmacologic agents aimed at improving patient outcomes after PCI. Optimizing ischemic prevention while minimizing bleeding complications remains the cornerstone of contemporary pharmacologic practice. Notably, this period has seen improvements in PCI with the use of radial artery access, more potent antiplatelet $P2Y_{12}$ receptor inhibitors, and the availability of bleeding risk calculators (i.e., Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines? [CRUSADE]); these advances, together with improvements in drug-eluting stent technology, have helped minimize the bleeding and ischemic risks during PCI.

Heparin, enoxaparin, and bivalirudin are the most widespread anticoagulant agents used in current PCI practice, and these form the basis of recommendations from major society guidelines. This chapter will discuss the current biologic basis of atherothrombosis and its key effector, thrombin; the pharmacology of the anticoagulant agents in current use; and the targets for future therapy. Also reviewed will be the landmark trials that support anticoagulant use in STEMI, non–ST-elevation myocardial infarction (NSTEMI), and elective PCI.

THE BIOLOGY OF ATHEROTHROMBOSIS

The coagulation cascade reflects the complex interplay among the coagulation proteins, platelets, and cellular phospholipid membranes of not only vascular endothelial cells but of a wide range of inflammatory cells that include monocytes and vascular smooth muscle cells.[1] The subsequent discussion will focus on the coagulation factors that serve as targets, although modern antithrombotic regimens, additional effects on platelet-mediated thrombosis, and vascular tissue function should not be ignored.

The Central Role of Thrombin

Disruption of endothelial integrity and expression of prothrombotic molecules such as tissue factor (TF) lead to the activation of the soluble coagulation proteins (Fig. 11-1). This amplifying cascade converges on the generation of activated factor X (FXa) and the prothrombinase complex, which leads to the conversion of thrombin from its parent molecule, prothrombin. Thrombin generation leads to multiple effects that influence the formation of thrombosis.[2] Specifically, thrombin catalyses the conversion of fibrin from fibrinogen; this enables clot formation and also activates factors V, VIII, and X; thus it promotes its own generation. In addition, via its direct effects on protease-activated receptors (PARs) 1 and 4, thrombin promotes platelet activation that leads to the expression of CD40 ligand, P-selectin, and the GP IIb/IIIa receptor as well as to the secretion of vasoactive agents that include adenosine diphosphate (ADP), serotonin, and thromboxane A_2 (TXA_2). Direct effects of thrombin on endothelial cells and smooth muscle cells result in the expression of adhesion molecules that enables platelet and leukocyte attachment, and its effect on endothelial membrane permeability contributes to the transmigration of the cellular- and cytokine-mediated inflammatory response within the vascular wall. Thrombin promotes vasodilation in the intact endothelium, and it contributes to vasoconstriction where the endothelium is damaged or denuded. Thrombin also appears to promote fibroblast cytokine production and is mitogenic (Fig. 11-2).[3]

However, thrombin has a short circulating half-life, and in the context of a normal endothelial barrier, the effects of thrombin are tightly controlled by a negative-feedback mechanism. Antithrombin is a single-chain plasma glycoprotein produced by the liver. As an inhibitor of coagulation, this molecule has the ability to bind to thrombin and activated factors X (FXa) and IX (FIXa) in equimolar concentrations. Antithrombin's action is increased over a thousandfold by the binding of pentasaccharide-chain containing heparins. The pentasaccharide sequence enables the binding of heparins to antithrombin and augments the binding affinity for thrombin and the other clotting factors. Antithrombin is also activated by the glycosaminoglycan heparin sulfate found on the surface of endothelial cells. However, other pathways for the inhibition of thrombin exist and include the binding of thrombin to thrombomodulin and to protein C together with protein S. This inactivates the upstream coagulation proteins, factors Va and VIIIa, and promotes the release of tissue plasminogen activator (TPA).

Hence thrombin plays a central effector role in the vascular response to balloon- and stent-induced vascular injury and remains an important therapeutic target for the prevention of ischemic complications during PCI. A schematic of the structure of the thrombin molecule is presented in Figure 11-3. Separate substrate recognition sites are involved in the binding of heparin, fibrinogen, and thrombomodulin, and the catalytic site is responsible for the serine protease activity that is blocked by the direct thrombin inhibitors.[3,4]

ADVERSE EVENTS FOLLOWING PERCUTANEOUS CORONARY INTERVENTION

Improvements in interventional techniques and refinements in antithrombotic therapies have led to a substantial decline in the incidence of ischemic complications following PCI.[5] Hence further iterations in antithrombotic strategies can be considered a double-edged sword, with improved prevention of ischemic complications potentially leading to an increase in bleeding complications associated with increased mortality, stroke, nonfatal myocardial infarction (MI), and stent thrombosis. The contemporary definition of *PCI-related MI* includes a troponin elevation more than five times the 99th percentile in patients with normal values before PCI or a rise greater than 20% if the baseline values are elevated and are stable or falling (Table 11-1).[6] Accompanying the troponin elevation must be at least one of the following three factors: (1) new symptoms or electrocardiographic (ECG) changes, (2) angiographic findings consistent with a procedural complication, or (3) imaging findings consistent with new ischemia. This definition has limitations, however, because the levels of post-PCI troponin elevation whereby long-term prognosis is affected has not been established. The troponin values in this definition are arbitrarily chosen and lack clinical utility to predict outcome.

More recently, definitions of *clinically meaningful postprocedural MI* have been proposed that are more in line with levels of myocardial injury used to define post–coronary artery bypass graft (CABG) MI.[7] These so-called clinically relevant values in patients with *normal baseline biomarkers* include a post-PCI creatinine kinase myocardial band (CK-MB) elevation 10 or more times the upper limit of normal (ULN) and a lower threshold five or more times the ULN in the presence of new Q-waves or left bundle branch block (LBBB). For patients with elevated CK-MB prior to PCI that is either *stable or falling*, an increment 10 or more times the ULN from the most recent level is considered diagnostic. The definition for those whose CK-MB level is *not* stable or falling includes a further rise above the most recently measured value of 10 or more times the ULN plus new ST elevation or depression plus signs consistent with a clinically relevant MI, such as new or worsening heart failure or hypotension.

Historical definitions of PCI-related MI have included CK elevation (2 times the ULN) but underestimated the incidence of periprocedural MI by 40% to 50%.[8] In an analysis of patients enrolled in the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 study, CK-MB elevation greater than or equal to three times the ULN was associated with a 3.5-fold excess risk of mortality at 12 months and accounted for 13.2% of all mortality seen by 12 months (Fig. 11-4).[9]

In one study, an isolated post-PCI troponin elevation, compared with no elevation, in patients with normal preprocedural values carried a small but increased risk of 30-day mortality (0.3% vs. 0.1%); however, this was not an independent predictor of long-term mortality.[8] Pre-PCI troponin elevation—as well as age, diabetes, and a history of congestive heart failure (CHF) and stroke—were all independent predictors of long-term mortality.

Non–CABG related bleeding within 30-days of PCI is strongly associated with increased mortality, stroke, non-fatal MI, and stent thrombosis (Table 11-2).[10,11] Factors that contribute to these outcomes include reduced myocardial oxygen delivery as a result of hypotension and anemia, cessation of antithrombotic and antiischemic agents, increased myocardial oxygen demand from the systemic inflammatory response syndrome, and the adverse effects of the storage lesion in the transfusion of red blood cells.[12,13] The bleeding rates after PCI in patients with acute coronary syndromes (ACSs) have been estimated

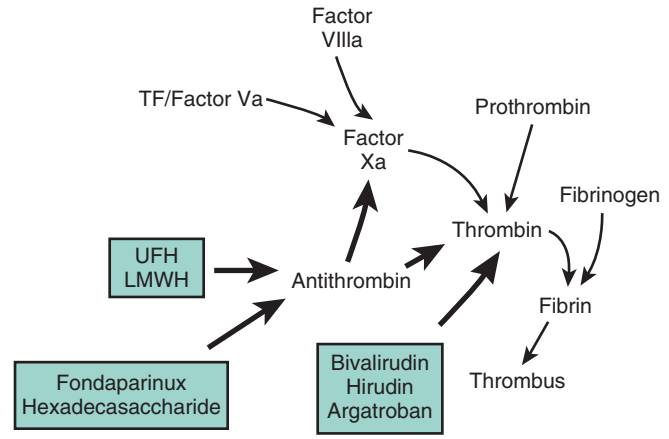

FIGURE 11-1 Schematic representation of the relationship between coagulation and arterial thrombosis. Specific targets for therapy are highlighted. *LMWH,* Low-molecular-weight heparin; *TF,* tissue factor; *UFH,* unfractionated heparin.

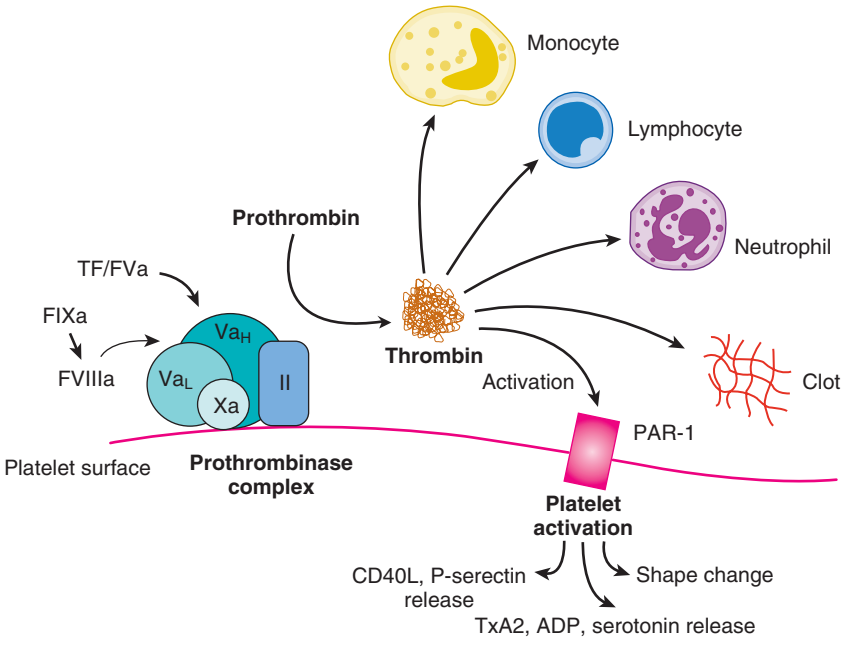

FIGURE 11-2 The central role of thrombin in thrombosis and inflammation. *ADP,* Adenosine diphosphate; *FVa,* activated factor V; *PAR-1,* protease-activating receptor 1; *TF,* tissue factor; *TxA2,* thromboxane A2.

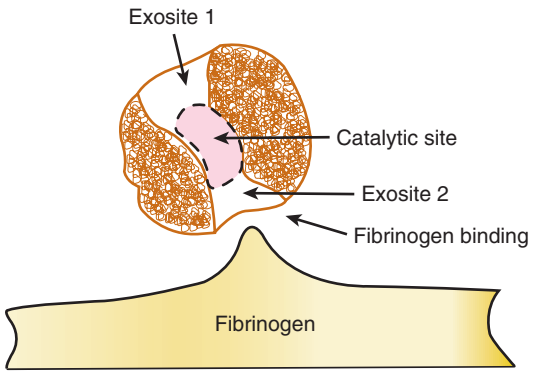

FIGURE 11-3 Thrombin binding sites.

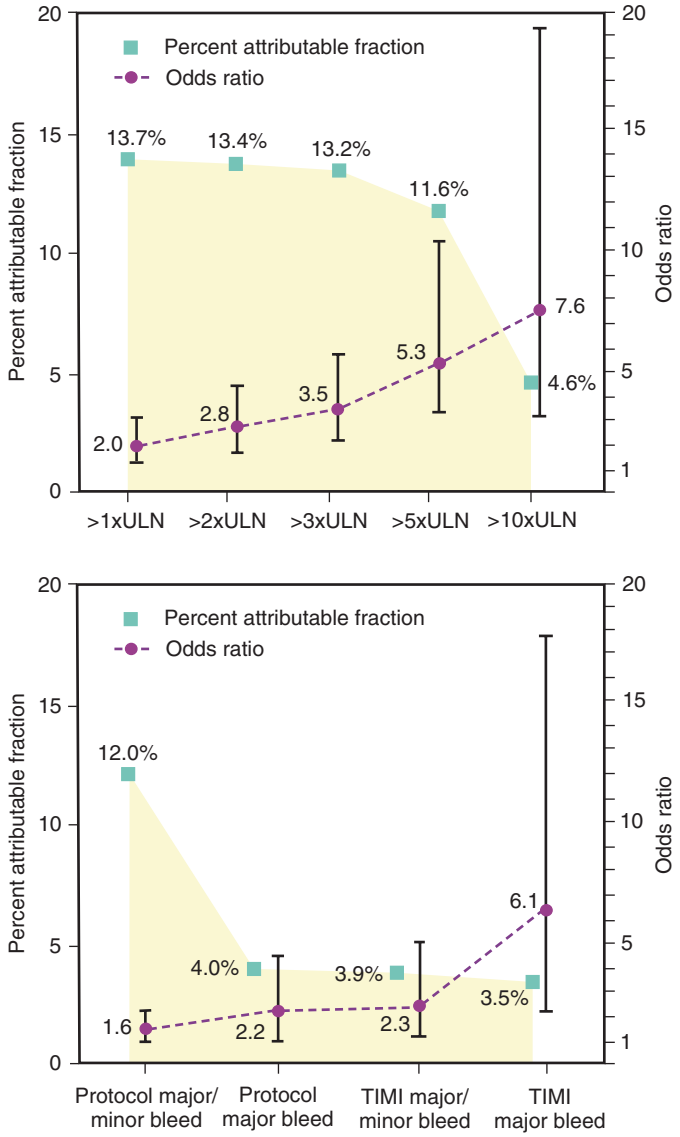

FIGURE 11-4 The relationship among ischemic events, bleeding events, and late mortality. *TIMI,* Thrombolysis in myocardial infarction; *ULN,* upper limit of normal.

TABLE 11-1 End Point Definitions of Bleeding and Ischemia Commonly Used in Clinical Trials of Antithrombotic Agents in Percutaneous Coronary Intervention

End Point	Definition
Myocardial infarction (post PCI)	Troponin elevation more than 5 times the 99th percentile of the ULN in patients with normal baseline values or a rise more than 20% if baseline values are elevated. In addition, at least one of the following must accompany the troponin elevation: supportive symptoms, new ECG changes, angiographic findings, or imaging findings. SCAI definition: Clinically meaningful MI CK-MB rise more than10 times the ULN or more than 5 times the ULN with new pathologic Q-waves in at least two contiguous leads or new persistent LBBB *OR* In the absence of baseline CK-MB, a cTn rise more than 70 times the ULN or a rise more than 35 times the ULN plus new pathologic Q-waves in at least two contiguous leads or new persistent LBBB
Myocardial infarction (post CABG)	Troponin elevation more than 10 times the 99th percentile in patients with normal baseline values; in addition, at least one of the following must accompany the troponin elevation: ECG changes (LBBB or new Q waves), angiographic findings, or imaging findings
Myocardial infarction (not periprocedural)	Detection of a rise and/or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile with at least one of the following: symptoms, ECG changes, imaging findings, or angiographic findings
TIMI major bleeding	Intracerebral hemorrhage or any bleeding associated with a more than 5g/dL fall in hemoglobin or a 15% absolute decrease in hematocrit*
TIMI minor bleeding	Any bleeding event associated with a more than 3 g/dL fall in hemoglobin or a 10% absolute decline in hematocrit or a more than 4 g/dL fall in hemoglobin or a 12% absolute decline in hematocrit in the absence of overt bleeding*
Major bleeding (REPLACE-2 definition)	Intracerebral hemorrhage or any bleeding event associated with a more than 3 g/dL fall in hemoglobin, a more than 4 g/dL fall in hemoglobin in the absence of overt bleeding, or any red cell transfusion of two or more units*
Severe or life-threatening bleeding (GUSTO definition)	Intracerebral hemorrhage or bleeding that causes hemodynamic compromise or requires intervention
Minor bleeding (GUSTO definition)	Bleeding that requires transfusion but does not cause hemodynamic compromise

*All calculations of drops in hemoglobin are adjusted for any transfusion by the Landefeld index.

CABG, Coronary artery bypass grafting; *CK-MB,* creatinine kinase myocardial band; *cTn,* cardiac troponin; *ECG,* electrocardiography; *GUSTO,* global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries; *LBBB,* left bundle branch block; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention; *REPLACE-2,* Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; *SCAI,* Society for Cardiovascular Angiography and Interventions; *TIMI,* thrombolysis in myocardial infarction; *ULN,* upper limit of normal.

TABLE 11-2 Clinical Factors Associated With Myocardial Infarction and Non–Coronary Artery Bypass Grafting–Related Bleeding Within 30 Days Among Patients With Acute Coronary Syndrome Undergoing Early Invasive Management

MYOCARDIAL INFARCTION			NON-CABG MAJOR BLEEDING		
Clinical Factor	**OR (95% CI)**	***P* value**	**Clinical Factor**	**OR (95% CI)**	***P* value**
Biomarker elevation	1.66 (1.40-1.97)	<.001	Male sex	0.42 (0.36-0.50)	<.001
Family history of CAD	1.48 (1.27-1.73)	<.001	Anemia (Hct < 39% in males and < 36% in females)	1.96 (1.63-2.36)	<.001
Age per 5 years	1.08 (1.04-1.11)	<.001	Age per 5 years	1.14 (1.10-1.19)	<.001
ST-segment deviation ≥ 1.0 mm	1.38 (1.18-1.61)	<.001	ST-segment deviation ≥ 1.0 mm	1.31 (1.10-1.54)	<.01
Prior MI	1.28 (1.08-1.50)	<.001	Prior PCI	0.70 (0.58-0.84)	<.01
			Creatinine per 0.1 mg/dL	1.08 (1.05-1.10)	<.001
			White cell count per	1.08 (1.05-1.11)	<.001
			Prior CVA	1.60 (1.21-2.10)	<.001

CABG, Coronary artery bypass grafting; *CAD,* coronary artery disease; *CI,* confidence interval; *CVA,* cerebrovascular accident; *Hct,* hematocrit; *MI,* myocardial infarction; *OR,* odds ratio; *PCI,* percutaneous coronary intervention.

TABLE 11-3 Academic Research Consortium Definition of Bleeding

Type	Definition
0	No bleeding
1	Bleeding that is not actionable (no investigations, treatment, or hospitalization is required); may include episodes of self-discontinuation of medical therapy by the patient
2	Any overt actionable sign of hemorrhage that does not fit criteria for type 3, 4, or 5 but does at least one of the following: (1) requires nonsurgical medical intervention, (2) leads to hospitalization or increased level of care, or (3) prompts evaluation
3	3a: Overt bleeding with Hb drop of 3 to 5 g/dL,* any transfusion with overt bleeding 3b: Overt bleeding with Hb of ≥5 g/dL,* cardiac tamponade, bleeding that requires surgical intervention or vasoactive agents 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation), intraocular bleed that compromises vision
4	CABG-related bleeding
5	5a: Probable fatal bleeding 5b: Definite fatal bleeding

*Provided Hb fall is related to the bleed.
CABG, Coronary artery bypass grafting; *Hb,* hemoglobin.

to be as high as 10%, and various risk calculators have been developed.[10] However, the definition of *bleeding* in the major PCI trials has varied over the last 20 years, which makes comparisons among trials more difficult. Many trials use their own definitions of bleeding, along with the commonly used thrombolysis in myocardial infarction (TIMI) and global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO) definitions, both originally developed to monitor bleeding complications in fibrinolytic trials. This lack of uniformity has made it more difficult to judge the effectiveness of anticoagulant therapies among trials. More recently, however, an Academic Consortium definition of bleeding has been created in an attempt to standardize trial data and better evaluate the safety and efficacy of antithrombotic therapies (Table 11-3).[11]

PHARMACOLOGY OF ANTICOAGULANT AGENTS USED IN CURRENT ERA PERCUTANEOUS CORONARY INTERVENTION

Unfractionated Heparin

Unfractionated heparin (UFH) is heterogeneous group glycosaminoglycans of various lengths (5000 to 30,000 Da) that exhibit a high affinity for antithrombin. This binding augments antithrombin's enzymatic inactivation of thrombin, FXa, and FIXa, but its effects on thrombin are the most pronounced.[14] UFH is considered an indirect antithrombin because its action requires the simultaneous binding to antithrombin and thrombin. Up to two thirds of UFH preparations contain shorter molecules (<18 saccharides) that lack sufficient length to simultaneously span antithrombin and thrombin, and they do not exhibit antithrombin activity. However, the anti-FXa effects of heparin are not dependent on simultaneous binding of both antithrombin and FXa, and therefore antithrombin effects are observed across a wider range of saccharide chain lengths.

The elimination of UFH is initially through rapid but saturable metabolism within endothelial cells and macrophages (zero-order kinetics) followed by slower renal clearance (first-order kinetics). The plasma half-life depends in the dose administered and is approximately 1 hour at doses of 100 IU/kg. In the context of excessive dosing or bleeding, UFH can be reversed by the administration of protamine; however, the clinical efficacy and safety of this strategy has not been well established.

Limitations of UFH include the activation of platelets, a dependence on antithrombin levels, nonspecific binding to plasma proteins, and an inability to inhibit clot-bound thrombin. In addition, direct binding to platelet factor IV can contribute to heparin-induced thrombocytopenia (HIT) in 1% to 3% of treated patients. Platelet activation by heparin is evidenced by an increase in the expression of platelet surface adhesion molecules.[15]

Enoxaparin

The low-molecular-weight heparins (LMWHs) are produced by chemical or enzymatic depolymerization of UFH, which results in heparin fragments with a mean molecular weight approximately 30% of most UFH preparations. However, the molecular size of the heparin molecules still varies; therefore anticoagulant characteristics remain heterogeneous, although they are more predictable when compared with heparin.[16] The principal effect of the LMWHs is the inhibition of anti-FXa via antithrombin. In comparison with UFH, the LMWHs have a longer half-life and demonstrate a more consistent dose response. Reduced platelet activation and fewer platelet factor IV interactions result in less HIT. Clearance is by renal excretion, however, and the biologic half-life is increased in people with renal failure (Table 11-4).

In one study, adequate levels of anti-FXa where observed among patients 2 to 8 hours following subcutaneous dosing of enoxaparin 1 mg/kg twice daily as well as in those receiving an additional 0.3 mg/kg intravenous (IV) dose 8 to 12 hours following subcutaneous dosing at 1.0 mg/kg.[17] Other investigators have suggested that doses as low as 0.5 mg/kg of IV enoxaparin may be safe and efficacious and may also enable easier sheath management, although a quarter of the patients

TABLE 11-4 Pharmacokinetic Characteristics of Commonly Used Anticoagulants

Property	Unfractionated Heparin	Enoxaparin	Fondaparinux	Bivalirudin
Mean molecular weight (Da)	15,000	5000	1728	2180
Dependence on antithrombin	Yes	Yes	Yes	No
Anti-FXa, anti-FIIa activity	Yes	2-4	No anti-FXa activity	No anti-FXa activity
Half-life	~60 min	~240 min	17-21 hr	25 min
Bioavailability	+ to +++	++++	++++ (Subcutaneous)	++++
Subcutaneous absorption	++	++++	++++	–
Binding to plasma proteins	+++	+	+	–
Binding to platelets/macrophages	++	+	–	–
Antigenicity/HIT	++	+	–/+ (Very rare)	–
Clearance	Renal	Renal	Renal	Renal/proteolysis
Protamine neutralization	++++	++	–	–

FIIa, Activated factor II; *FXa,* activated factor X; *HIT,* heparin-induced thrombocytopenia.

in this study also received a GP IIb/IIIa inhibitor.[18] Some evidence suggests that enoxaparin may be reversed by the IV administration of protamine, but these data are limited.

Fondaparinux

Fondaparinux, a pentasaccharide, is a synthetic molecule that mimics the biologically active sequence of heparin in its interaction with antithrombin. Given that these molecules are short, their principal effect is the inactivation of FXa.[19] Similarly, these agents have relatively long half-lives and therefore offer once-daily dosing regimens. These agents are not reversed by protamine and require the administration of factor VII concentrates. Fondaparinux does not affect activated partial thromboplastin time (APTT), prothrombin time (PT), or activated clotting time (ACT), and routine monitoring is not performed. However, anti-FXa assays may be measured if monitoring is required, and fondaparinux may be used as the calibrator.

Direct Thrombin Inhibitors

The direct thrombin inhibitor hirudin, a 65–amino acid protein, is the prototypical molecule of this class.[19] Hirudin forms a stable noncovalent complex with thrombin by inhibiting the catalytic site and the anion binding exosite in a two-step process.[4] Generally the direct thrombin inhibitor molecules are smaller than the indirect thrombin inhibitors, and they demonstrate greater efficacy for the inhibition of clot-bound thrombin.[19]

The hirudin-thrombin interaction offers a method for categorizing the other direct thrombin inhibitors, which have been divided into univalent and bivalent molecules. The *univalent molecules*—dabigatran, argatroban, and melagatran—inhibit only the catalytic site and inactivate only fibrin-bound thrombin. The *bivalent molecules*, recombinant hirudin and bivalirudin, bind to the catalytic site and to at least one of the exosites. Whereas the interaction between hirudin and thrombin is irreversible, the inhibition provided by bivalirudin is more transient. Bivalirudin is a synthetic 20–amino acid molecule with a shorter half-life than hirudin, and bivalirudin is the only direct thrombin inhibitor in current use for PCI (see Table 11-4). With the exception of argatroban, these agents are cleared renally, and clearance is attenuated in the setting of reduced renal function. In the setting of excessive dosing or bleeding, these agents can be removed by hemofiltration. Bivalirudin also undergoes proteolysis within the plasma, which contributes to its shorter half-life and relatively constant elimination characteristics even among patients with mild to moderate renal impairment. Nevertheless, dose attenuation is required among patients with creatinine clearance below 30 mL/min. These agents are not reversed by protamine and have no specific antidote. Nonspecific measures—such as transfusion of blood products, including fresh frozen plasma (FFP)—and local measures are recommended in the context of active bleeding. Monitoring is not routinely required with the use of bivalirudin, however, the ACT and PT are prolonged in a nonlinear fashion. If needed, however, the dose-linear escarin clotting time can be used to monitor bivalirudin's activity.

NEW PHARMACOLOGIC TARGETS

Multiple novel targets in the coagulation cascade have the potential for pharmacologic inhibition and prevention of thrombus formation, although few have reached phase III clinical trials for use in PCI; nevertheless, the potential for future development remains.

Agents that target the tissue–factor VIIa complex involved in the initiation phase of coagulation include tifacogin and active site–inhibited recombinant FVIIa.[14] Tifacogin is a recombinant form of tissue factor pathway inhibitor whose use has been limited so far to the treatment of severe sepsis. Both remain only theoretic targets for the use in PCI.

Agents that target the coagulation proteases in the amplification phase include FIXa inhibitors (pegnivacogin), FVIIa inhibitors (TB-402), and joint FVa/FVIIIa inhibitors (drotrecogin, recomodulin, and solulin).[14] Pegnivacogin is a first in its class of molecule, known as an *aptamer*.[20] Aptamers are oligonucleotide RNA molecules capable of not only binding target proteins with high affinity and specificity but also allowing complementary antidote binding that can reverse their pharmacologic activity.[21] The Randomized, Partially Blinded, Multicenter, Active-Controlled, Dose-Ranging Study Assessing the Safety, Efficacy, and Pharmacodynamics of the REG1 Anticoagulation System Compared to Unfractionated Heparin or Low Molecular Weight Heparin in Subjects With Acute Coronary Syndromes (RADAR) was a phase IIb dose-finding randomized trial that comprised 640 patients with NSTEMI to assess the optimal level of reversal agent, known as *anivamersen,* required to allow safe femoral sheath removal.[22] The ongoing Study to Determine the Efficacy and Safety of REG1 Compared to Bivalirudin in Patients Undergoing PCI (REGULATE PCI) is a large phase III clinical trial to assess whether pegnivacogin can result in fewer ischemic events than bivalirudin in patients undergoing PCI with stable angina and NSTEMI.

The direct FXa inhibitor otamixaban was studied in the large phase III clinical trial Anticoagulation With Otamixaban and Ischemic Events in Non-ST Elevation Acute Coronary Syndromes (TAO).[23] This double-blind, active, controlled superiority trial randomized 13,229 patients with NSTEMI to either otamixaban or UFH plus downstream eptifibatide. No reduction was seen in the primary efficacy outcome; however, increased TIMI major and minor bleeding was noted with otamixaban (3.1% vs. 1.5%, $P < .01$), and otamixaban is no longer recommended based on the findings of this trial. The other orally active FXa inhibitors, rivaroxaban and apixaban, have been studied in patients

after treatment for an ACS but have not been formally assessed in the peri-PCI setting.

ANTICOAGULANT THERAPY IN STEMI, NSTEMI, AND ELECTIVE PERCUTANEOUS CORONARY INTERVENTION

ST-Elevation Myocardial Infarction (STEMI)

Sudden and complete thrombotic occlusion of an epicardial coronary artery underpins the need for urgent restoration of blood flow in patients with STEMI. In contrast to fibrinolysis, the use of anticoagulant therapy in primary PCI (PPCI) is aimed at offsetting the thrombotic risk of mechanical coronary intervention. Clinical trial data support several pharmacologic approaches that include UFH, LMWH, or bivalirudin in STEMI patients. This section will outline the major trials of recent times that have driven changes in clinical practice.

The Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial studied the role of bivalirudin monotherapy versus heparin and GP IIb/IIIa inhibition among patients with STEMI undergoing PPCI.[24] This open-label trial was the first randomized study of bivalirudin in such patients, and it preceded the introduction of prasugrel, ticagrelor, and mainstream use of radial artery vascular access. Significantly in the 3602 patients randomized, a 41% reduction in major bleeding was reported in the bivalirudin arm (bivalirudin 4.9% vs. heparin–GP IIb/IIIa 8.3%; $P < .001$), one of the trial's two primary end points. Notably, no difference was found in major adverse cardiac events (MACEs: death, reinfarction, target-vessel revascularization [TVR] for ischemia, or stroke) between the two arms. The statistically significant reduction in major bleeding with bivalirudin, however, accounted for a reduction in the other primary end point of the trial, net adverse clinical events (NACEs; 12.1% vs. 9.2%, respectively; $P = .005$), a composite of major bleeding and MACEs.

A slight increase in early stent thrombosis was reported in the bivalirudin arm, although this did not translate to an increase in late mortality; both cardiac mortality (2.1% vs. 3.8%, respectively; $P = .005$) and all-cause mortality (3.5% vs. 4.8%, respectively; $P = .037$) favored bivalirudin at 12 months. The open-label nature of the trial, along with approximately 65% of the bivalirudin arm receiving UFH at some point, highlighted shortcomings of the trial design. All-cause mortality was sustained at 3 years in favor of bivalirudin (5.9% vs. 7.7%, $P = .03$).

The introduction of radial-access PCI, the more potent $P2Y_{12}$ inhibitors ticagrelor and prasugrel, and a reduction in the use of GP IIb/IIIa inhibitors led to the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) trial.[25] This trial was a pre-PCI hospital-led protocol of ambulance or peripheral hospital initiation of either bivalirudin or UFH (with or without GP IIb/IIIa inhibitors) in 2198 patients with STEMI. This open-label trial used radial arterial access in around 47% of patients and ticagrelor or prasugrel in around 60% of patients. The primary composite of death from any cause and non-CABG major bleeding at 30 days favored bivalirudin (5.1% vs. 8.5%, $P = .001$). As seen in HORIZONS-AMI, a statistically significant reduction in major bleeding (2.6% vs. 6.0%, $P < .001$) and an increase in early (<24 hr) stent thrombosis was seen with bivalirudin (1.6% vs. 0.5%, $P = .02$), but it did not maintain significance at 30 days with the latter. Of note, no differences in death (either from cardiac or noncardiac causes) or major adverse cardiovascular or cerebrovascular events (MACCEs; a composite of death, reinfarction, ischemia-driven reinfarction, or stroke) were reported between the two groups.

This study was noteworthy for its large size and for its being performed in an era of radial access with new $P2Y_{12}$ agents; in addition, it supported some of the findings from HORIZONS-AMI—namely, that bivalirudin reduces bleeding and improves net clinical outcome. A small increase in early stent thrombosis in the bivalirudin group was again seen despite the extended use of bivalirudin for 4 hours after the procedure and the use of newer, more potent $P2Y_{12}$ inhibitors. This, however, was not reflected by an increase in ischemic end points at 30 days.

Limitations of EUROMAX were its open-label use of the study drugs and that the primary end point was changed part way through recruitment in an effort to reach significance. The definition of *major bleeding* in this trial included the use of any blood product, and in a patient population that may have coexisting anemia, the potential for bias is present with an open-label design.

One moderate-sized, single-center, nonblinded randomized trial to compare bivalirudin with UFH has called into question the value of routine bivalirudin in the setting of PPCI.[26] How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention? (HEAT-PPCI), an open-label trial of 1829 patients undergoing PPCI for STEMI, found a statistically significant increase in the stent thrombosis rate, reinfarction rate, and unplanned TVR rate in patients receiving bivalirudin. No differences in bleeding outcomes were reported between the two groups. The predominant route of arterial access was radial (~81%); ticagrelor was used in just over 60% of patients in both groups, and GP IIb/IIIa was used in around 14%. This may explain why bivalirudin failed to achieve superiority as it has in other trials, in which it was compared against heparin plus a GP IIb/IIIa inhibitor.

The Acute Myocardial Infarction Treated With Primary Angioplasty and Intravenous Enoxaparin or Unfractionated Heparin to Lower Ischemic and Bleeding Events at Short- and Long-Term Follow-Up (ATOLL) included 910 patients in a randomized open-label trial design.[27] Pre-PCI hospital or ambulance administration of either enoxaparin or UFH occurred in 71% of both study arms.

Patients who received enoxaparin were administered an IV bolus of 0.5 mg/kg, and if the procedure was prolonged by more than 2 hours or the clinician required stronger anticoagulation, an additional 0.25 mg/kg was administered. No dose adjustment was made for patients with renal failure, and patients who required ongoing anticoagulation for other reasons were given enoxaparin 1 mg/kg subcutaneously twice daily with a dose adjustment for renal failure. Radial access was used in approximately two thirds of patients; however, 93% of patients received clopidogrel.

The primary composite end point of death, complication of MI, or major bleeding was nonsignificantly lower with enoxaparin (28% vs. 34%, $P = .063$). The main secondary end point, to evaluate ischemic risk—a composite of death, recurrent ACS, or urgent revascularization—was significantly reduced in the enoxaparin group (7% vs. 11%, $P = .015$). No difference in mortality or bleeding by 30 days was seen, and clopidogrel was the sole $P2Y_{12}$ antagonist. It should be noted that prehospitalization administration may be challenging in certain hospital networks.

The Sixth Organisation for the Assessment of Strategies for Ischemic Syndromes (OASIS-6) was a large, randomized, double-blind trial of fondaparinux versus UFH in STEMI patients.[28] In addition to patients managed with PPCI (~31% of the study population), the study included patients managed with fibrinolysis (~45%) and with CABG (~1%). Prerandomization use of UFH and GP IIb/IIIa inhibitors was permitted and occurred in 20.8% of patients randomized to fondaparinux.

The study's primary outcome of death or MI for all patients was significantly reduced at 30 days with fondaparinux (9.7% vs. 11.2%, $P = .08$). However, subgroup analysis of the patients who received PPCI did not reveal a mortality difference at 30 days (fondaparinux 4.5% vs. UFH 3.9%, $P = .36$). In addition, no difference was found in the rate of severe bleeding between the two groups, and concerns regarding excess catheter thrombosis with fondaparinux alone were largely avoided with the use of additional heparin during the procedure.

Summary

Based on the current available trial data and clinical guidelines, no clear consensus has been reached in regard to the most optimal anticoagulant in STEMI patients for PPCI. Formal randomized trials to examine the dose of UFH have not been undertaken, although

bivalirudin and enoxaparin appear to be preferred; however, factors such as hospital protocols, physician familiarity, and cost will influence decision making. Further blinded large-scale trials in the future may provide insights into optimizing the critical balance of bleeding and ischemic risk in STEMI patients.

Non–ST-Elevation Myocardial Infarction (NSTEMI)

It is well recognized that anticoagulation should accompany antiplatelet agents in patients with NSTEMI who present for invasive management, as seen in multiple small randomized trials and meta-analyses that predominantly compared UFH with placebo. The main agents in current clinical use with established efficacy are UFH, enoxaparin, fondaparinux, and bivalirudin.

Fondaparinux is the anticoagulant with the most favorable efficacy-to-safety profile based on a subgroup analysis of the OASIS-5 trial.[29] This trial included 20,078 patients with unstable angina or NSTEMI who were randomized to receive fondaparinux or enoxaparin. PCI was performed in 6889 patients in whom no differences were present in regard to ischemic complications; however, bleeding events were significantly lower in the fondaparinux group at 48 hours (enoxaparin, 3.4% vs. fondaparinux, 1.4%; $P < .001$), and this reduction in bleeding was only statistically significant in patients with a glomerular filtration rate (GFR) less than 58 mL/min/1.73 m^2.[30] An important finding of OASIS-5 was an increased rate of guiding catheter thrombosis in the fondaparinux group (0.9% vs. 0.4%) despite the amendment to allow a 200 IU flush of UFH. Despite this, however, in the PCI group, the rate of death, MI, stroke, major bleeding, or any procedural complication was significantly lower at 9 days in the fondaparinux group (16.6% vs. 20.6%, $P < .001$).

The optimal dose of adjunctive heparin for patients with NSTEMI undergoing PCI who receive fondaparinux was studied in the Fondaparinux Trial With Unfractionated Heparin During Revascularization in Acute Coronary Syndromes OASIS-8 (FUTURA OASIS-8), which compared standard-dose UFH (85 U/kg or 60U/kg with GP IIb/IIIa use) or fixed low-dose UFH (50 U/kg) in 2026 patients.[31] The primary outcome of PCI-related major and minor bleeding was similar between the groups (standard dose, 5.8%, vs. low dose, 4.7%; $P = .27$); however, the key secondary outcome of death, MI, and TVR was higher in the low-dose group (4.5% vs. 2.9%, $P = .06$). Standard heparin dosing is therefore recommended as adjunctive therapy during PCI for those anticoagulated with fondaparinux.

UFH and enoxaparin have been compared in several trials. Superior Yield of the New Strategy of Enoxaparin Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) was a prospective open-label trial of 10,027 patients with NSTEMI in which PCI was performed in about 47% of patients. Approximately 62% of patients received clopidogrel.[32] The primary end point of death or nonfatal MI was similar between enoxaparin and heparin (14.0% vs. 14.5%, $P = 0.96$). However, the increase in TIMI major (non-CABG related) bleeding events was significant (2.4% vs. 1.8%, $P = .03$). Important limitations to the findings of SYNERGY were that 75% of patients received antithrombin therapy prior to enrollment. In the patients who did not receive prerandomization antithrombin therapy or in whom the prerandomization therapy was the same as the randomly assigned therapy, a reduction in the primary end point was reported with enoxaparin (13.3% vs. 15.9%,) along with similar rates of bleeding. A meta-analysis that included 13 trials of patients with NSTEMI and elective PCI found no difference in all-cause mortality in those treated with enoxaparin compared with those treated with heparin.[33]

Bivalirudin in NSTEMI has been studied in two major trials, Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) and Intracoronary Stenting and Antithrombosis Research Rapid Early Action for Coronary Treatment 4 (ISAR-REACT 4).[34,35] ACUITY was an open-label, randomized, multicenter trial that compared heparin plus a GP IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor, and bivalirudin alone in patients with unstable angina (~42%) or NSTEMI (~58%) who were undergoing an early invasive strategy with planned PCI.[34] This trial comprised 13,819 patients enrolled across 450 centers in 17 countries, and 53% of patients underwent PCI. The main finding of ACUITY was that bivalirudin alone, compared with heparin plus a GP IIb/IIIa inhibitor, resulted in a significantly reduced rate of major bleeding (3.0% vs. 5.7%). This subsequently resulted in a superior net clinical outcome end point, defined as the composite ischemic end point and major bleeding (bivalirudin, 10.1%, vs. UHF/GP IIb/IIIa inhibition, 11.7%; $P = .02$; Fig. 11-5).

In contrast to ACUITY, ISAR-REACT 4 was a trial that only enrolled NSTEMI patients. This double-blind randomized trial of 1721 patients compared bivalirudin with the combination of UFH and abciximab in patients with a planned early invasive approach. Notably, all patients received clopidogrel, and most coronary angiograms were performed through the femoral artery. The primary end point—a composite of death, recurrent MI, urgent TVR, or major bleeding at 30 days—was similar between both groups (10.9% vs. 11.0%; $P = .94$). However, a significant reduction in major bleeding was observed in patients treated with bivalirudin (2.6% vs. 4.6%; $P = .02$).

Summary

A large body of heterogeneous, and at times conflicting, clinical trial evidence exists for the use of various anticoagulant agents in patients with NSTEMI in whom an invasive approach has been planned. Some trial data are confounded by variables such as the open-label trial design, predominant femoral artery access, use of clopidogrel, and prerandomization use of anticoagulant agents. The choice of anticoagulant agent will depend on factors such as bleeding risk, choice of antiplatelet $P2Y_{12}$ inhibition, renal function, local hospital protocols, drug availability, and cost.

Percutaneous Coronary Intervention for Stable Coronary Artery Disease

The rationale for anticoagulation in patients with stable angina presenting for elective PCI is to (1) prevent thrombus formation on the coronary guidewire and PCI catheter, (2) allow adequate thrombin inhibition where intracoronary thrombus is present (seen in up to 65% of patients with stable angina), and (3) to balance the prothrombotic and inflammatory responses of stenting.[14,20] Two moderate-sized randomized controlled trials (RCTs) have been undertaken that have challenged this dogma, both trials of heparin versus placebo in patients presenting for elective PCI.

The Efficacy and Safety of Triple Antiplatelet Therapy With and Without Concomitant Anticoagulation During Elective Percutaneous Coronary Intervention (REMOVE) trial randomized 159 patients undergoing elective PCI to eptifibatide alone or eptifibatide plus UFH. All patients received aspirin and clopidogrel.[36] The primary end point of bleeding (measured by the Landefeld bleeding severity index) was significantly reduced in the group who did not receive heparin (3.0% vs. 3.9%, $P = .03$). No difference was found in the composite end point of death and ischemic and bleeding end points. Limitations to REMOVE included the trial protocol having to be amended as a result of spontaneous thrombus formation during bifurcation-lesion PCI.

REMOVE was followed up by the larger Coronary Interventions Antiplatelet-Based Only (CIAO) trial.[37] This double-blind RCT compared the safety and efficacy of antiplatelet therapy alone versus use of UFH in 700 patients who presented for elective PCI of uncomplicated lesions. Of note, patients with high-risk angiographic characteristics such as calcification, long lesions, small vessels, bifurcation lesions, and vein graft lesions were excluded. Antiplatelet therapy consisted of aspirin and either ticlopidine or clopidogrel. All procedures were performed via femoral artery access, and GP IIb/IIIa inhibitors were not used. No difference was found in the 30-day primary end point (death, MI, or TVR) between the heparin and placebo groups (3.7% vs. 2.0%, respectively; $P = .17$), although less bleeding was reported in the placebo group; however, the absolute number of bleeding events was small, and significance was only reached in the Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation

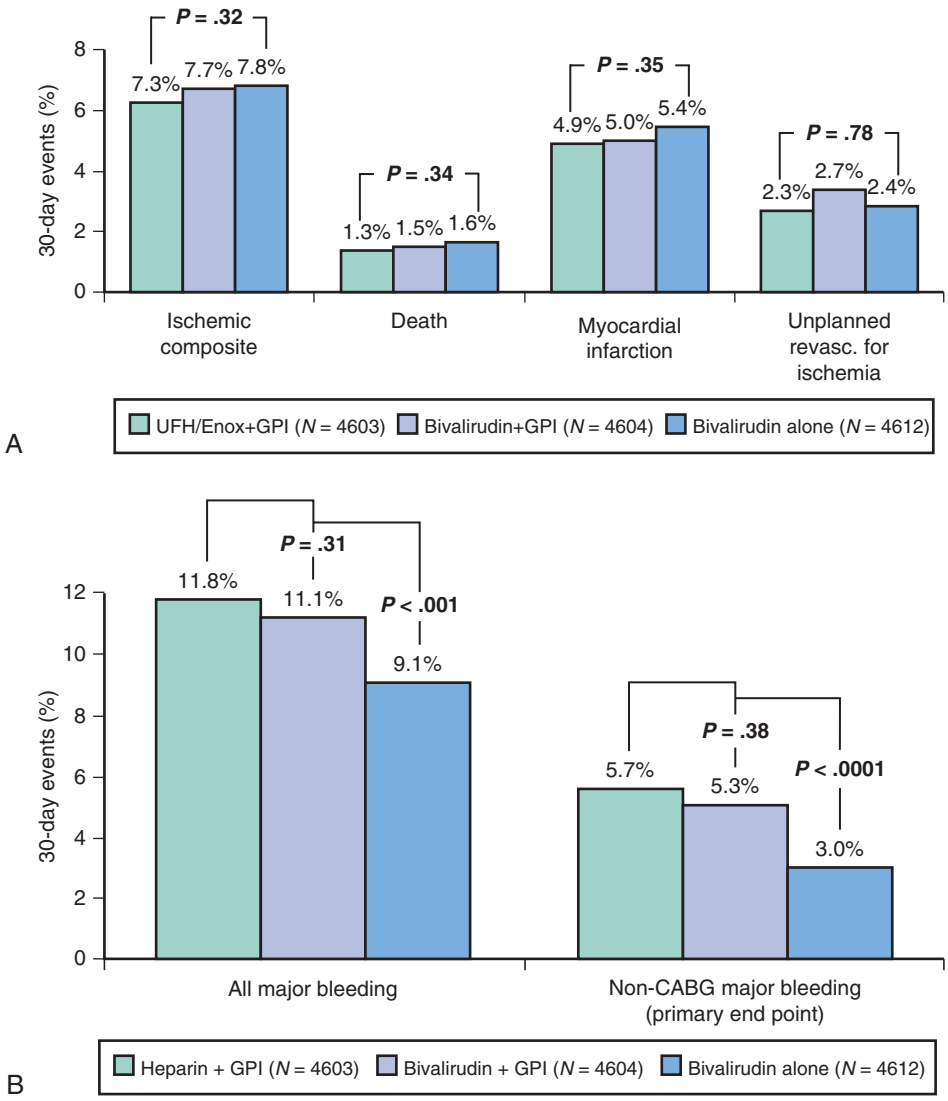

FIGURE 11-5 Ischemic (**A**) and bleeding (**B**) outcomes with bivalirudin versus bivalirudin/glycoprotein IIb/IIIa inhibition (GPI) versus unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH)/GPI in the ACUITY trial. *CABG,* Coronary artery bypass grafting; *Enox,* enoxaparin; *revasc.,* revascularization.

(STEEPLE) bleeding-score assessment, not in TIMI, ACUITY, or GUSTO bleeding scores.

Given the pathobiologic basis for the important role of thrombin inhibition in elective PCI and the shortcomings of the REMOVE and CIAO trials, anticoagulation has become the standard of care for patients who present for elective PCI. The choice of agent is less clear because only one large RCT was specifically designed for patients undergoing elective PCI.

STEEPLE was an open-label multicenter trial that enrolled 3528 patients; it was designed to assess the safety of IV enoxaparin (0.75 or 0.5 mg/kg regardless of the use of GP IIb/IIIa inhibitors) versus UFH (IV bolus 70 to 100 IU followed by adjustment according to an ACT between 300 to 350 seconds).[38] The dose of UFH was reduced with the use of GP IIb/IIIa inhibitors (bolus intravenous dose of 50 to 70 IU and target ACT 200 to 300 seconds). Approximately 94% of patients had received a thienopyridine on the day of PCI. All arterial access was via the femoral artery, and sheath removal for the 0.75 mg/kg enoxaparin group occurred 4 to 6 hours after PCI but was done immediately for the 0.5 mg/kg enoxaparin group. Sheath removal for the UFH group occurred when the ACT was between 150 and 180 seconds. The primary end point of non-CABG–related major and minor bleeding within the first 48 hours was lowest in the 0.5 mg/kg enoxaparin group (5.9%); it was 6.5% in the 0.75 mg/kg enoxaparin group and 8.5% in the UFH group (Fig. 11-6). A statistically significant reduction was noted between the 0.5 mg/kg and UFH groups ($P = .01$), whereas the difference between the 0.5 mg/kg and 0.75 mg/kg enoxaparin groups met the prespecified criteria for noninferiority. In patients who did not receive GP IIb/IIIa inhibitors, even less bleeding was reported in the patients who received enoxaparin. No differences in ischemic end points were reported among the three groups, although the trial was not sufficiently powered to determine these effects.

Bivalirudin has been studied in elective PCI in a subgroup of ISAR-REACT 3 that comprised approximately 82% of the study population. As mentioned, this large trial compared bivalirudin and UFH at high doses (140 U/kg) in patients pretreated with 600 mg clopidogrel and showed no difference in net clinical benefit between the two agents, although a significant reduction was seen in major bleeding with bivalirudin.

Summary

Anticoagulation remains the standard of care during elective PCI based on the atherothrombotic potential of stable plaque and the

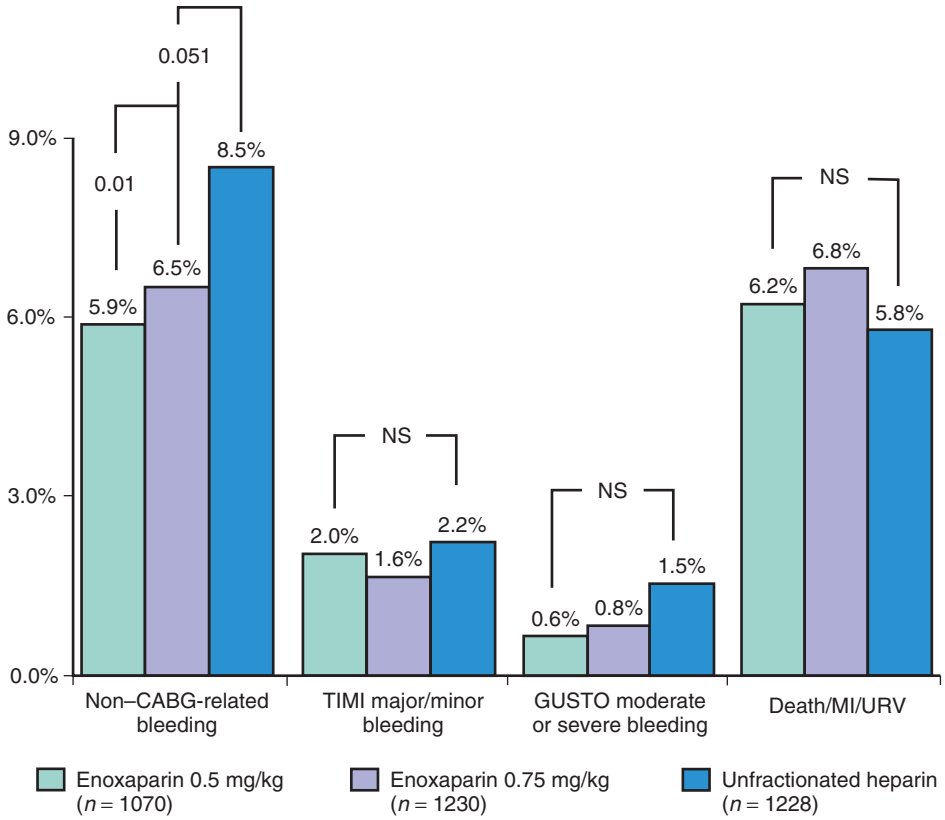

FIGURE 11-6 Protocol-defined major bleeding and ischemic events in the STEEPLE trial. *CABG,* Coronary artery bypass grafting; *GUSTO,* global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries; *MI,* myocardial infarction; *NS,* nonsignificant; *TIMI,* thrombolysis in myocardial infarction; *URV,* urgent revascularization.

prothrombotic effect of stenting. This is despite two RCTs of REPLACE-2 and CIAO that challenged this assertion, although both trials have limitations. The choice of anticoagulation is more difficult because of the paucity of large RCTs with the currently available agents. Evidence from STEEPLE suggests that enoxaparin may be superior to heparin; however, radial arterial access and the newer-generation $P2Y_{12}$ antiplatelet agents were not in use, which limited this trial's applicability to current practice.

SPECIAL PATIENT GROUPS

With the broad array of therapies available, weighing the limitations and benefits of each approach is often difficult. In many patients, the use of UFH remains a safe and efficacious choice, especially in the context of pretreatment with a $P2Y_{12}$ inhibitor and the planned used of GP IIb/IIIa inhibition. However, in specific high-risk populations, the decision to use an alternative antithrombotic strategy may be considered.

Patients Transitioning From "Upstream" Management to the Catheterization Lab

Extrapolation of the clinical experience with UFH suggests that the degree of anticoagulation required during PCI is greater than that required during the medical management of ACS patients. As a result, strategies have evolved to optimize the antithrombin therapies among ACS patients proceeding to PCI while already receiving one of these agents. Among patients being treated with heparin, an ACT-guided approach is recommended, with an additional 20 to 50 U/kg IV administered to achieve an ACT greater than 200 to 250 seconds when concomitant GP IIb/IIIa inhibition is planned and more than 300 to 350 seconds when heparin is the sole agent. Data with enoxaparin suggest that PCI can proceed without additional dosing when the procedure is occurring within 8 hours of the subcutaneous dose, whereas an additional IV bolus of 0.3 mg/kg is recommended when the delay will be from 8 to 12 hours. Outside this window, a dose of 0.75 mg/kg by IV should be administered regardless of GP IIb/IIIa inhibition use based on the SYNERGY study. Among patients receiving infusions of bivalirudin, an addition bolus of 0.5 mg/kg and an increase in the infusion rate to 1.75 mg/kg was shown to be safe and efficacious in the ACUITY study, again regardless of GP IIb/IIIa use (Table 11-5). Observations from the ACUITY study also suggest that patients who receive bivalirudin after initial heparin or enoxaparin continued to experience a reduced rate of bleeding complications without compromise to ischemic benefits.

Patients With Renal Impairment

Increased ischemic and bleeding events are observed among patients with renal dysfunction. Analyses of the RCT experience with bivalirudin suggests the relative benefits of this agent are preserved in terms of bleeding complications and ischemic complications.[34,39-40] Hence in absolute terms, among patients with at least moderate renal dysfunction (creatinine clearance <60 mL/min), bivalirudin is associated with a greater absolute benefit with respect to bleeding without an excess risk of ischemic events (Fig. 11-7). With enoxaparin and fondaparinux, limited data are available from small studies that have examined the relative risks and benefits in the context of renal impairment; however, reports of relative safety must be confirmed in larger studies.

Diabetic Patients

Subgroup analysis of RCTs appears to indicate that abciximab provides substantial benefits in terms of reduced repeat revascularization and

TABLE 11-5 Dosing of Currently Available Antithrombin Agents

	Unfractionated Heparin	Enoxaparin	Fondaparinux	Bivalirudin
No prior treatment	60-100 U/kg IV*	0.5-0.75 mg/kg IV	2.5 mg SC	0.75 mg/kg IV with 1.75 mg/kg/hr infusion
Upstream ACS management	60 IU/kg IV and 800-1000 IU/hr infusion	1.0 mg/kg SC BID	UFH bolus recommended (see text)	0.1 mg/kg IV with 0.25 mg/kg/hr infusion
Additional bolus prior to PCI	20-50 IU/kg*	<8 hr since last dose: None 8-12 hr since last SC dose: 0.3 mg/kg IV	2.5 mg IV with a GP IIb/IIIa inhibitor or 5 mg IV without a GP IIb/IIIa inhibitor	0.5 mg/kg IV bolus
Infusion during PCI	None	None	None	1.75 mg/kg/hr infusion

*Targeting an activated clotting time (ACT) greater than 200 seconds with concomitant glycoprotein IIb/IIIa inhibition or ACT greater than 300 to 350 seconds without concomitant glycoprotein IIb/IIIa inhibition.
ACS, Acute coronary syndrome; *BID,* twice daily; *GP,* glycoprotein; *IV,* intravenous; *PCI,* percutaneous coronary intervention; *SC,* subcutaneous; *UFH,* unfractionated heparin.

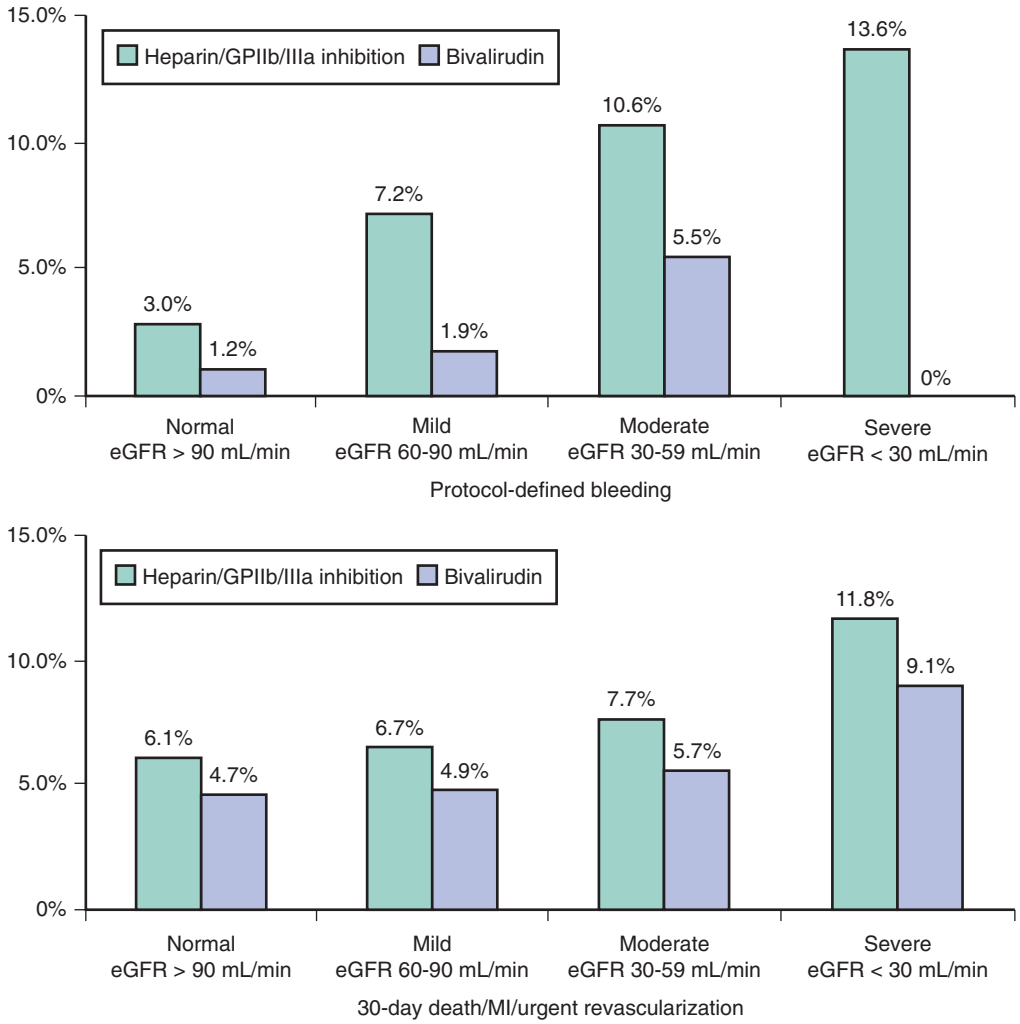

FIGURE 11-7 Relationship between renal function and outcomes with bivalirudin. *DTI,* Direct thrombin inhibitor; *eGFR,* estimated glomerular filtration rate; *GP,* glycoprotein; *MI,* myocardial infarction; *UFH,* unfractionated heparin.

mortality among diabetic patients, with comparable effects observed with tirofiban. Clinical trial evidence with bivalirudin supports similar conclusions. In the REPLACE-2 study, bivalirudin and provisional GP IIb/IIIa inhibition was compared with heparin and GP IIb/IIIa inhibition; bivalirudin-treated diabetic patients experienced a lower but nonsignificant (NS) rate of mortality at 12 months (2.3% vs. 3.9%, P = NS). No difference in the rate of 30-day bleeding and ischemic outcomes was observed.[41] Whereas the effects of enoxaparin-based strategies among diabetic patients have yet to be reported, a substantial rate of concomitant GP IIb/IIIa use in these studies will limit the interpretation of this data.

Patients With Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) precludes the use of UFH during PCI. Whereas the rate of HIT is less frequent with the LMWHs, cross-reactivity with these agents is observed and may be associated with increased rates of ischemic and bleeding complications.

Fondaparinux has been used successfully to treat HIT, but the need for intraprocedural heparin with this agent precludes its use in PCI. Bivalirudin is well suited to the management of HIT patients who require PCI.[42] A registry of 52 HIT patients who received bivalirudin prior to PCI reported a 96% rate of freedom from death, Q-wave MI, and emergent CABG. Thrombocytopenia (platelet count <50 10^9/L) was not observed among these patients, which suggests bivalirudin is also an alternative anticoagulation strategy within this infrequent but high-risk subgroup.[43]

GLYCOPROTEIN IIB/IIIA SPARING, COMBINATION APPROACHES, AND ECONOMIC CONSIDERATIONS

When required, combination antithrombotic strategies that include pretreatment with $P2Y_{12}$ inhibitors, IV GP IIb/IIIa inhibition, and either the direct or indirect thrombin inhibitors appear to be safe. However, given the cost of GP IIb/IIIa inhibition and the increased risk of bleeding events, efforts to refine the antithrombotic approach and define patient subsets that may not derive incremental benefits from these agents have continued. Optimization of anticoagulant therapies may mitigate the dependence on potent platelet inhibition. To date, with respect to antithrombin therapy and GP IIb/IIIa sparing, the most robust data are found with bivalirudin, given the study designs used in the REPLACE-2, ACUITY, and HORIZONS-AMI studies. Whereas pretreatment with thienopyridines did not appear to influence this relationship, success with more potent oral agents, such as prasugrel and ticagrelor, may provide a further rationale for glycoprotein sparing, although this should be formally examined in optimally designed clinical trials.[44] Given reductions in drug costs and costs associated with bleeding, the bivalirudin strategy is economically attractive.[45] The increased bleeding risk among older adults and among female patients also favors greater absolute benefits with bivalirudin in this context. However, therapies associated with reduced bleeding but comparable ischemic outcomes may be of limited value in the context of radial access PCI, in which bleeding risks are substantially lower. With increased emphasis on reducing procedural cost, some centers have moved to formally assessing the bleeding risk score and are using bivalirudin solely for patients at higher bleeding risk.[46]

CONCLUSION

Substantial clinical trial evidence now supports the use of novel coagulants among patients undergoing PCI. These agents generally demonstrate improved efficacy and safety when compared with heparin and enable less use of GP IIb/IIIa inhibition.

REFERENCES

1. Schwartz RS, Borissoff JI, Spronk H: The hemostatic system as a modulator of atherosclerosis. *N Engl J Med* 364:1746–1760, 2011.
2. Davie EW, Kulman JD: An overview of the structure and function of thrombin. *Semin Thromb Hemost* 32(Suppl 1):3–15, 2006.
3. Zucker TP, Bönisch D, Muck S, et al: Thrombin-induced mitogenesis in coronary artery smooth muscle cells is potentiated by thromboxane A2 and involves upregulation of thromboxane receptor mRNA. *Circulation* 97:589–595, 1998.
4. Tulinsky A: Molecular interactions of thrombin. *Semin Thromb Hemost* 22:117–124, 1996.
5. Fox K, Steg PG, Eagle KA, et al: Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. *JAMA* 297(17): 1892–1900, 2007.
6. Thygesen K, Alpert JS, Jaffe AS, et al: Third universal definition of myocardial infarction. *J Am Coll Cardiol* 60:1581–1598, 2012.
7. Moussa ID, Klein LW, Shah B, et al: Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol* 62(17):1563–1570, 2013.
8. Lansky AJ, Stone GW: Periprocedural myocardial infarction: prevalence, prognosis, and prevention. *Circulation Cardiovasc Interv* 3:602–610, 2010.
9. Chew DP, Bhatt DL, Lincoff AM, et al: Clinical end point definitions after percutaneous coronary intervention and their relationship to late mortality: an assessment by attributable risk. *Heart* 92:945–950, 2006.
10. Mehran R, Pocock S, Nikolsky E, et al: Impact of bleeding on mortality after percutaneous coronary intervention. *JACC Cardiovasc Interv* 4:654–664, 2011.
11. Mehran R, Rao SV, Bhatt DL, et al: Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 123: 2736–2747, 2011.
12. Wang TY, Xiao L, Alexander KP, et al: Antiplatelet therapy use after discharge among acute myocardial infarction patients with in-hospital bleeding. *Circulation* 118:2139–2145, 2008.
13. Rao SV, Jollis JG, Harrington RA, et al: Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA* 292:1555–1562, 2004.
14. De Caterina R, Husted S, Wallentin L, et al: Parenteral anticoagulants in heart disease: current status and perspectives (section II). *Thromb Haemost* 109:769–786, 2013.
15. Xiao Z, Theroux P: Platelet activation with unfractionated heparin at therapeutic concentrations and comparisons with a low-molecular-weight heparin and with a direct thrombin inhibitor. *Circulation* 97:251–256, 1998.
16. Weitz JI: Low-molecular-weight heparins. *N Engl J Med* 337:688–698, 1997.
17. Martin JL, Fry ET, Sanderink GJ, et al: Reliable anticoagulation with enoxaparin in patients undergoing percutaneous coronary intervention: the pharmacokinetics of enoxaparin in PCI (PEPCI) study. *Catheter Cardiovasc Interv* 61:163–170, 2004.
18. Choussat R, Montalescot G, Collet JP, et al: A unique, low dose of intravenous enoxaparin in elective percutaneous coronary intervention. *J Am Coll Cardiol* 40(11):1943–1950, 2002.
19. Weitz JI, Bates SM: New anticoagulants. *J Thromb Haemost* 3(8):1843–1853, 2005.
20. Dyke CK, Steinhubl SR, Kleiman NS, et al: First-in-human experience of an antidote-controlled anticoagulant using RNA aptamer technology: a phase 1a pharmacodynamic evaluation of a drug-antidote pair for the controlled regulation of factor IXa activity. *Circulation* 114:2490–2497, 2006.
21. Bompian KM, Monroe DM, Church FC, et al: A high affinity, antidote-controllable prothrombin and thrombin-binding RNA aptamer inhibits thrombin generation and thrombin activity. *J Thromb Haemost* 10:870–880, 2012.
22. Povsic TJ, Vavalle JP, Aberle LH, et al: A phase 2, randomized, partially blinded, active-controlled study assessing the efficacy and safety of variable anticoagulation reversal using the REG1 system in patients with acute coronary syndromes: results of the RADAR trial. *Eur Heart J* 34:2481–2489, 2013.
23. Steg PG, Mehta S, Pollack C, Jr, et al: Anticoagulation with otamixaban and ischemic events in non–ST-segment elevation acute coronary syndromes. *JAMA* 310:1145–1154, 2013.
24. Stone GW, Witzenbichler B, Guagliumi G, et al: Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 358:2218–2230, 2008.
25. Steg PG, van 't Hof A, Hamm CW, et al: Bivalirudin started during emergency transport for primary PCI. *N Engl J Med* 369:2207–2217, 2013.
26. Shahzad A, Kemp I, Mars C, et al: Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet* 384(9957):1849–1858, 2014.
27. Montalescot G, Zeymer U, Silvain J, et al: Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. *Lancet* 378:693–703, 2011.
28. Yusuf S, Mehta S, Chrolavicius S, et al: Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 295:1519–1530, 2006.
29. Yusuf S, Mehta S, Chrolavicius S, et al: Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 354:1464–1476, 2006.
30. Cavusoglu E, Lakhani M, Marmur JD: The activated clotting time (ACT) can be used to monitor enoxaparin and dalteparin after intravenous administration. *J Invasive Cardiol* 17(8):416–421, 2005.
31. Steg PG, Jolly SS, Mehta SR, et al: Low-dose vs standard-dose unfractionated heparin for percutaneous coronary intervention in acute coronary syndromes treated with fondaparinux: the FUTURA/OASIS-8 randomized trial. *JAMA* 304:1339–1349, 2010.
32. Ferguson JJ, Califf RM, Antman EM, et al: Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. *JAMA* 292(1):45–54, 2004.
33. Silvain J, Beygui F, Barthelemy O, et al: Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. *Br Med J* 344:e553, 2012.
34. Stone GW, McLaurin BT, Cox DA, et al: Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 355:2203–2216, 2006.
35. ISAR-REACT 4 Trial Investigators: Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. *N Engl J Med* 365:1980–1989, 2011.
36. Valencia R, Price MJ, Sawhney N, et al: Efficacy and safety of triple antiplatelet therapy with and without concomitant anticoagulation during elective percutaneous coronary intervention (the REMOVE trial). *Am J Cardiol* 100(7):1099–1102, 2007.
37. Stabile E, Nammas W, Salemme L, et al: The CIAO (Coronary Interventions Antiplatelet-based Only) study. *JAMA* 52:1293–1298, 2008.
38. Montalescot G, White HD, Gallo R, et al: Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. *N Engl J Med* 355:1006–1017, 2006.
39. Chew DP, Bhatt DL, Kimball W, et al: Bivalirudin provides increasing benefit with decreasing renal function: a meta-analysis of randomized trials. *Am J Cardiol* 92(8):919–923, 2003.
40. Chew DP, Lincoff AM, Gurm H, et al: Bivalirudin versus heparin and glycoprotein IIb/IIIa inhibition among patients with renal impairment undergoing percutaneous coronary intervention (a subanalysis of the REPLACE-2 trial). *Am J Cardiol* 95(5):581–585, 2005.
41. Gurm HS, Sarembock IJ, Kereiakes DJ, et al: Use of bivalirudin during percutaneous coronary intervention in patients with diabetes mellitus: an analysis from the randomized evaluation in percutaneous coronary intervention linking angiomax to reduced clinical events (REPLACE)-2 trial. *J Am Coll Cardiol* 45(12):1932–1938, 2005.
42. Kelton JG, Arnold DM, Bates SM: Non-heparin anticoagulants for heparin-induced thrombocytopenia. *N Engl J Med* 368:737–744, 2013.
43. Mahaffey KW, Lewis BE, Wildermann NM, et al: The anticoagulant therapy with bivalirudin to assist in the performance of percutaneous coronary intervention in patients with heparin-induced thrombocytopenia (ATBAT) study: main results. *J Invasive Cardiol* 15(11):611–616, 2003.
44. Saw J, Lincoff AM, DeSmet W, et al: Lack of clopidogrel pretreatment effect on the relative efficacy of bivalirudin with provisional glycoprotein IIb/IIIa blockade compared to heparin with routine glycoprotein IIb/IIIa blockade: a REPLACE-2 substudy. *J Am Coll Cardiol* 44:1194–1199, 2004.
45. Cohen DJ, Lincoff AM, Lavelle TA, et al: Economic evaluation of bivalirudin with provisional glycoprotein IIB/IIIA inhibition versus heparin with routine glycoprotein IIB/IIIA inhibition for percutaneous coronary intervention: results from the REPLACE-2 trial. *J Am Coll Cardiol* 44:1792–1800, 2004.
46. Rao SC, Chhatriwalla AK, Kennedy KF, et al: Pre-procedural estimate of individualized bleeding risk impacts physicians' utilization of bivalirudin during percutaneous coronary intervention. *J Am Coll Cardiol* 61(18):1847–1852, 2013. doi: 10.1016/j.jacc.2013.02.017.

Lipid Lowering in Coronary Artery Disease

12

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KEY POINTS

- Epidemiologic studies suggest a linear relationship between cholesterol and risk for coronary artery disease (CAD).
- A linear relationship exists between the magnitude of low-density lipoprotein cholesterol (LDL-C) reduction and clinical benefit.
- Randomized trials have shown that intensive statin therapy reduces major cardiovascular events by 16% and heart failure by 27% compared with moderate statin therapy.
- In patients with CAD, LDL-C should be lowered to less than 1.8 mmol/L or by 50% (European Society of Cardiology [ESC] 2011 guidelines) and LDL-C should be lowered by 50% with a high-intensity statin (American College of Cardiology [ACC]/American Heart Association [AHA] 2013 guidelines).

EPIDEMIOLOGY

CAD is the primary cause of premature death in the Western world (Fig. 12-1). A person is born with an LDL-C level of 0.8 mmol/L, which increases throughout life (Fig. 12-2, *A*). Several epidemiologic studies have demonstrated a relationship between elevated total cholesterol and LDL-C and an increased risk of death or nonfatal myocardial infarction (MI).[1-4] The relationship between cholesterol and risk of CAD is linear, with no apparent threshold below which risk declines (see Fig. 12-2, *B*), which suggests that interventions that reduce cholesterol the most are also likely to have the greatest impact on CAD risk reduction.[5] The central role of cholesterol in the pathophysiology of CAD has pushed lipid-lowering therapy to the forefront of medical management of this condition.

The largest observational study to date involved over 1 million person-years worth of observation and more that 10,000 cases of fatal or nonfatal MI; it has shed further light on the relevance of simultaneous assessment of triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), and non–HDL-cholesterol (non–HDL-C). Non–HDL-C consists of very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and LDL-C.[6] After adjustment for non–HDL-C and HDL-C, no association has been found between TG and risk of CAD (Fig. 12-3). In contrast, the inverse association between HDL-C and risk persists with some attenuation above 70 mg/dL. One practical implication of this observation is that among individuals with an HDL-C greater than 70 mg/dL, use of the total cholesterol (TC)/HDL-C ratio underestimates cardiovascular (CV) risk derived from risk calculators. As with LDL-C, a positive relationship has been observed between non–HDL-C and risk of CAD with little attenuation. Because non–HDL-C captures all atherogenic lipoproteins, not just LDL, it is proportionally about one third more strongly associated with coronary heart disease (CHD) than LDL-C for each standard deviation.[6] No difference has been observed between fasting and nonfasting levels and risk, suggesting that lipid measurements can be simplified by using non–HDL-C (the difference between TC and HDL-C) and HDL-C levels. Data suggest that TGs are unlikely to be causative factors but rather are markers of risk and that risk is conferred by the concomitant low levels of HDL-C and high levels of non–HDL-C. These latter two factors, rather than TGs, should be the targets of treatment in people with elevated TG levels, providing independent support for the U.K. National Cholesterol Education Programme (NCEP) goals.

The LDL-C level incompletely measures atherogenic lipoproteins. Measurement of the concentration of apolipoprotein B (apo B), a direct measurement of the concentration of proatherogenic particles (e.g., LDL-C, VLDL, IDL), and measurement of apo AI, the major protein in HDL particles, provide an alternative approaches to risk prediction. The debate regarding the choice of the best lipid parameter has intensified because of apparently conflicting evidence between prospective studies.[6-8] In approximately 100,000 individuals with about half a million person-years worth of follow-up, it is now clear that overall apo B (the major lipoprotein) in atherogenic particles is equivalent to non–HDL-C and that apo AI, the major protein in HDL particles, is equivalent to HDL-C (Fig. 12-4); this suggests that the choice of assays should be informed by availability and cost.

Lipoprotein(a), or Lp(a), consists of one apo B particle bonded to a protein apolipoprotein. Lp(a) is hepatically synthesized under genetic control, which makes it the most reproducible biomarker known.[9] Elevated Lp(a) levels potentially increase the risk of cardiovascular disease (CVD) via two main mechanisms: first, through a prothrombotic/antifibrinolytic effect because Lp(a) possesses structural homology with plasminogen and plasmin, and second, through accelerated atherogenesis due to intimal deposition of Lp(a) cholesterol. Observational data from 126,634 individuals suggest a curvilinear association between levels and risk of CAD and stroke that persists even after adjustment for conventional risk factors and other lipid fractions (Fig. 12-5).[10] It is likely that this factor is causally related and specific for CVD because no association exists with nonvascular deaths (a prerequisite of the Bradford-Hill criteria for causality). Mendelian randomization has provided consistent data for an association of Lp(a) genotype with Lp(a) levels and, in turn, between genotypes and CAD risk.[11] Further strong evidence for a causal relationship is provided by gene chip analysis of single-nucleotide polymorphisms in the large Precocious Coronary Artery Disease (PROCARDIS) cohort of patients with and without CAD.[12] Two Lp(a) gene variants were identified that were strongly associated with both increased Lp(a) levels and an increased risk of CAD. After adjusting for Lp(a) levels, the association between the *LPA* genotype and CAD risk disappeared, which further supports a causal association.

INTERNATIONAL GUIDELINES

The NCEP, launched in 1985 in the United Kingdom, was the first step toward providing consensus criteria for the measurement, detection, and treatment of patients with hypercholesterolemia.[13] Dietary modification was the cornerstone of therapy with drug therapy reserved for those at especially high risk or for those in whom lifestyle intervention had failed. Total cholesterol levels of 200 mg/dL (5.2 mmol/L) and 240 mg/dL (6.2 mmol/L) were deemed to be the relevant age-dependent thresholds for intervention.

Over the last 30 years, a number of national and international guidelines have been developed that have to varying degrees incorporated new data as they have become available. Arguably the two most important of these guidelines are the ACC/AHA 2013 guidelines on the prevention of atherosclerotic cardiovascular disease and the 2011 ESC/European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias.[14,15]

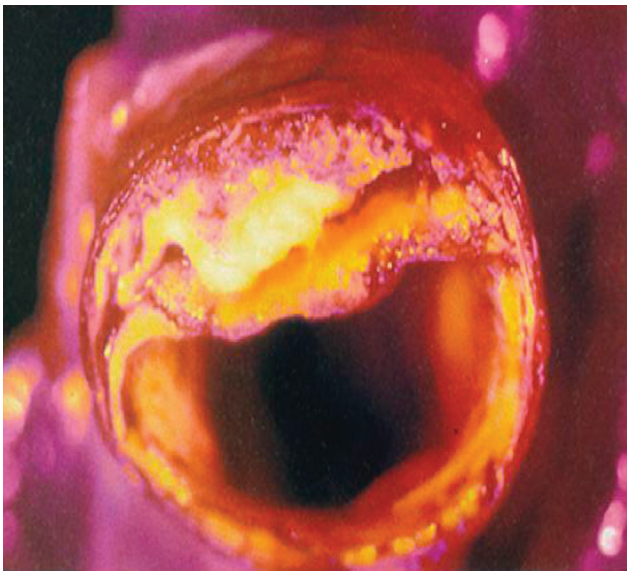


FIGURE 12-1 Lipid-rich atherosclerotic plaque in a coronary artery.

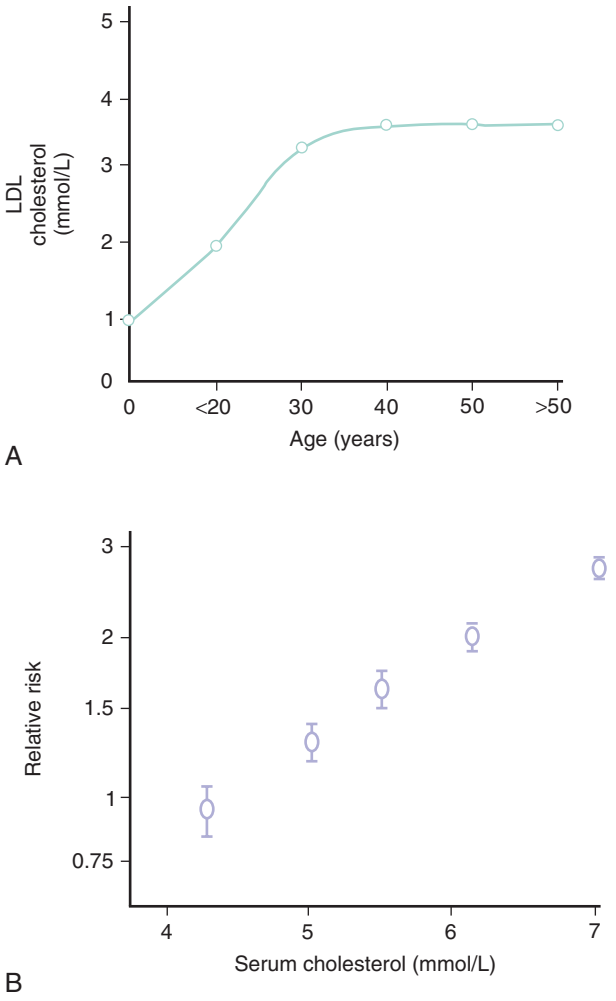


FIGURE 12-2 **A,** The change in low-density lipoprotein (LDL) cholesterol levels throughout life. **B,** The relationship between cholesterol and long-term risk of coronary heart disease. (**A,** Data from Freedman DS, Srinivasan SE, Cresanta JL, et al: Cardiovascular risk factors from birth to 7 years of age: the Bogalusa Heart Study. Serum lipids and lipoproteins. *Pediatrics* 80[Pt 2]:789-796, 1987; and Webber LS, Srinivasan SE, Wattigney WA, Berenson GD: Tracking of serum lipids and lipoproteins from childhood to adulthood. The Bogalusa Heart Study. *Am J Epidemiol* 133:884-899, 1991; **B,** Data from Law MR, Wald NJ: Risk factor thresholds: their existence under scrutiny, *BMJ* 324:1570-1576, 2002.)

The two guidelines share a number of core similarities, and both agree with the following:

- LDL-C is a major causal factor in the development of atherosclerotic CVD.
- Lifestyle and behavior modification should be actively pursued, but drug therapy—primarily with statins—should be initiated early in those at elevated risk.
- Patients with established CVD, diabetes mellitus, or familial hypercholesterolemia and those stratified to a high-risk category after global risk assessment all benefit from a lipid-lowering strategy.

However, a number of key differences exist between the guidelines that merit discussion. Notably, the recommendations of the two guidelines are different. Because the 2011 ESC/EAS guidelines comprehensively assessed all sources of data—as opposed to the 2013 ACC/AHA guidelines, which stringently included only randomized-controlled trial (RCT) data—its scope is broader in that it addresses a wider range of conditions, such as those with significant hypertriglyceridemia, and scenarios, such as those with statin intolerance (Table 12-1). Additionally, the interpretation of the level of evidence (LOE) in both guidelines is different (Table 12-2).

At the heart of any prevention-focused guideline is appropriate risk stratification. The tools and criteria used to identify those at elevated risk are substantially different. The ESC/EAS combines the Systematic Coronary Risk Evaluation (SCORE) predictor-derived risk together with LDL-C levels to determine therapy for primary prevention. The mixed-pool model used by the ACC/AHA has not been fully validated and is not applicable to a number of populations, such as those of Asian origin. It classifies a large proportion of subjects as being high risk when compared with the SCORE risk calculator used by the ESC/EAS. For instance, a 10-year mixed-pool risk for CVD death of 7.5%—a key threshold in the ACC/AHA guidelines—corresponds to only a 2.5% risk using the SCORE risk predictor. This difference in categorization has far-reaching implications: using the ACC/AHA guidelines, almost two thirds of the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC)–Norfolk prospective population study would be eligible for commencement on statin therapy.[16] Similarly, in the United States, 48.6% of healthy individuals would now be eligible for statins in primary prevention, including almost 88% of men and 54% of women aged 60 to 75 years.[17] For secondary prevention, the ESC/EAS guidance allows findings from imaging studies to be taken into consideration when identifying those with established CVD in the absence of a prior clinical history, whereas the ACC/AHA guidelines do not.

A fundamental difference is that the ACC/AHA guidance abandons lipid levels as a therapeutic target in favor of a percentage reduction in LDL-C in order to achieve a reduction in risk, citing lack of treatment-to-target RCT quality evidence to support this approach. The ESC/EAS has acknowledged the available observational data and meta-analyses from over 150,000 subjects, which highlight the log-linear relationship of LDL-C levels and other key lipid fractions—such as non–HDL-C, TG-rich lipoproteins, remnants that contribute to "residual risk"—with CVD risk, and such measurements feature heavily in their guidance. Additionally the loss of LDL-C monitoring may well leave some individuals, such as those with familial hypercholesterolemia (FH) and CAD, at very high absolute risk despite achieving a 50% reduction in LDL-C. Furthermore, without monitoring LDL-C, we miss the opportunity to assess efficacy and compliance.

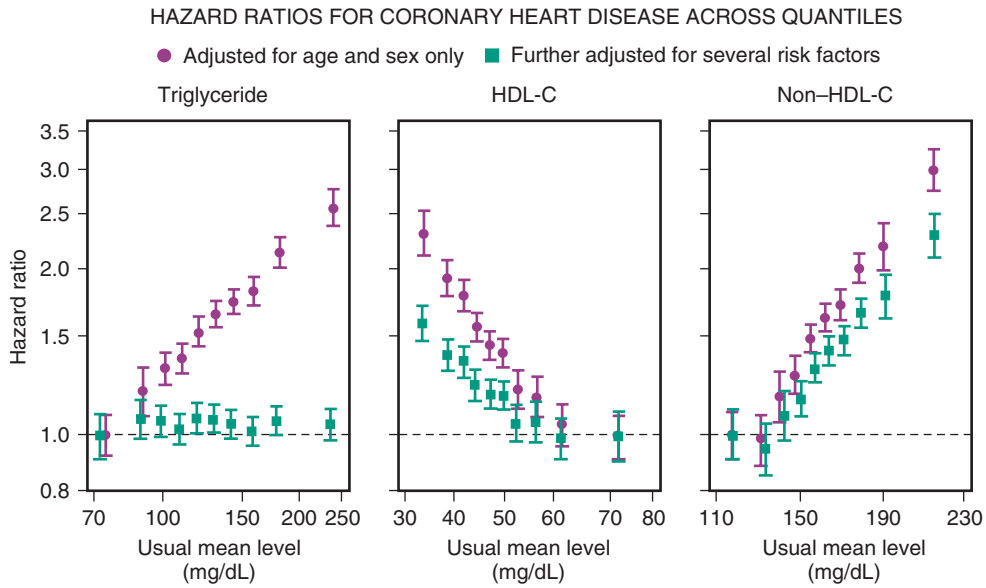
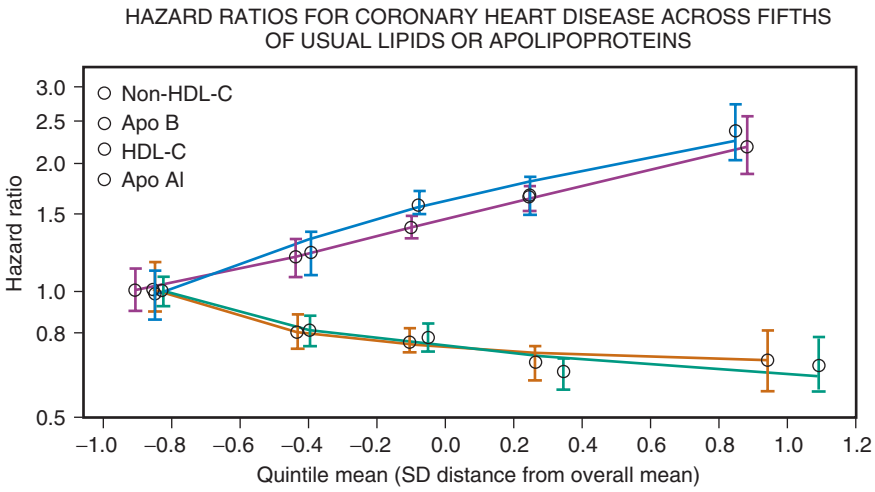


FIGURE 12-3 Relationship among usual levels of triglyceride, high-density lipoprotein cholesterol (HDL-C), and non–HDL-C and incident coronary artery disease. (Emerging Risk Factors Collaboration: Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 302[18]:1993-2000, 2009.)



Quintile	1	2	3	4	5
		Mean usual level (mg/dL)			
Non-HDL-C	125	145	159	173	198
Apo B	85	99	108	118	137
HDL-C	37	44	49	55	66
Apo AI	126	139	148	158	178

FIGURE 12-4 Relationship between cholesterol content or lipoprotein level and risk of incident coronary artery disease. *Apo,* Apolipoprotein; *HDL-C,* high-density lipoprotein cholesterol; *SD,* standard deviation. (Emerging Risk Factors Collaboration: Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 302[18]:1993-2000, 2009.)

Early Nonstatin Lipid-Lowering Trials

In the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), cholestyramine therapy resulted in a 13% reduction in LDL-C and a significant 19% reduction in fatal and nonfatal MI at 7 years (Table 12-3).[18] During the first 2 years of the trial, higher event rates occurred in the cholestyramine group compared with the placebo group. The Coronary Drug Project evaluated the effects of estrogen, dextrothyroxine, clofibrate, and niacin on recurrent disease in men. Clofibrate resulted in an 8% reduction in total cholesterol and a 25% reduction in triglycerides but no significant reduction on the combined end point of cardiac death and nonfatal MI at 5 years.[19] Subjects who were assigned to niacin treatment achieved a 10% reduction in total cholesterol and a 25% reduction in triglyceride levels. At 5 years, a dose of niacin (3 g/day) was associated with a significant reduction in CAD death and MI (25.6% vs. 30.1%, $P < .005$).[20] Benefit was not evident after the second year of therapy. The Stockholm Ischaemic Heart Disease Prevention trial evaluated the combination of niacin (3 g/day) and clofibrate (2 g/day).[21] Total mortality and notably CAD mortality were significantly reduced in the lipid-lowering therapy group (16.8% and 21.9% vs. the control group rates of 26.4% and 29.7%; $P < .05$ and $P < .01$, respectively). A significant reduction in nonfatal MI was reported at 44 months (6.8% vs. 13.6%, $P < .01$). No significant benefit from gemfibrozil therapy was observed in the secondary prevention arm of the Helsinki Heart Study.[22] However, gemfibrozil therapy did reduce the rates of MI and CAD death in men in the secondary prevention Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT).[23]

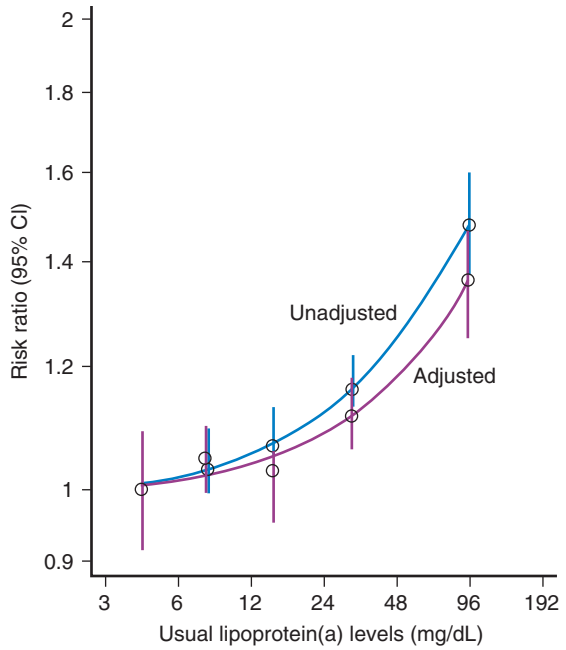


FIGURE 12-5 Shape of the association between usual lipoprotein(a) levels with risk of coronary artery disease with and without adjustment for risk factors. *CI,* Confidence interval. (From Emerging Risk Factors Collaboration: Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA* 302[4]:412-423, 2009.)

Early Secondary Prevention Statin Trials

During a decade of clinical research, successive trials using statins have demonstrated the benefit of lowering serum cholesterol in a wide range of clinical conditions compared with diet alone. The first of these trials was the Scandinavian Simvastatin Survival Study (4S), which randomized 4444 patients with angina pectoris or previous MI and serum cholesterol levels of 215 to 312 mg/dL (5.5 to 8.0 mmol/L) to a lipid-lowering diet or to treatment with simvastatin (average dose of 20 mg/day).[24] Over 5 years, simvastatin produced mean reductions in total cholesterol and LDL-C levels of 25% and 35%, respectively. Statin therapy was associated with an absolute 4% reduction in mortality and a relative risk reduction in all-cause mortality of 30% ($P = .0003$). Significant reductions were also observed for CAD death (42%), a major CAD event (34%), and the need for revascularization (37%). This was the first trial in the modern era that provided definitive proof that lipid-lowering therapy was safe and reduced the risk of cardiac death and nonfatal MI. The Cholesterol and Recurrent Events (CARE) trial quickly followed 4S with consistent findings, demonstrating a reduction in major coronary events with pravastatin (40 mg) versus placebo, as well as reductions in the rates of revascularization and stroke, in patients with normal cholesterol levels.[25] The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial ($N = 9014$) was the largest of the three early secondary prevention trials and confirmed the mortality findings of 4S in a population with an overall lower total baseline cholesterol level.[26] LIPID demonstrated that among patients with a history of MI or hospitalization for unstable angina and initial plasma total cholesterol levels of 155 to 271 mg/dL (3.97 to 6.95 mmol/L), pravastatin (40 mg/day) reduced CAD death by 1.9% and resulted in a 24% relative risk reduction ($P < .001$). Similarly, overall mortality was reduced (22%), as were rates for recurrent MI

TABLE 12-1 Comparison of Individuals Who Should Be Targeted for Lipid Modification

ACC/AHA (2013) Guidelines for the Treatment of Blood Cholesterol to Reduce Atherosclerotic CVD Risk in Adults		ESC/EAS (2011) Guidelines for the Management of Dyslipidemias	
Clinical Risk Categories	**Treatment**	**Clinical Risk Categories**	**Treatment**
Those with clinical ASCVD	High-intensity statin therapy; if 50% reduction is not reached, drug combination may be considered	Those with CVD	LDL-C <1.8 mmol/L or 50% reduction in LDL-C
Diabetes mellitus (types 1 and 2) without ASCVD but with LDL-C between 1.8 and 4.9 mmol/L	*High risk:* high-intensity statin therapy *Low risk:* moderate-intensity statin therapy	Diabetes mellitus type 1 or 2 with target organ damage	LDL-C <1.8 mmol/L or 50% reduction in LDL-C
Those with primary elevation of LDL-C >4.9 mmol/L	High-intensity statin therapy aimed at achieving at least a 50% reduction of LDL-C	Familial dyslipidemia (FH, FCH, or chylomicronemia)	LDL-C <2.5 mmol/L or maximal reduction in LDL-C with any possible drug combination plus LDL apheresis
If none of the above but with an estimated 10-year ASCVD risk of 7.5% or more using a pooled populations risk calculator If assessment is risk based or treatment decision is uncertain, assessment of one or more of family history, hsCRP, CAC SCORE, or ABPI may be considered (class Ib, LOE E), contribution of apo B, CKD, microalbuminuria, or cardiorespiratory fitness is uncertain (LOE N) and CIMT is not recommended for routine assessment of individual patients (LOE N)	Moderate- to high-intensity statin therapy is reasonable if ASCVD risk >7.5%. If risk of a CVD event is 5% to 7.5%, it is reasonable to consider moderate-intensity statin therapy.	If none of the above, estimate 10-year risk of a first fatal atherosclerotic CV event (SCORE); a SCORE >10% is considered very high risk, 5% to 10% is considered high risk, and 1% to 5% is moderate risk; risk can be modified if additional information is available on TGs, social deprivation, central obesity, Lp(a), FH, subclinical atherosclerosis, CKD, family history of premature CVD (women ×1.7, men ×2), very high HDL-C, family history of longevity	Very high-risk LDL-C <1.8 mmol/L or 50% reduction in LDL-C, high-risk LDL-C <2.5 mmol/L, moderate risk LDL-C <3.0 mmol/L

ABPI, Ankle-brachial pressure index; *ACC,* American College of Cardiology; *AHA,* American Heart Association; *apo B,* apolipoprotein B; *ASCVD,* atherosclerotic cardiovascular disease; *CAC,* coronary artery calcium; *CIMT,* carotid intima media thickness; *CKD,* chronic kidney disease; *CV,* cardiovascular; *CVD,* cardiovascular disease; *EAS,* European Atherosclerosis Society; *ESC,* European Society of Cardiology; *FCH,* familial combined hyperlipidemia; *FH,* familial hypercholesterolemia; *HDL-C,* high-density lipoprotein cholesterol; *hsCRP,* high-sensitivity C-reactive protein; *LDL-C,* low-density lipoprotein cholesterol; *LOE,* level of evidence; *Lp(a),* lipoprotein A; *SCORE,* Systematic Coronary Risk Evaluation; *TG,* triglyceride.

(29%), stroke (19%), and coronary revascularization (20%). These three trials demonstrated the cumulative benefit of statins across a range of baseline cholesterol values.

Heart Protection Study and Cholesterol Treatment Trial Meta-Analysis

The large Heart Protection Study (HPS) demonstrated that the magnitude of benefit from statin therapy (simvastatin 40 mg) was similar at each level of baseline LDL-C, including subjects with an LDL-C level below 100 mg/dL (2.56 mmol/L).[27] HPS studied over 20,000 patients who were able to tolerate simvastatin (after a run-in phase) over 5 years and assessed the on-treatment effect, rather than the intention-to-treat effect, of a standard dose of a statin rather than a specific cholesterol or LDL-C target. HPS, however, included a range of patients with CAD: those with prior vascular disease, such as peripheral vascular disease (PVD) or stroke, and subjects without prior clinical manifestations of vascular disease who were considered at high risk because of diabetes.[28]

TABLE 12-2 Gradation of Evidence Base

ACC/AHA Guidelines	ESC/EAS Guidelines
Use a high-intensity statin for men and women <75 years with clinical ASCVD unless contraindicated (class I, LOE A). If a high-intensity statin is contraindicated or a risk of statin adverse events is present, use moderate-intensity statin (class I, LOE A). If clinical ASCVD and patient is aged >75 years, evaluate benefits and risks of moderate- or high-intensity statin treatment. It is reasonable to continue statin treatment started before age 75 (class IIa, LOE E). If LDL-C is >4.9 mmol/L or TG is >5.68 mmol/L, evaluate for secondary causes of dyslipidemia (class I, LOE B). If aged >21 and LDL-C >4.9 mmol/L, treat with high-intensity statin unless contraindicated then use moderate-intensity statin (class I, LOE B). If aged >21 and untreated primary LDL-C >4.9 mmol/L, it is reasonable to intensify statin treatment to achieve ≥50% ↓ in LDL-C (class IIa, LOE E). If aged >21 years with untreated LDL-C >4.9 mmol/L, addition of a nonstatin cholesterol-reducing drug may be considered after maximal intensity statin treatment is achieved to further lower LDL-C. Evaluate risks and benefits (class IIb, LOE E). Moderate-intensity statin treatment is recommended for all people with type 1 or 2 DM aged between 40 and 75 years (class I, LOE A). High-intensity statin treatment is reasonable if aged 40 to 75 years with type 1 or 2 DM and 10-year ASCVD risk is >7.5% (class IIa, LOE E). In adults with type 1 or 2 DM aged <40 or >75 years, it is reasonable to consider the benefits and risks of statin treatment (class IIa, LOE E). Use pooled cohort equations to estimate 10- year ASCVD risk (class I, LOE E). If 10-year ASCVD risk is >7.5% and patient is aged 40 to 75 years, treat with moderate- to high-intensity statin (class I, LOE A). If 10-year ASCVD risk is between 5% and 7.5% and age is 40 to 75 years, it is reasonable to offer moderate-intensity statin treatment (class IIa, LOE C). Decisions about treatment should be discussed with the patient (class IIa, LOE E). In those who would not otherwise qualify for statin treatment, it is reasonable to consider additional risk factors: evidence of genetic dyslipidemia, family history of premature CVD (<55 yr, first-degree males; <65 yr, first-degree females), hsCRP >2, CAC >300 or >75th percentile, ABPI <0.9, ↑ lifetime risk (class IIb, LOE E).	Those with known CVD, type 2 DM or type 1 DM with target-organ damage, moderate-to-severe CKD, or a SCORE level >10%, the LDL-C goal is <1.8 mmol/L or a 50% reduction (class I, LOE A). In patients at high CVD risk as defined by markedly elevated single risk factors (FH or hypertension) or a SCORE level of 5% to 10%, the LDL-C target is <2.5 mmol/L (class IIa, LOE A). In patients at moderate CVD risk as defined by a SCORE level of 1% to 5%, an LDL-C target of <3.0 mmol/L (class IIa, LOE C) LDL-C is recommended as a target for treatment (class I, LOE A). Total cholesterol to be considered a target if LDL-C is not available (class IIa, LOE A). TGs should be measured during treatment if initially high (class IIa, LOE B). Non–HDL-C to be considered a secondary target in DM, MetS (class IIa, LOE B). Apo B to be considered a secondary target (class IIa, LOE B). HDL-C is not recommended as a target of treatment (class III, LOE C). Apo B/Apo A1 and non–HDL-C/HDL-C are not recommended as targets (class III, LOE C).

ABPI, Ankle-brachial pressure index; *ACC,* American College of Cardiology; *AHA,* American Heart Association; *Apo,* apolipoprotein; *ASCVD,* atherosclerotic cardiovascular disease; *CAC,* coronary artery calcium; *CKD,* chronic kidney disease; *CVD,* cardiovascular disease; *DM,* diabetes mellitus; *EAS,* European Atherosclerosis Society; *ESC,* European Society of Cardiology; *FH,* familiar hyperlipidemia; *HDL-C,* high-density lipoprotein cholesterol; *hsCRP,* high-sensitivity C-reactive protein; *LDL-C,* low-density lipoprotein cholesterol; *LOE,* level of evidence; *MetS,* metabolic syndrome; *SCORE,* Systematic Coronary Risk Evaluation; *TG,* triglyceride.

TABLE 12-3 Early Trials of Lipid Lowering With Nonstatin Regimens

Trial	Therapy	Lipid Differential	Outcome Treatment Versus Controls	*P* Value
Lipid Research Clinics–Coronary Primary Prevention Trial (LRC-CPPT)	Cholestyramine	–9% TC –13% LDL-C	CAD death or MI 7% vs. 8.60%	<.05
Coronary Drug Project	Clofibrate	–8% TC –25% TG	CAD death 14.1% vs. 16.20%	.06
	Niacin	–10% TC –25% TG	CAD death 15.9% vs. 16.20%	.5
Stockholm Ischemic Heart Disease	Niacin + clofibrate	–13% TC –19% TG	CAD death 16.8% vs. 26.40%	<.01
Helsinki Heart	Gemfibrozil	–10% TC –41% TG	CAD death or MI 7.4% vs. 6.3%	.14
Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)	Gemfibrozil	–4% TC –31% TG	CAD death 17.3% vs. 21.70%	.006
Bezafibrate Infarction Prevention (BIP)	Bezafibrate	–4% TC –21% TG	CAD death or MI 13.6% vs. 15%	.26

CAD, Coronary artery disease; *LDL-C,* low-density lipoprotein cholesterol; *MI,* myocardial infarction; *TC,* total cholesterol; *TG,* triglycerides.

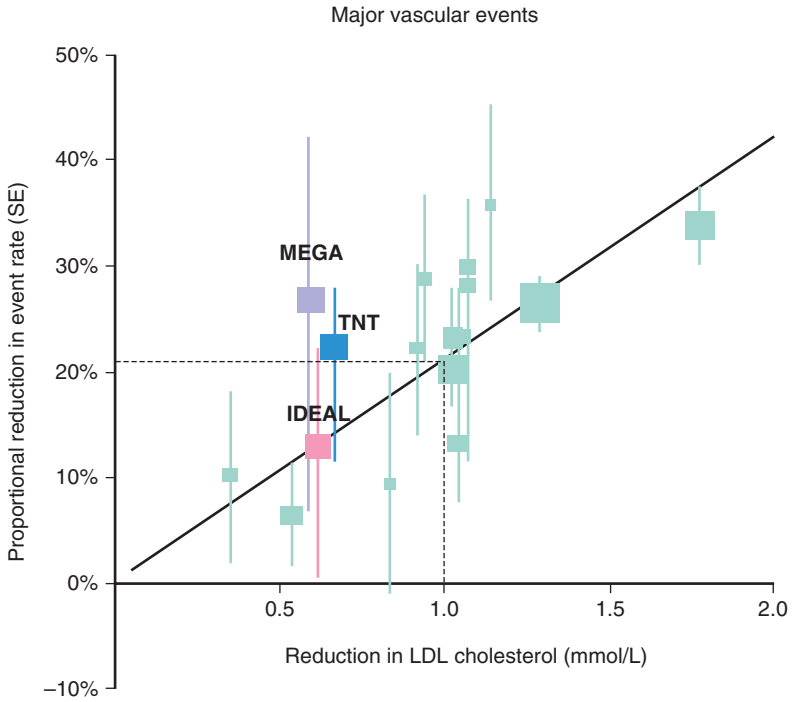


FIGURE 12-6 Updated Cholesterol Treatment Trial (CTT) meta-analysis, including the Treating to New Targets (TNT), Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL), and Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) trials showing the linear relationship between low-density lipoprotein (LDL) cholesterol reduction and clinical risk reduction. *SE,* Standard error. (Modified from Baigent C, Keech A, Kearney PM, et al: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 366: 1267-1278, 2005.)

The implications of this trial for clinical practice were that physicians did not need to treat to specific targets because subjects with vascular disease all derived similar proportional reductions in risk with simvastatin (40 mg). Preliminary evidence indicated that some overall benefit existed for statin therapy in different circumstances, such as in different ages and sexes and with various levels of established risk factors, but additional data involving several thousand more patients were needed to provide large-scale evidence of benefit in individual subgroups.

The Cholesterol Treatment Trial (CTT) collaborators set out to undertake a prospective meta-analysis of mortality and morbidity from all relevant large-scale randomized trials of statin therapy.[29] Data on 90,056 individuals were combined. During a mean follow-up of 5 years, a significant 12% reduction was observed in all-cause mortality per 38.6-mg/dL (1-mmol/L) reduction in LDL-C, a 19% reduction in coronary mortality, a 24% reduction in the need for revascularization, and a 17% reduction in stroke. Overall, a 38.6-mg/dL (1-mmol/L) reduction in LDL-C was associated with a 21% to 23% reduction in any major vascular event (Fig. 12-6). Notably, a similar proportional benefit was observed across age groups, sexes, baseline lipid levels (including TGs and HDL-C), and equally among those with prior CAD and CV risk factors and in those without. The CTT meta-analysis collected data on 5103 new cases of cancer and found no evidence that statins increased the overall incidence of any form of cancer (hazard ratio [HR], 1.0; $P = .9$).

These data demonstrate that compared with placebo, statin therapy is safe and reduces the 5-year incidence of major coronary events, coronary revascularization, and stroke among those at high risk for vascular disease or with preexisting disease. This magnitude of benefit is related to the magnitude of LDL-C reduction and is independent of the initial lipid profile or other presenting characteristics. The absolute benefit correlates chiefly with an individual's absolute risk of CV events, which reinforces the need to consider long-term statin therapy for all individuals at high risk for any type of major vascular event.

Intensive Statin Therapy for Acute Coronary Syndrome

The early trials looking at treatment of acute coronary syndrome (ACS)—4S, CARE, and LIPID—excluded patients within the first 4- to 6-month period after ACS. The Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL) trial provided the first evidence that statin therapy initiated early after ACS reduces adverse clinical events within 16 weeks.[30] However, the higher-than-usual dose of statin (atorvastatin 80 mg) and lack of an active comparator coupled with an absence of long-term safety data limited the widespread applicability of its findings.

PROVE IT–TIMI 22 Trial

The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22 (PROVE IT–TIMI 22) trial was the first large-scale trial of statin therapy to compare two active comparators. In the PROVE IT–TIMI 22 trial,[31] patients who had been hospitalized for ACS within the preceding 10 days ($N = 4162$) were randomized to 40 mg of pravastatin (i.e., standard therapy) or 80 mg of atorvastatin daily (intensive therapy). The primary end point was a composite of death from any cause, MI, unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke.

In this trial, the median LDL-C level achieved during treatment was 95 mg/dL (2.46 mmol/L) in the standard-therapy group and 62 mg/dL (1.60 mmol/L) in the high-dose group ($P < .001$). Kaplan-Meier estimates of the rates of the primary end point at 2 years were 26.3% for standard therapy and 22.4% for intensive therapy, reflecting a 16% reduction in the hazard ratio in favor of intensive therapy ($P = .005$). Muscle-related side effects were low and were not significantly different between groups, and no cases of rhabdomyolysis were reported.

The A to Z Trial

The Aggrastat to Zocor (A-to-Z) trial compared the early initiation of an intensive statin regimen against the delayed initiation of a less-intensive regimen in patients with ACS.[32] Patients with ACS ($N = 4497$) received 40 mg of simvastatin for 1 month, followed by 80 mg thereafter, which was compared with placebo for 4 months followed by 20 mg of simvastatin. The primary end point was a composite of CV death, nonfatal MI, readmission for ACS, and stroke. In the delayed initiation, less intensive therapy group, the median LDL-C level at 1 month on placebo was 122 mg/dL (3.16 mmol/L) and at 8 months on

20 mg of simvastatin, it was 77 mg/dL (1.99 mmol/L). In the early initiation, intensive therapy group, the median LDL-C concentration achieved at 1 month on 40 mg of simvastatin was 68 mg/dL (1.76 mmol/L), and at 8 months on 80 mg of simvastatin, it was 63 mg/dL (1.63 mmol/L). Overall, 16.7% in the placebo-plus-simvastatin group experienced the primary end point, compared with 14.4% in the simvastatin-only group (40 mg/80 mg), reflecting an HR of 0.89 (P = 0.14). Myopathy (i.e., creatine kinase >10 times the upper limit of normal [ULN] with muscle symptoms) occurred in 9 patients (0.4%) receiving 80 mg of simvastatin, in no patients receiving lower doses of simvastatin, and in 1 patient receiving placebo (P = .02).

The PROVE IT–TIMI 22 and A-to-Z trials compared similar intensive and moderate statin therapy after ACS with apparently disparate results. An analysis comparing and contrasting the two trials observed differences between the trials in baseline demographic characteristics, geographic locations, and use of percutaneous coronary intervention (PCI).[33] The LDL-C level difference was greater early in the A-to-Z trial than in PROVE IT (≤4 months), but the difference was less late in the trials. Significant C-reactive protein (CRP) reduction also occurred earlier in PROVE IT. With common end points, an early favorable separation of event curves was seen in PROVE IT but not in the A to Z trial. Clinical end point rates and reductions were similar in both trials after 4 months; factors that might explain this disparity include the statin regimen in the early phase, leading to differences in the magnitude of LDL-C lowering and CRP levels, and differences in the early use of PCI. In summary, the results of these trials support a strategy of early, intensive statin therapy coupled with revascularization when appropriate in patients after ACS.[33]

Intensive Statin Therapy in Stable Coronary Artery Disease

Despite the landmark results from PROVE IT, which led to the NCEP recommending an optional LDL-C goal of less than 70 mg/dL in high-risk patients, several questions arose, such as whether intensive statin therapy was safe over a longer period and whether intensive statin therapy was as beneficial in subjects with stable CAD as in ACS patients.[34] The Treating to New Targets (TNT) trial and the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trial addressed these issues and provided approximately 50,000 patient-years of data on the safety and efficacy of intensive statin therapy.[35,36]

The TNT Trial

The TNT trial compared a strategy of intensive lipid lowering using 80 mg of atorvastatin with 10 mg of atorvastatin in patients with stable CAD in 10,001 subjects over 5.5 years.[35] The definition of CAD in the trial population included patients with previous MI, those with stable angina with objective evidence of atherosclerotic CAD, or patients who had undergone revascularization. After an open-label run-in phase with 10 mg of atorvastatin for 8 weeks, patients were randomized to 10 or 80 mg of atorvastatin (i.e., double-blind period). The primary end point of TNT was the time to occurrence of a major cardiovascular event, defined as CAD death, nonfatal MI, resuscitated cardiac arrest, and fatal or nonfatal stroke. During the open-label phase, LDL-C levels fell from 152 mg/dL (3.9 mmol/L) to a mean of 98 mg/dL (2.6 mmol/L). Among those randomized to 80 mg of atorvastatin after the open-label phase, LDL-C fell further by 21.4% to a mean of 77 mg/dL (2 mmol/L). A significant further reduction in triglycerides was observed with the 80-mg dose, but no significant difference was reported in HDL-C levels between doses. The primary end point occurred in 8.7% of the 80-mg atorvastatin group and in 10.9% of the 10-mg atorvastatin group, reflecting a 22% risk reduction (HR, 0.78; P < .001). Clinical benefit appeared within 6 months against a background of aggressive medical therapy. This benefit was largely driven by significant reductions in nonfatal MI (HR, 0.78; 95% confidence interval [CI], 0.66 to 0.93; P = .004) and fatal or nonfatal stroke (HR, 0.75; P = .02). A trend in favor of CV death was also observed but was not significant. Overall, intensive therapy was found to be safe, with no increased risk of adverse effects.

IDEAL Trial

The Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trial was a randomized, open-label trial that compared a strategy of achieving an approximately 35% reduction in LDL-C using the 20-mg/40-mg dose of simvastatin versus a strategy of achieving a 55% reduction in LDL-C using 80 mg of atorvastatin in patients with a history of prior MI. Patients were recruited months to years after the index MI, making IDEAL comparable in design to the 4S and CARE trials.[24,25] Approximately 70% of patients were on statin therapy before trial entry, and about 50% of participants had been previously enrolled in the 4S trial. The primary end point was coronary death, nonfatal MI, or resuscitated cardiac arrest. IDEAL enrolled 8888 patients and had a mean follow-up period of 4.8 years. During follow-up, the mean LDL-C level was 104 mg/dL (2.69 mmol/L) in the 20-mg/40-mg simvastatin group and 82 mg/dL (2.12 mmol/L) in the 80-mg atorvastatin group. Major coronary events tended to be lower with intensive therapy (HR, 0.89; P = .07) but did not achieve statistical significance. Major CV events and any coronary event were significantly reduced by 13% (P = .02) and 16% (P < .001), respectively, in the 80-mg atorvastatin group. No excess risk of noncardiovascular death was found with intensive therapy (HR, 0.92; P = .47), and with the exception of transient elevations in liver transaminase levels, no significant differences were found between treatments.

The results of the TNT and IDEAL trials further established the important role for intensive statin therapy in the management of patients with stable CAD and extended the observations from PROVE IT–TIMI 22 in ACS patients to those with stable disease. The IDEAL trial disproved the earlier concerns raised by TNT that intensive statin therapy might be associated with an increased risk of noncardiovascular mortality and provided further safety data on 80 mg of atorvastatin in more than 20,000 patient-years of follow-up. Some observers have questioned the importance of TNT and IDEAL, citing that the benefit of intensive therapy in these trials tended to be driven by the so-called soft end points, such as recurrent MI or revascularization—compared, for instance, with the landmark 4S trial, in which total mortality was reduced in the statin group compared with placebo. However, in the decade since 4S was completed, the management of CAD has improved dramatically with greater use of additional cardioprotective medication and greater use of revascularization. It is therefore unlikely that a significant benefit in all-cause mortality would be observed with intensive therapy compared with standard therapy unless a much larger trial (perhaps requiring about 50,000 patients) with a longer follow-up is conducted.

SEARCH Trial

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial is the largest and the most recent of the trials in stable coronary disease and randomized 12,064 participants to simvastatin 20 mg versus 80 mg and accrued events over 6.7 years of follow-up.[37] The trial had a lower threshold of total cholesterol (TC) such that individuals had to have a TC of at least 3.5 mmol/L if they were on statin therapy or 4.5 mmol/L if they were statin naïve. At trial entry, baseline TC was 4.23 mmol/L and LDL-C was 2.50 mmol/L. The average LDL-C difference between more versus less intensive therapy was 0.35 mmol/L, which resulted in a nonsignificant 6% reduction in any major vascular event (HR, 0.94; 95% CI, 0.88 to 1.01). Similarly, no significant reductions were seen in stroke, coronary death, or coronary revascularizations. The only end point to show significant benefit was nonfatal MI, in which a 1.1% absolute reduction in risk was observed (7.7% vs. 6.6%).

Although consistent with other lower-is-better trials, the data would suggest that simvastatin 80 mg is a far weaker LDL-C–lowering regimen than that tested in the TNT and IDEAL trials. Notably, by virtue of size and duration, this trial demonstrated the significant increased risk observed from simvastatin 80 mg not observed with other high-intensity statins. Creatine kinase (CK) elevations greater than five times the ULN and up to ten times the ULN occurred in 1.3% versus 0.5% in the simvastatin 80 mg versus 20 mg doses, respectively,

and elevations were more than 40 times the ULN in 0.4% versus 0%, respectively. Myopathy was also more common and occurred at a rate of 90 of 10,000 individuals exposed versus 3 of 10,000 people exposed. These data have resulted in both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) issuing warnings of increased risk of myopathy with simvastatin 80 mg. Atherosclerosis is a chronic disease, and patients who are commenced on statins require this treatment for the remainder of their lives. The benefits of intensive therapy observed over about 5 years are likely to translate into even greater reductions in the number of events over a longer period, providing significant benefits for individuals and health care systems.

Meta-Analysis of Intensive Versus Standard Therapy

The four intensive versus standard therapy trials—PROVE IT–TIMI 22, A-to-Z, TNT, and IDEAL—used different end points to assess clinical benefit and were each underpowered to assess the historical end point of CAD death or nonfatal MI.[31,32,35,36] A literature-based meta-analysis was conducted to obtain consistent large-scale evidence across trials.[38] All eligible trials were required to have at least 1000 participants and a treatment duration of at least 2 years. The four trials discussed previously—PROVE IT–TIMI 22, A-to-Z, TNT, and IDEAL—were identified and provided information on 27,548 patients and approximately 120,000 patient-years of follow-up data. A separate meta-analysis of the same four trials also assessed the effect of intensive versus standard therapy for reductions in hospitalization with heart failure.[39] The average, pooled baseline LDL-C level in the four trials was 130 mg/dL (3.3 mmol/L), which was reduced on average to 101 mg/dL (2.59 mmol/L). With intensive therapy, the average LDL-C level was lowered further to 75 mg/dL (1.92 mmol/L).[38] This additional reduction in LDL-C was associated with a 16% reduction in the risk of CAD death or MI (odds ratio [OR], 0.84; $P = .00003$). Similarly, a reduction was seen in the risk of any major CV event by 16% ($P < .0001$). The trend was favorable toward reduction in CAD death (OR, 0.88; $P = .054$), and no excess risk in noncardiovascular mortality was observed (OR, 1.03; $P = .73$). Reductions were observed for stroke (OR, 0.82; $P = .012$) and for hospitalization for congestive heart failure (CHF; OR, 0.73; $P < .001$).[39] The modest effects overall on all-cause mortality may, in part, reflect contemporary background therapy and also the differential risk between patients with stable CAD and ACS. There is clear evidence of an all-cause mortality benefit within 2 years of ACS from an individual participant meta-analysis of the PROVE IT–TIMI 22 and the A-to-Z trials.[40] Over approximately 20,000 person-years worth of follow-up, intensive statin therapy reduced all-cause mortality by 23% (HR, 0.77; 95% CI, 0.63 to 0.95) and in absolute terms by 1.3% (number needed to treat [NNT], 77 over 2 years to prevent one death from any cause) from 4.9% to 3.6%. Statin therapy is now recommended for all patients with established atherosclerotic vascular disease. This meta-analysis extends the earlier findings (i.e., the CTT meta-analysis) and demonstrates that beyond standard therapy, additional intensive LDL-C reduction provides a further 16% reduction in risk of CAD, nonfatal MI, or any major CV event, an approximate 50% reduction compared with placebo.

Given the chronic, lifelong nature of these diseases, these benefits throughout an individual's life would be expected to translate into greater absolute benefits by preventing recurrent, multiple events. In addition, analytic techniques that take only time to first event into account underestimate the overall benefits of any treatment regimen; as therapies reduce the second and third events among those on more intensive treatments, the real benefit and cost-effectiveness of more intensive regimens are even greater. For instance, in the PROVE IT–TIMI 22 trial, over 2 years for every 2000 individuals treated, an additional 65 events could be averted by intensive therapy ($P = .009$).[40] Similar, consistent observations were made in the TNT trial in stable CAD, in which beyond the first event, intensive statin therapy for approximately every 5000 individuals treated for 5 years resulted in 166 fewer second events, 92 fewer third events, 55 fewer fourth events, and 33 fewer fifth events.[41] Taken together, these data support the value of long-term atheroprotection with intensive lipid lowering over time and also highlight the need for continuation of therapy.

In their second round of analyses, the CTT investigators provided individual participant data on five trials and 39,612 individuals.[42] Overall, more intensive statin therapy resulted in a 0.53 mmol/L lowering of LDL-C and a 15% risk reduction in first major vascular event (relative risk [RR], 0.85; 95% CI, 0.82 to 0.89), with considerable heterogeneity between studies ($P < .0001$). However, when studies were standardized per mmol/L lowering of LDL-C, the corresponding risk reduction overall was 28% (RR, 0.72; 95% CI, 0.66 to 0.78) with no significant evidence of heterogeneity across studies. Taken together, these data suggest that the differences observed among studies reflect the relative efficacies of the more versus less intensive statin-lowering regimens. Of importance, there was no lower threshold for LDL-C in which a 1 mmol/L additional lowering of LDL-C with intensive therapy over and above standard therapy was not beneficial. For instance, even among those with a baseline LDL-C less than 2.0 mmol/L, a further 1 mmol/L lowering resulted in a 29% risk reduction (RR, 0.71; 95% CI, 0.52 to 0.98), which was similar to the benefit observed among those with an LDL-C greater than 3.5 mmol/L ($P = .2$; Fig. 12-7) .

Early Benefits of Intensive Statin Therapy for Acute Coronary Syndrome

The risk of adverse clinical events is greatest in the first 6 months after an index ACS event. The early trials of statin therapy in patients with stable CAD suggested that the benefits of statin therapy appeared only after 1 to 2 years.[24,25] Although plaque rupture is a feature of ACS, it has become apparent that ACS is a pancoronary process with multiple vulnerable or ruptured plaques. Although angioplasty and stenting treat a culprit lesion effectively, potent systemic therapy is required to passivate other vulnerable sites.[43] The PROVE IT trial, conducted in patients enrolled within 10 days of experiencing an ACS, demonstrated the superiority of intensive statin therapy versus standard statin therapy in patients over a period of 2 years, but it was unclear whether this benefit was related principally to a very early benefit, to a late benefit after patients had stabilized, or to a combination of the two. Using a composite end point of death, MI, or rehospitalization for recurrent ACS (i.e., the common end point in ACS trials), the benefit of intensive statin therapy was assessed in the first 30 days after ACS and in more stable patients from 6 months through end of the trial.[44] This particular analysis demonstrated that the composite end point occurred in 15.7% of patients assigned to 80 mg of atorvastatin and in 20.0% of patients assigned to 40 mg of pravastatin, reflecting a risk reduction of 24% ($P = .0002$).

Benefit in favor of 80 mg of atorvastatin was observed as early as 15 days after randomization and was significant by day 30. The composite end point occurred in 3.0% of the intensive-therapy group and in 4.2% of the standard-therapy group at 30 days, reflecting a 28% risk reduction at 30 days ($P = .046$) with 80 mg of atorvastatin (Fig. 12-8). In addition to greater reductions in LDL levels, 80 mg of atorvastatin reduced CRP levels to a greater extent than did 40 mg of pravastatin independent of effects on LDL (1.6 mg/L vs. 2.3 mg/L, $P < .0001$). Commencing 6 months after ACS to the end of the trial, the composite end point occurred in 9.6% of the intensive-therapy group and in 13.1% of the standard-therapy group, representing a 28% further risk reduction ($P = .003$) in favor of high-dose atorvastatin (80 mg). This suggests that among patients who tolerate high-dose statin therapy, continuation of high-dose therapy is beneficial and provides early and late benefits. PROVE IT demonstrated that high-dose statin therapy lowers LDL-C and CRP concentrations at 30 days and is associated with a reduction in clinical events. In contrast, the A-to-Z trial showed a greater difference in resulting LDL levels between intensive statin regimens versus moderate statin regimens, but it revealed no difference in CRP levels at 30 days and, significantly, no early benefit was observed.[32,33] Despite matching for LDL-C at day 30, subjects allocated atorvastatin were less likely to have had an MI or recurrent ACS in the

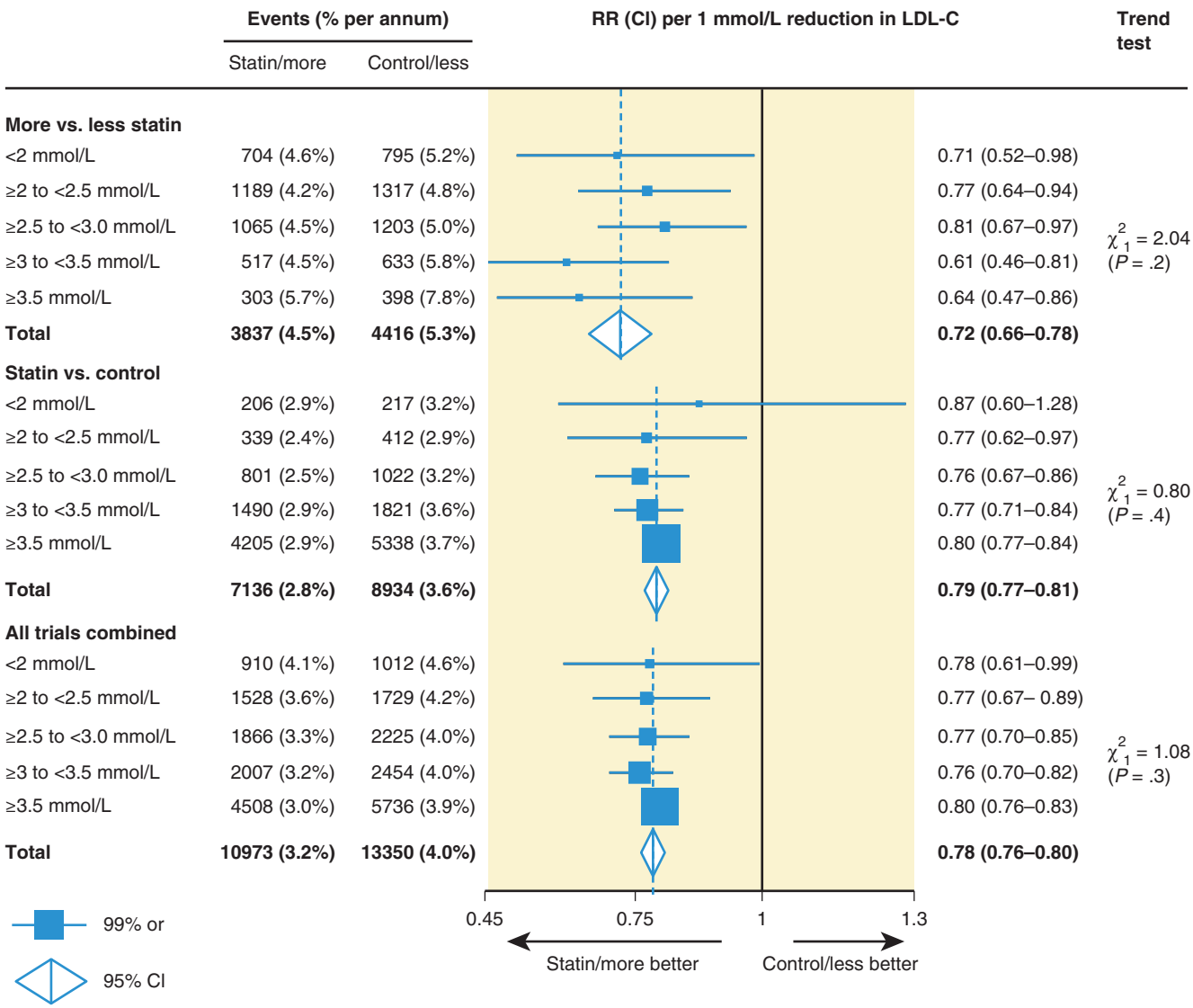


FIGURE 12-7 Effects on major vascular events per 1.0 mmol/L reduction in low-density lipoprotein cholesterol (LDL-C) by baseline LDL-C concentration on the less intensive or control regimen. *CI,* Confidence interval; *RR,* relative risk. (Data from Cholesterol Treatment Trialists' [CTT] Collaboration: Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 376[9753]:1670-1681, 2010.)

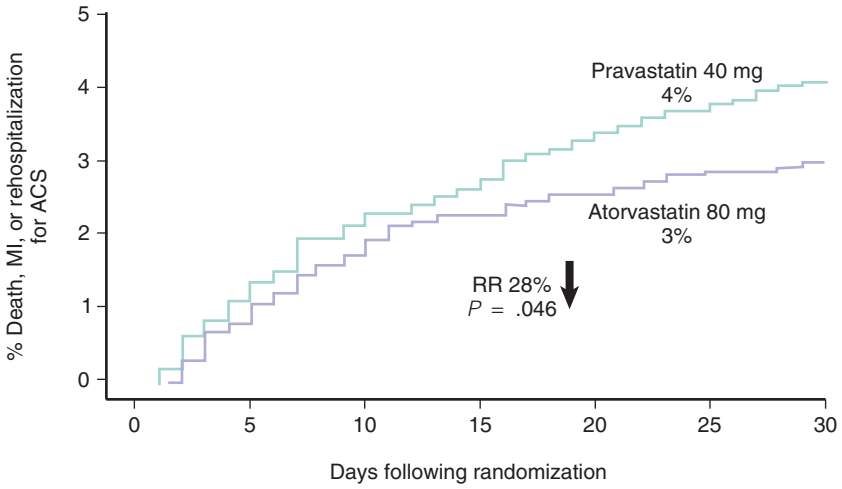


FIGURE 12-8 Early benefit of intensive standard statin therapy within 30 days after acute coronary syndrome (ACS) in the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial. *MI,* Myocardial infarction; *RR,* relative risk. (Data from PROVE IT–TIMI 22 Investigators: Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT–TIMI 22 trial. *J Am Coll Cardiol* 46:1405-1410, 2005.)

previous 30 days, suggesting that the early benefit is related to effects beyond the concentration of LDL-C and that lowering CRP levels may reduce inflammation and may be more important than lipid lowering with respect to early benefits.[45]

A meta-analysis of 13 randomized trials of early statin therapy for management of ACS assessed the early benefit of statin therapy using cumulative data on 17,963 patients.[46] Only five of the trials enrolled more than 1000 patients, and of these, only three trials had follow-up periods of more than 4 months, and only two trials followed up patients for more than 1 year. This meta-analysis assessed major CV events, including stroke. In particular, the latter end point requires about 2 years to demonstrate a clinical benefit and might have attenuated any observed early composite benefits on CVD. In this analysis, early composite benefit was not observed at 1 month after ACS (HR, 1.02) but appeared by 4 months (HR, 0.84) and was significant by 6 months (HR, 0.76).

Intensive Statin Therapy and Atherosclerotic Burden

Given the clinical impact of statin therapy on CV event reduction in patients with CAD, it is intuitive to expect that statins would reverse the atherosclerosis disease burden. Several trials used angiography to assess the impact of standard-dose statin therapy on the extent of angiographic disease. Although standard doses of statins reduced LDL-C levels by 20% to 30%, they failed to demonstrate regression of disease burden but rather consistently showed that in the presence of CAD, statins reduce the rate of progression of disease.[47]

REVERSAL Trial

The Reversing Atherosclerosis With Aggressive Lipid Lowering (REVERSAL) trial compared the effects of two statin regimens administered for 18 months in 654 patients, of whom 502 had serial intravascular ultrasound (IVUS) measurements. Patients were randomized to a moderate lipid-lowering regimen consisting of 40 mg of pravastatin or an intensive lipid-lowering regimen consisting of 80 mg of atorvastatin.[48] The primary efficacy parameter was the percentage of change in atheroma volume; secondary efficacy parameters included change in total atheroma volume, change in percentage of atheroma volume, and change in atheroma volume in the most severely diseased 10-mm vessel subsegment.

The baseline LDL-C concentration fell from 150.2 mg/dL (3.89 mmol/L) in both treatment groups to 110 mg/dL (2.85 mmol/L) in the pravastatin group and to 79 mg/dL (2.05 mmol/L) in the atorvastatin group ($P < .001$). CRP levels decreased 5.2% with pravastatin and 36.4% with atorvastatin ($P < .001$). In subjects receiving standard therapy, the percentage of change in atheroma volume from baseline was 2.7% ($P < .001$), and in those allocated to intensive therapy, it was −0.4% ($P = .98$; for the difference between groups, $P = .02$). Similar differences between groups were observed for secondary efficacy parameters, including change in total atheroma volume ($P = .02$), change in percentage of atheroma volume ($P < .001$), and change in atheroma volume in the most severely diseased 10-mm vessel subsegment ($P < .01$).

ASTEROID

A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) assessed whether intensive statin therapy with 40 mg of rosuvastatin could cause regression of atherosclerosis in patients with CAD assessed by IVUS.[49] A motorized IVUS pullback was used to assess coronary atheroma burden at baseline and after 24 months of treatment in 507 patients, of whom 349 had serial IVUS measurements. The mean (standard deviation [SD]) baseline LDL-C level of 130.4 mg/dL declined to 60.8 mg/dL; mean HDL-C level at baseline was 43.1 mg/dL, increasing to 49.0 mg/dL; and the median concentration of triglycerides fell from 135 mg/dL to 109 mg/dL. The mean change in percentage of atheroma volume from baseline for the entire vessel was −0.98%. The mean change in atheroma volume in the most diseased 10-mm subsegment was −6.1 mm^3 ($P < .001$ vs. baseline). Change in total atheroma volume showed a 6.8% median reduction ($P < .001$ vs. baseline).

SATURN

The largest of the high-intensity statin IVUS regression/progression studies was the Effect of Two Intensive Statin Regimens on Progression of Coronary Disease (SATURN),[50] in which 1039 patients with coronary disease were randomized to atorvastatin 80 mg or rosuvastatin 40 mg. After 2 years, 75% had baseline and follow-up IVUS data available: baseline LDL-C levels of 120 mg/dL fell to 70.2 and 62.6 in the atorvastatin 80 mg and rosuvastatin 40 mg groups, respectively. The primary end point of percentage atheroma volume regressed in approximately two thirds of each treatment group but with no significant difference between groups. In subjects receiving atorvastatin 80 mg, the percentage of change in atheroma volume from baseline was −0.99% ($P < .001$), and in those allocated to rosuvastatin 40 mg, it was −1.22%. The secondary end point of normalized total atheroma volume was significantly lower in the rosuvastatin group than in the atorvastatin group. The frequency and size of regression was greater than demonstrated previously, and greater regression was seen in those with higher HDL-C levels. The magnitude of regression in SATURN was greater than that seen in REVERSAL and ASTEROID, and it is important to note that the HDL-C levels were much higher in SATURN. In both groups, the incidence of adverse events, such as MI, stroke, and surgical revascularization, were extremely low and did not differ between groups.

These studies using IVUS confirm that standard statin therapy does not arrest the progression of atherosclerosis and that more intensive therapy is required to stop or even regress preexisting disease burden. An analysis of the data available from 4137 patients in six clinical trials that used serial IVUS reveals a strong relationship between baseline percentage or total atheroma volume with the risk of major adverse cardiovascular events (MACEs; Fig. 12-9, *A*).[51] Additionally, these data demonstrate a lowered risk of MACEs in those with plaque burden regression, the converse being true for those with disease progression (see Fig. 12-9).

Mechanisms of Benefit

Intensity of Low-Density Lipoprotein Reduction

Given the prior epidemiologic data and clear evidence that a statin is better than placebo and that an intensive statin regimen is better than a standard-dose statin regimen, subjects with CAD who achieved the lowest levels of LDL-C would be expected to be at lowest risk for recurrent events. In the CTT meta-analysis, when all trials were considered and a regression line was forced through zero, a linear relationship between lower LDL-C levels and risk reduction was observed. The current intensive statin therapy versus moderate statin therapy trials also fit this regression model and suggest that the greater the LDL-C difference between two strategies, the greater the clinical benefit (see Fig. 12-6).

However, the long-term efficacy of statin therapy in patients achieving very low LDL-C levels (<100 mg/dL) remained poorly assessed until recently. In an analysis from PROVE IT–TIMI 22, the relationship between achieved LDL-C levels and clinical outcomes with 80 mg of atorvastatin was assessed by dividing these patients into subgroups by achieved LDL-C levels at 4 months (>80 to 100, >60 to 80, >40 to 60, ≤40 mg/dL) and correlating this with risk of subsequent adverse events.[52] Among almost 2000 subjects for whom 4-month LDL-C data were available, about 90% had LDL-C levels below 100 mg/dL (2.59 mmol/L). Compared with the reference group (LDL-C level of 80 to 100 mg/dL), the hazard of death, MI, stroke, recurrent ischemia, and revascularization was lower among patients with LDL-C levels between 40 and 60 (HR, 0.76) and was lowest among those with LDL-C levels less than or equal to 40 mg/dL (HR, 0.61). No increased risk of adverse events was found at these low levels of LDL-C. It is not necessary to reduce the dose of a statin if the resultant LDL-C levels fall well below guideline recommendations. These results suggest the possibility

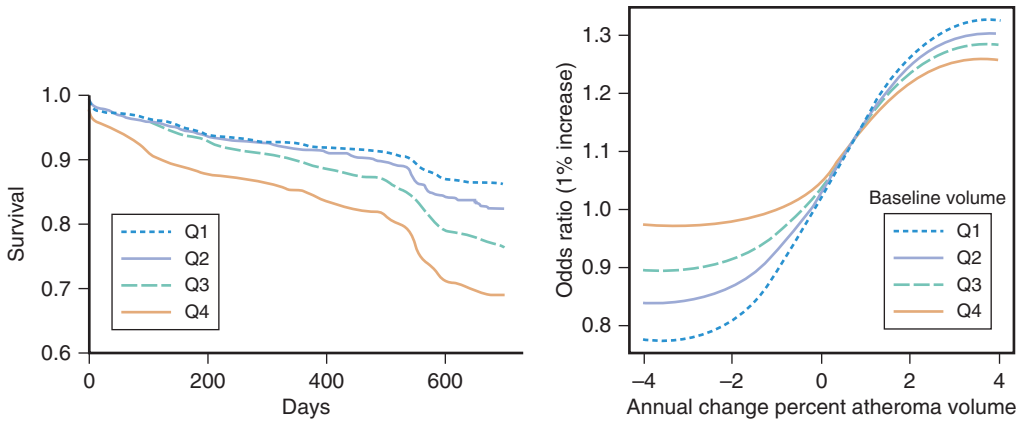


FIGURE 12-9 Baseline plaque burden and cardiovascular events (CVEs) and change in plaque burden and CVEs. (Data from Nicholls SJ, Hsu A, Wolski K, et al: Intravascular ultrasound–derived measures of coronary atherosclerotic plaque burden and clinical outcome. *J Am Coll Cardiol* 55[21]:2399-2407, 2010.)

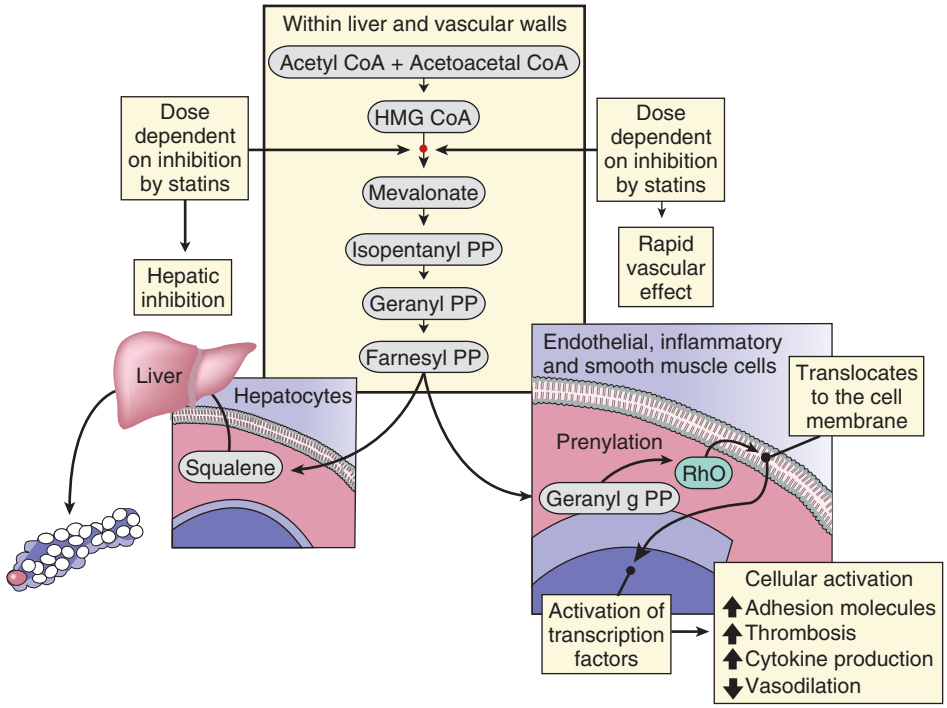


FIGURE 12-10 Inhibition of hydroxymethyl glutaryl–coenzyme A (HMG-CoA) reductase leads to effects mediated by low-density lipoprotein cholesterol (LDL-C) through the liver and non–lipid-related effects in the vessel wall. *PP,* Pyrophosphate; *RhO,* a small GTPase protein. (From Ray KK, Cannon CP: The potential relevance of the multiple lipid-independent [pleiotropic] effects of statins in the management of acute coronary syndromes. *J Am Coll Cardiol* 46:1425-1433, 2005.)

that further LDL-C lowering beyond the goal of less than 70 mg/dL (1.8 mmol/L) may translate into additional clinical benefit.

Reduction in C-Reactive Protein Levels

Statins possess pleiotropic effects mediated by hydroxymethyl glutaryl–coenzyme A (HMG-CoA) reductase but are not dependent on lowering of LDL-C levels (Fig. 12-10). All statins lower CRP levels, partly in relation to the statin dose. In PROVE IT, the median baseline levels of CRP were similar in the 80-mg atorvastatin and 40-mg pravastatin groups at trial entry, but they were significantly lower in the atorvastatin group than in the pravastatin group at 30 days, 4 months, and the end of the trial. Although the levels of LDL-C and CRP were reduced by statin therapy at 30 days, the correlation between the achieved values was weak (Correlation Coefficient r 0.16; $P = .001$). Despite the minimal correlation between LDL-C and CRP levels, an identical difference in the age-adjusted rates of events was also observed among patients in whom statin therapy resulted in CRP levels of less than 2 mg/L, compared with those in whom statin therapy resulted in higher CRP values (2.8 vs. 3.9 events per 100 person-years, $P = .006$). Patients who had achieved LDL-C levels below 70 mg/dL and CRP levels below 2 mg/L had the lowest risk of recurrent events, whereas those with LDL-C levels above 70 mg/dL and CRP levels above 2 mg/L had the highest risk. Hazard ratios for recurrent events among patients whose values were above 70 mg/dL for LDL-C and below 2 mg/L for CRP, those whose values were below 70 mg/dL for LDL and above 2 mg/L for CRP, and those whose values were above 70 mg/dL for LDL-C and above 2 mg/L for CRP—compared with those whose values of achieved LDL-C were less than 70 mg/dL and whose CRP

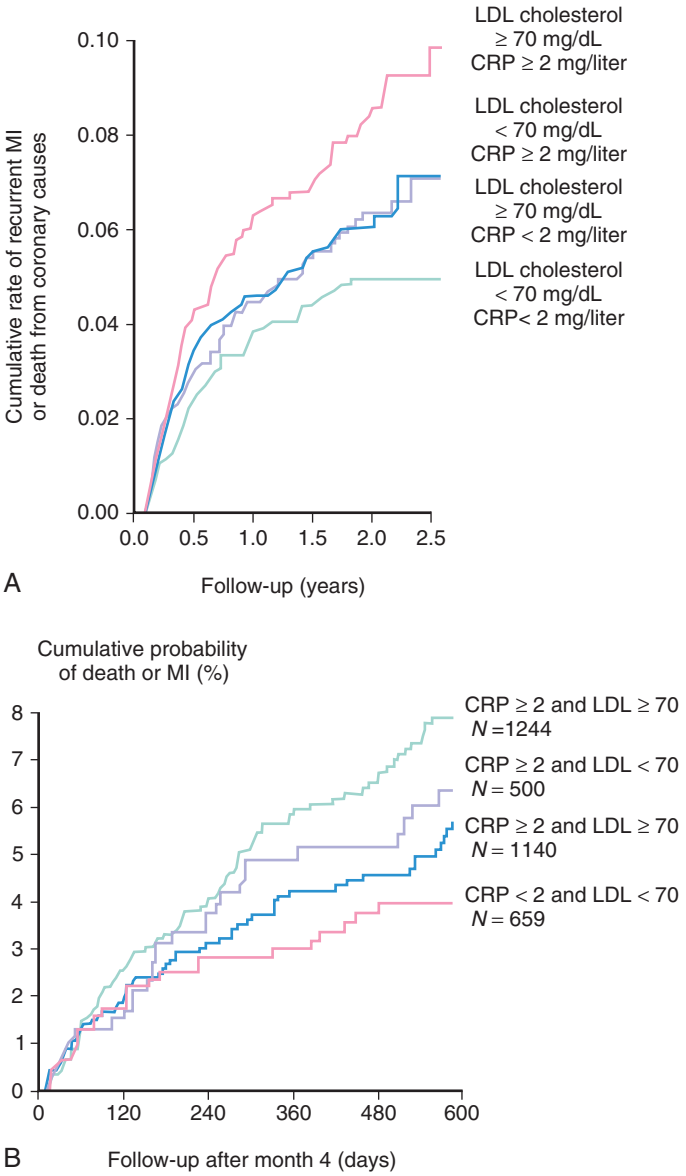


FIGURE 12-11 Clinical benefit of achieving the dual goals of low-density lipoprotein (LDL) less than 70 mg/dL and C-reactive protein (CRP) levels of less than 2 mg/L with statin therapy in the PROVE IT-TIMI 22 trial (**A**) and the A to Z trial (**B**), showing the benefit of achieving dual goals. *MI,* Myocardial infarction. (**A,** From the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) Investigators: C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 352:20-28, 2005; **B,** From Morrow DA, de Lemos JA, Sabatine MS, et al: Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor Trial. *Circulation* 114:281-288, 2006.)

was less than 2 mg/L (i.e., reference group)—were 1.3, 1.4, and 1.9, respectively (for trend across groups, $P < .001$; Fig. 12-11, *A*). Similar data have emerged from the **J**ustification for the **U**se of Statins in Primary **P**revention: An **I**ntervention **T**rial **E**valuating **R**osuvastatin trial (JUPITER)[53] and A-to-Z[54] trials, showing that subjects who achieve a low CRP level with high-dose statin therapy are at lower risk for recurrent events (see Fig. 12-11, *B*).

The JUPITER trial randomized 17,802 patients with an LDL-C of less than 130 mg/dL and a high-sensitivity CRP (hsCRP) of more than 2 mg/L to rosuvastatin 20 mg or placebo. Reductions of LDL-C levels by 50% and in hsCRP levels by 37% were seen in those receiving rosuvastatin. The trial was stopped early at a median of 1.9 years of follow-up given its positive result. The combined primary end point of MI, cerebrovascular accident (CVA), arterial revascularization, hospitalization for unstable angina, or CV death was significantly reduced in those who received rosuvastatin, and this effect was seen in all subgroups, including those with Framingham risk scores of less than 10%, LDC-C below 100 mg/dL, and those with elevated hsCRP levels but no other major risk factors.

These primary and secondary prevention data demonstrate that using statin therapy to achieve target levels of both LDL-C and CRP decreases the risk of MI and CAD death in both populations. Whether CRP is causally related to risk or is a marker remains unclear, but several lines of evidence suggest that it is an important player in mediating CV risk (Fig. 12-12). These data support the hypothesis that therapies designed to reduce inflammation after ACS may improve CV outcomes.

Apolipoproteins

Observational data from individuals free from CVD does not support using apolipoproteins over and above traditional lipids. Although the clinical benefits of statins appear to be predominantly related to LDL-C–mediated effects, other lipid markers—such as the concentration of apolipoprotein B (apo B), non–HDL-C, TC/HDL ratio, or apo B/apo A-I ratio—provide alternative approaches. In statin trials, data conflict about on-treatment lipid values alone that explain the totality of the benefits of statin therapy. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) trial,[55] on-treatment apo B values appeared to be a superior marker of on-treatment efficacy compared with LDL-C levels, and the on-treatment apo B/apo A-I ratio appeared to explain the entire benefit of statin therapy in this trial. In contrast, the much larger LIPID trial[56] suggested that the proportion of the treatment effect explained by reductions in LDL-C was 52%, compared with 67% for apo B, suggesting that non–lipid-related effects may also contribute to the long-term benefit of statins.

In the PROVE IT–TIMI 22 trial, non–HDL-C provided similar information to apo B, and neither non–HDL-C nor the apo B/apo AI or TC/HDL ratios improved risk prediction over and above LDL-C. Risk prediction was improved, however, by the addition of hsCRP to any lipid component. In contrast to the lipid findings in PROVE IT–TIMI 22, in the larger combined dataset of stable patients in the TNT and IDEAL trials, both non–HDL-C and apo B were significantly associated with risk in multivariable models containing LDL-C, whereas the latter was attenuated and nonsignificant in the same models.[57] Overall, no meaningful differences were found between apo B and non–HDL-C, nor were any meaningful differences found in the ratio of TC/HDL over apo B/apo AI, although these factors were not formally tested in risk-prediction models. Reconciling these apparently disparate findings is difficult in the absence of access to primary data. However, one explanation may reside with the high preponderance of individuals with metabolic syndrome, at least in the TNT trial, which indicated that insulin resistance may contribute to higher levels of VLDL and IDL and small, dense LDL-C, such that LDL-C less closely approximates to non–HDL-C or apo B. What is clear is that there is little conclusive evidence to suggest that apo B should be measured as an alternative to non–HDL-C (the optional secondary NCEP III target) in routine clinical practice.

Oxidized Low-Density Lipoprotein

Oxidized phospholipids (OxPLs) exist within atherosclerotic plaques and are bound by Lp(a) in plasma. Circulating levels of oxidized LDL are strongly associated with angiographically documented CAD and therefore may contribute to the pathogenesis of atherosclerosis.[58] In the MIRACL trial,[59] high-dose atorvastatin reduced the total apo B–containing OxPLs and apo B levels by approximately 30%. When normalized per apo B 100, compared with placebo, atorvastatin increased the OxPL/apo B level (9.5% vs. −3.9%, $P < .0001$). These data suggest

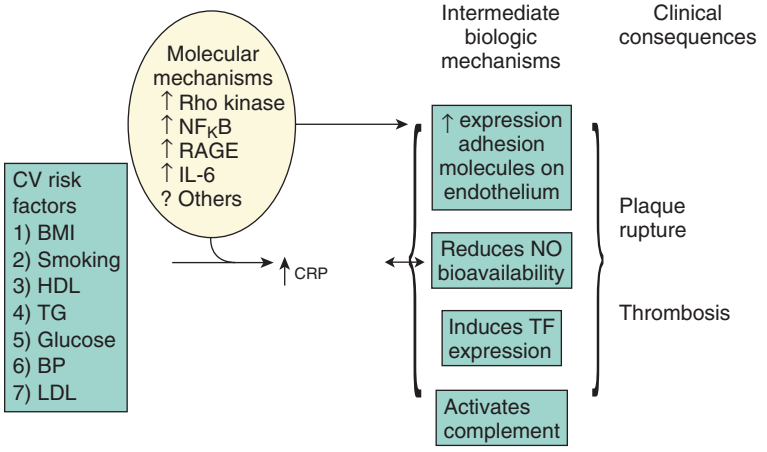


FIGURE 12-12 Schematic of putative mechanisms by which C-reactive protein (CRP) may mediate cardiovascular (CV) risk. *BMI,* Body mass index; *BP,* blood pressure; *HDL,* high-density lipoprotein; *IL-6,* interleukin 6; *LDL,* low-density lipoprotein; *NFκB,* nuclear factor kappa B; *NO,* nitric oxide; *TF,* tissue factor; *TG,* triglyceride.

that atorvastatin treatment results in enrichment of OxPLs on a smaller pool of apo B particles, which may contribute to the reduction in ischemic events after ACS observed in MIRACL.

Genetic variation controlling proinflammatory pathways, oxidized LDL-C formation, and the presence of CAD have been clearly linked.[60] In a recent study, almost 500 patients undergoing coronary angiography were genotyped for interleukin 1 (IL-1) locus variants—key drivers of proinflammatory pathways—and had levels of OxPL/apo B measured. A composite genotype termed *interleukin 1 positive* (IL-1+) was defined by an *IL-1* gene cluster polymorphism associated with higher levels of proinflammatory cytokines, with all other *IL-1* genotypes being termed *IL-1 negative* (IL-1−).

In the *IL-1+* cohort, the highest quartile of OxPL/apo B was significantly associated with a higher CAD risk compared with the lowest quartile (OR 2.84), the magnitude of this effect being greater in patients aged less than 60 years (OR 7.03). However, this association was not seen in IL-1− patients. In IL-1+ patients aged less than 60 years, hsCRP, Lp(a), and OxPL/apo B were independent predictors of CAD. This strongly suggests that the risk from elevated levels of oxidized LDL-C is highest in those who are younger and in those who have an *IL-1β* proinflammatory profile.[61] *IL-1+* patients above the median OxPL/apo B had significantly earlier presentations to the cardiac catheterization laboratory and worse 4-year event-free survival.

The ongoing Canakinumab Antiinflammatory Thrombosis Outcomes Study (CANTOS) trial[61a] randomized patients with stable CAD and high hsCRP to a monoclonal antibody to IL-1β and will likely shed further light on inflammatory pathways as a novel therapeutic focus because it targets the upstream part of the inflammatory cascade. If this treatment is shown to reduce CVD events, it will be the first anti-inflammatory treatment to show clinical benefit. Recently, two treatments targeted phospholipase A2, including the soluble and the lipoprotein-associated forms, but have failed to show any significant benefit with respect to CVD reduction.[62]

Raising High-Density Lipoprotein Cholesterol Levels

HDL as a carrier of increased cellular cholesterol in the reverse cholesterol transport pathway is believed to provide protection against atherosclerosis (Fig. 12-13). In reverse cholesterol transport, peripheral tissues (e.g., vessel-wall macrophages) remove their excess cholesterol through the adenosine triphosphate (ATP)–binding cassette transporter A1 (*ABCA1*) to poorly lipidated apo A-I, forming pre-HDL. HDL consists of a heterogeneous class of lipoproteins that contain approximately equal amounts of lipid and protein. The various HDL subclasses differ in quantitative and qualitative contents of lipids, apolipoproteins, enzymes, and lipid transfer proteins, resulting in differences in shape, density, size, charge, and antigenicity. Assessment of HDL-C measures the cholesterol content of all these HDL subclasses and is therefore a crude marker of reverse cholesterol transport. The American National Cholesterol Education Program considers HDL-C to be an optional secondary target of lipid treatment, whereas the European Consensus Panel recommends a minimum target for HDL of 40 mg/dL (1.03 mmol/L) in certain patients, such as those with diabetes, but the relevance of the latter recommendation is unclear in light of limited data from clinical trials.[34,35]

Most strategies to specifically target an increase in HDL-C have been disappointing. Most notably, niacin failed to improve outcomes in both Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes study (AIM-HIGH)[62a] and Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events study (HPS2-THRIVE)[62b] despite promising initial data from the old Coronary Drug Project. The cholesteryl ester transfer protein (CETP) class notwithstanding (described below), HDL-C increases with other routinely used agents thus far have been modest at best.

Apo A-I Milano is an apo A-I variant that was first identified in the 1980s, having been found in Italian families with very low HDL-C but no increase in CAD. Recombinant apo A-I Milano infusions in animal models was associated with impressive regression of atheroma within short time spans. In 2003, infusion of a recombinant form of apo A-I to a small number of early post-MI patients suggested a trend toward atheroma regression on IVUS studies within just 5 weeks.[63] However, further efforts with this agent have been hampered by challenging manufacturing, and no subsequent trials have been performed.

Further trials using apo A-I harvested from human plasma and also autotransfusion of the patient's own delipidated HDL have suggested some promise but are not ready for large-scale clinical trials.[64,65] Several companies are looking to develop apo A-I Milano with the focus on improving HDL function rather than achieving significant differences in HDL-C.

The novel oral inducer of apo A-I synthesis, RVX-208, has undergone a short-term preliminary safety and efficacy analysis in patients already receiving statins. A dose-dependent modest increase in apo AI, HDL-C, and large HDL particles was observed, but further data on clinical end points using different time horizons are still required.[66] In a small IVUS trial, RVX-208 failed to show a significant difference in total atheroma versus placebo against a backdrop of intensive stain therapy.[67]

The recent Effect of CER-001 on Atherosclerosis in Acute Coronary Syndrome Patients–Efficacy and Safety (CHI-SQUARE) trial[68] attempted an alternative approach by infusing a novel engineered lipoprotein particle, CER-001, that mimics pre–β-HDL. At the dose used in the trial, CER-001 infusions did not impact coronary atheroma burden as measured on IVUS and quantitative coronary angiography (QCA) when compared with placebo.

Cholesterol Ester Transfer Protein Inhibition

Humans with CETP deficiency caused by molecular defects in the *CETP* gene have markedly elevated plasma levels of HDL-C and apo

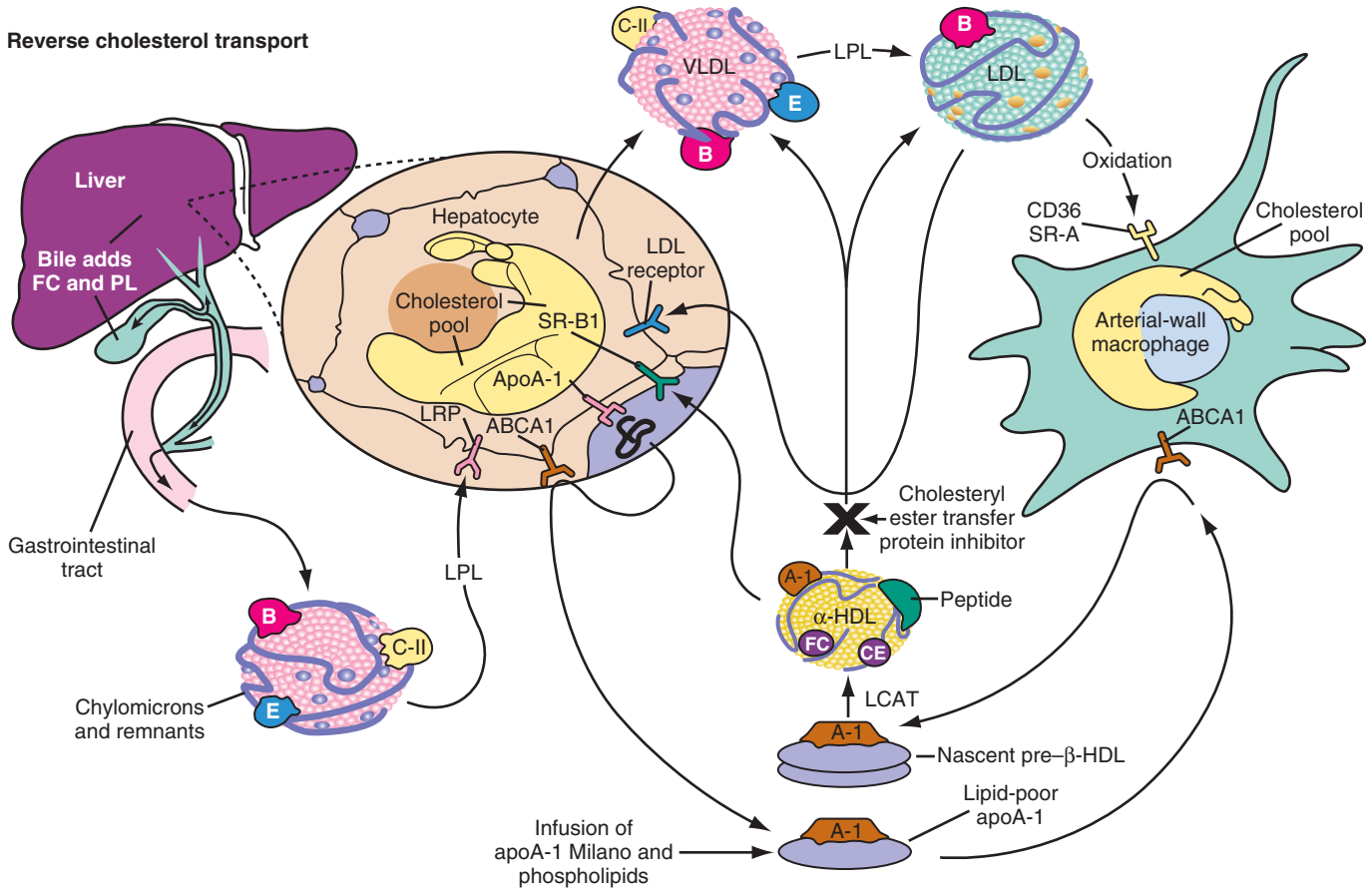


FIGURE 12-13 The reverse cholesterol transport pathway of high-density lipoprotein (HDL). Lipid-poor pre–β-HDL cholesterol, rich in apolipoprotein AI (apo AI), is synthesized by the liver or intestinal mucosa and is released into the circulation, where it promotes the transfer of excess cellular-free cholesterol (FC) from macrophages to apo AI by interacting with the adenosine triphosphate (ATP)-binding cassette transporter A1 (*ABCA1*) in arterial wall macrophages. Plasma lecithin-cholesterol acyltransferase (LCAT) converts free cholesterol in pre–β-HDL cholesterol to cholesteryl ester (CE), resulting in the maturation of pre–β-HDL cholesterol to mature α-HDL cholesterol. The α-HDL cholesterol is transported to the liver by a direct or indirect pathway. In the direct pathway, selective uptake of CE by hepatocytes occurs with the scavenger receptor, class B, type 1 (SR-B1). In the indirect pathway, HDL cholesterol CE is exchanged for triglycerides in apo B–rich particles (**B**), low-density lipoprotein cholesterol (LDL-C), and very-low-density lipoprotein (VLDL) cholesterol through cholesteryl ester transfer protein (CETP), with the uptake of CE by the liver through the low-density lipoprotein receptor (LDLR). Cholesterol returned to the liver is secreted as bile acids and cholesterol. Acquired triglycerides in the modified HDL cholesterol particle are subjected to hydrolysis by hepatic lipase (HL) and thereby regenerate small HDL cholesterol particles and pre–β-HDL cholesterol for participation in reverse cholesterol transport. *ABCA,* ATP-binding cassette transporter; *B,* apolipoprotein B (apo B); *C-II,* apolipoprotein C-II (apo C-II); *E,* apolipoprotein-E–rich particles; *LPL,* lipoprotein lipase; *LRP,* low density lipoprotein receptor-related protein; *PL,* plasma lecithin; *SR-A/B,* scavenger receptor type A/B. (Modified from Brewer HB Jr: Increasing HDL cholesterol levels. *N Engl J Med* 350:1491-1494, 2004.)

AI, suggesting that CETP inhibition may increase HDL-C levels. To date, four CEPT inhibitors have been evaluated in humans: torcetrapib, dalcetrapib, anacetrapib, and evacetrapib.

Preliminary data from phase II trials to assess the relative efficacy of torcetrapib demonstrated significant increases in HDL-C levels. However, in December 2006, Pfizer halted the development of torcetrapib because of a 60% observed increase in deaths in a Study Examining Torcetrapib/Atorvastatin and Atorvastatin Effects on Clinical CV Events in Patients With Heart Disease (ILLUMINATE).[69] Exploratory analyses from the Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE), which used IVUS to follow up on patients randomized to torcetrapib/atorvastatin or atorvastatin monotherapy, suggest there is no harm associated with higher levels of HDL-C, and among those who achieved higher HDL-C levels, regression of atherosclerosis and a lower event rate were observed.[70] The adverse events now seem to be related to an "off-target" drug-specific effect, with the observation that torcetrapib raises blood pressure and activates the renin-angiotensin system; this also occurs in animal species that lack CETP activity, which further supports an off-target effect.[71] The potential for HDL-C raising has received further impetus with observations that anacetrapib not only raises HDL-C by 138% but produces a near 40% lowering of LDL-C but does not result in adverse effects on blood pressure.[72,73] The Study to Assess the Tolerability and Efficacy of Anacetrapib in Patients With Coronary Heart Disease (CHD) or CHD Risk-Equivalent (DEFINE)[74] demonstrated anacetrapib to have an acceptable side-effect profile. Further evaluation of this trial cohort following anacetrapib cessation reveals similar acceptable safety, albeit with profoundly prolonged durations required for drug clearance, with drug levels still detectable 4 years after last dosing.[75] The ongoing Randomized Evaluation of the Effects of Anacetrapib Through Lipid-Modification (REVEAL) of

30,000 patients receiving atorvastatin background therapy with anacetrapib against placebo is currently ongoing (Clinical Trials.gov identifier NCT01252953).

The Vascular Effects and Safety of Dalcetrapib in Patients With or at Risk of Coronary Heart Disease (dal-VESSEL)[76] and the Safety and Efficacy of Dalcetrapib on Atherosclerotic Disease Using Novel Noninvasive Multimodality Imaging (dal-PLAQUE)[77] studies demonstrated the tolerability and safety of dalcetrapib. A Study of RO4607381 in Stable Coronary Heart Disease Patients With Recent Acute Coronary Syndrome (dal-OUTCOMES),[78] which comprised over 15,000 post-ACS patients randomized to dalcetrapib or placebo, was terminated early for futility. Despite significantly favorable effects on the lipid profile, the primary efficacy composite end point of death from CHD, nonfatal MI, ischemic stroke, unstable angina, or cardiac arrest with resuscitation was not significantly different between the active or comparator groups. The Effect of Cholesteryl Ester Transfer Protein Inhibition on Lipids, Lipoproteins, and Markers of HDL Function After an Acute Coronary Syndrome (dal-ACUTE) trial[79] was designed to investigate the short- to medium-term effects of CETP inhibition with dalcetrapib on HDL-C, apo AI, HDL function, and inflammatory biomarkers in the immediate post-MI period. This is the largest trial to date to look at the effects of HDL-raising interventions on cholesterol efflux. Three hundred patients were randomized to dalcetrapib or placebo within 1 week of an ACS, and the primary end point was HDL-C percent after 4 weeks. Secondary end points included apolipoprotein levels, markers of HDL function, and inflammation. Cholesterol efflux was raised by almost 10%, HDL-C by 32%, and apo AI by 11%. Overall the trial suggests that CETP inhibition creates functional HDL-C that is effective at mediating cholesterol efflux. It has been previously demonstrated that cholesterol efflux capacity has a strong inverse association with carotid intima media thickness (CIMT) and the likelihood of angiographic CAD independent of the HDL-C level.[80]

Important molecular differences exist between dalcetrapib and anacetrapib. Anacetrapib physically forms a tertiary complex among HDL2 particles and apo B–containing lipoproteins, whereas dalcetrapib is a modulator that works in the CETP tunnel, and its binding causes conformational changes in CETP that allows it to bind to HDL2 particles but not to apo B. Whether these differences contribute to cardiovascular outcomes is a hypothesis that will be answered in the immediate future with the completion of large phase III trials.

Evacetrapib has demonstrated similarly impressive increases in HDL-C and appears to have an acceptable safety and tolerability profile.[81,82] By contrast to anacetrapib, evacetrapib levels are almost undetectable after a 4- to 6-week washout period. Clinical outcomes data are currently lacking but should be addressed by the phase III Study of Evacetrapib in High-Risk Vascular Disease (ACCELERATE) trial (ClinicalTrials.gov identifier NCT01687998).

Niacin

A variety of studies have assessed the relative merit of raising HDL-C levels using niacin (discussed previously). A meta-analysis of these data suggests that there is a 1.7% reduction per 1% rise in HDL-C levels with niacin.[83] Niacin raises HDL-C by levels of approximately 28%, but its use has been limited by adverse effects, notably flushing mediated by prostaglandins. Using ultrasound and measurements of carotid intima media thickness, niacin has been shown to attenuate and may reverse atherosclerosis.[84] In a trial assessing carotid intima media thickness (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis [ARBITER 6–HALTS]),[85] niacin reduced the progression of atherosclerosis compared with ezetimibe, which was associated with progression ($P = .01$). This is particularly interesting, and niacin and ezetimibe both produce about a 20% reduction in LDL-C. This suggests that differences between agents with respect to atherosclerosis may relate more to niacin's 30% rise in HDL-C and a 20% lowering of Lp(a). Magnetic resonance imaging (MRI) techniques to image carotid plaques have similarly shown that niacin reduces atheroma burden. An MRI trial to assess the effect of 2 g of niacin on carotid atherosclerosis further supported these observations by demonstrating regression of atherosclerosis within 12 months.[86]

However, recent large-scale trials to evaluate niacin have yielded disappointing results. The AIM-HIGH trial of 3414 patients with established CVD was terminated early at 3 years because of a lack of efficacy. In addition to background lipid-lowering therapy, patients were randomized to extended-release niacin or placebo. As background therapy, all patients received simvastatin (40 to 80 mg) plus ezetimibe 10 mg, if required, in order to achieve an LDL-C level of 40 to 80 mg/dL (1.03 to 2.07 mmol/L). Following reductions in LDL-C from 74 mg/dL to 62 mg/dL and an increase in HDL-C from 35 mg/dL to 42 mg/dL in the niacin-treated group, no significant difference was seen in the primary end point—composite of death from CHD, nonfatal MI, ischemic stroke, hospitalization for an ACS, or symptom-driven coronary or cerebral revascularization—between the two groups.[87]

Published full-outcomes data from the larger ($n = 25,673$) HPS2-THRIVE are still pending; however, salient information from the negative trial was disseminated at the American College of Cardiology's Scientific Sessions 2013. Similar to AIM-HIGH, all patents with occlusive arterial disease received simvastatin 40 mg and, if required, ezetimibe 10 mg. The active-arm participants received niacin in combination with laropiprant, a prostaglandin receptor antagonist that reduces niacin-related flushing symptoms, and the comparator arm received placebo. The primary end point—combined coronary death, nonfatal MI, stroke, or coronary revascularization—was similar in both groups. An excess number of adverse events was reported in the niacin group; however, over 10,000 participants were of Chinese origin, a group that has historically tolerated niacin and statin therapy less well.[88]

Despite these negative results, it is important to consider the real-world use of niacin. Clinicians do not routinely use niacin in well-treated patients with LDL-C levels below 70 mg/dL unless further progression of disease is evident. Niacin is often used in patients who cannot tolerate high-intensity statins, or any statins whatsoever, in order to achieve a 20% reduction in LDL-C or in patients with FH who have high LDL-C despite statin therapy and thus remain at high CVD risk.

Fibrates

Data for fibrates conflict. Although some studies, such as VA-HIT and the Helsinki Heart study, have shown benefit in specific populations, more recent trials have suggested little benefit. Overall, the positive effects of fibrates on the lipid profile are modest when compared with statins (Fig. 12-14). This was demonstrated in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study,[89] in which long-term treatment with fenofibrate to raise HDL-C concentrations and lower TG levels was assessed in subjects with type 2 diabetes and total blood cholesterol concentrations of less than 251 mg/dL (6.5 mmol/L). Overall, the FIELD trial failed to demonstrate a significant benefit of an agent that predominantly reduces TG levels and raises HDL levels modestly in a high-risk population. This finding might have resulted from an unequal, increased use of statin therapy in subjects allocated to placebo.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[90] assessed whether adding a fibrate to statin therapy reduced CV risk among diabetics. In this trial, the baseline LDL-C was 2.59 mmol/L, TG was 2.12 mmol/L, and HDL-C was 0.98 mmol/L. LDL-C fell in both the placebo group (to 2.07 mmol/L) and in the fenofibrate group (to 2.10 mmol/L) with little difference between treatments. TG levels fell to 1.92 mmol/L in the placebo group and to 1.66 mmol/L in the fenofibrate group ($P < .001$). HDL-C rose to 1.05 mmol/L in the placebo group and to 1.07 mmol/L in the fenofibrate group ($P = .01$). This trial is significant for providing important information on safety because no significant differences were found in transaminase levels or creatine kinase (CK) levels greater than 10 times the ULN between treatment groups. This reinforces the safety of fenofibrate when combined with a statin. The effect of fenofibrate on the combined end point of fatal and nonfatal CAD or stroke was an 8% reduction, but this did not reach statistical significance (HR, 0.92; 95% CI, 0.79 to 1.08).

	Drug	Fibrate Mean	Fibrate SD	Fibrate Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, random, 95% CI
LDL									
LOCAT (1997)[27]	Gemfibrozil	3.39	0.56	197	3.83	0.59	198	31.8%	−0.45 (−0.56 to −0.34)
Helsinki heart (1987)[26]	Gemfibrozil	4.48	0.79	2046	4.95	0.79	2035	33.9%	−0.47 (−0.52 to −0.42)
FIELD (2005)[16]	Fenofibrate	2.43	0.65	4895	2.6	0.78	4900	34.2%	−0.17 (−0.20 to −0.14)
Total (95% CI)				**7138**			**7133**	**100.0%**	**−0.36 (−0.59 to −0.13)**
Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 120.85$, df = 2 ($P < .00001$); $I^2 = 98\%$									
Test for overall effect: $Z = 3.03$ ($P = .002$)									
HDL									
LOCAT (1997)[27]	Gemfibrozil	0.98	0.17	197	0.88	0.15	198	31.0%	0.10 (0.07 to 0.13)
Helsinki heart (1987)[26]	Gemfibrozil	1.32	0.3	2046	1.26	0.27	2035	34.1%	0.06 (0.04 to 0.08)
FIELD (2005)[16]	Fenofibrate	1.13	0.3	4895	1.12	0.29	4900	34.9%	0.01 (−0.00 to 0.02)
Total (95% CI)				**7138**			**7133**	**100.0%**	**0.05 (0.01 to 0.10)**
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 41.20$, df = 2 ($P < .00001$); $I^2 = 95\%$									
Test for overall effect: Z=2.22 ($P = .03$)									
Triglyceride									
LOCAT (1997)[27]	Gemfibrozil	1.02	0.37	197	1.69	0.68	198	25.2%	−0.67 (−0.78 to −0.56)
Helsinki heart (1987)[26]	Gemfibrozil	1.3	0.76	2046	2.0	1.06	2035	26.4%	−0.70 (−0.76 to −0.64)
FIELD (2005)[16]	Fenofibrate	1.47	0.78	4895	1.87	0.96	4900	26.8%	−0.40 (−0.43 to −0.37)
Hanefeld (1991)[30]	Clofibrateil	1.98	1.54	379	2.09	1.25	382	21.6%	−0.11 (−0.31 to 0.09)
Total (95% CI)				**7517**			**7515**	**100.0%**	**−0.48 (−0.69 to −0.28)**
Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 103.39$, df = 3 ($P < .00001$); $I^2 = 97\%$									
Test for overall effect: $Z = 4.54$ ($P < .00001$)									
Total cholesterol									
LOCAT (1997)[27]	Gemfibrozil	4.83	0.63	197	5.48	0.68	198	24.7%	−0.65 (−0.78 to −0.52)
Helsinki heart (1987)[26]	Gemfibrozil	6.38	0.88	2046	7.04	0.82	2035	26.4%	−0.66 (−0.71 to −0.61)
FIELD (2005)[16]	Fenofibrate	4.23	0.78	4895	4.56	0.9	4900	26.6%	−0.33 (−0.36 to −0.30)
Hanefeld (1991)[30]	Clofibrateil	5.96	1.41	379	6.06	1.4	382	22.3%	−0.10 (−0.30 to 0.10)
Total (95% CI)				**7517**			**7515**	**100.0%**	**−0.44 (−0.67 to −0.22)**
Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 130.77$, df = 3 ($P < .00001$); $I^2 = 98\%$									
Test for overall effect: $Z = 3.80$ ($P = .0001$)									

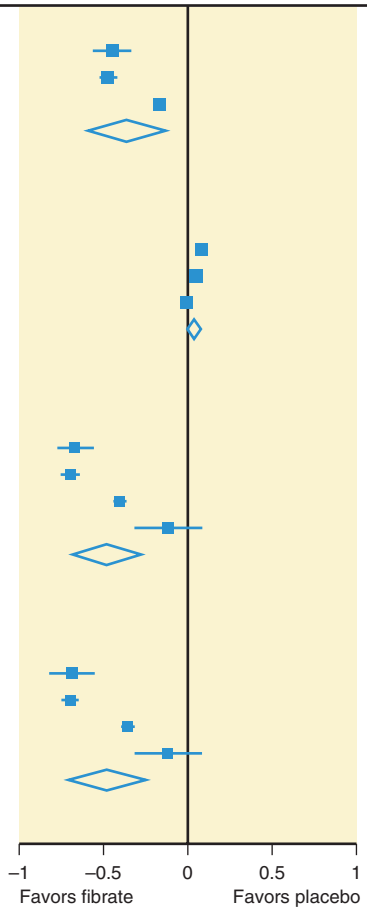


FIGURE 12-14 Effect of lipid level differences between fibrate treatment and placebo groups. *CI,* Confidence interval; *IV,* inverse variance; *SD,* statistical deviation. (Data from Jun M, Foote C, Lv J, et al: Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet* 375[9729]:1875-1884, 2010.)

A meta-analysis of 18 fibrate trials, including a mixture of primary and secondary preventions, provided useful new information (see Fig. 12-14).[91] It showed a 19% relative risk reduction in nonfatal MI, no effect on stroke, no effect on CV death, and no effect on all-cause mortality (RR, 1.0; 95% CI, 0.93 to 1.08). A reduction was seen in the need for revascularization, and a trend toward increased risk of noncardiovascular deaths was also observed. Taken together, these data suggest modest benefits on nonfatal MI and revascularization only. Among people with an elevated TG greater than 2 mmol/L, a proportionately greater reduction in coronary events was observed (32% lower vs. 19%; *P* interaction = .03); a similar trend was observed in individuals with a baseline HDL less than 1 mmol/L (23% vs. 14%), although this difference was not statistically significant. These results are derived from access to trial-level data only, rather than to individual-level data, and require further validation, such as that intended in the third cycle of the Cholesterol Treatment Trialists Collaboration, which will weigh the benefit of fibrates by changes in TG, HDL-C, and non–HDL-C. In a meta-analysis of five trials, the relative risk reduction in vascular events was greater among those with an atherogenic dyslipidemia profile at baseline (high TG, low HDL; OR 0.65 vs. 0.94). In contrast to the data for fibrates, RCT data from the Collaborative Atorvastatin Diabetes Study (CARDS) trial[92] and subgroups of other major RCTs and the CTT meta-analysis firmly establish the benefit of statins as first-line therapy for the prevention of CVD among those with diabetes irrespective of their baseline lipid profiles.[29]

Ezetimibe and Colesevelam

Ezetimibe is a compound that binds to the Niemann-Pick receptor in the intestine and reduces the absorption of cholesterol esters. Numerous studies have demonstrated its excellent tolerability and a 20% reduction in LDL-C when administered in addition to statin therapy or as monotherapy. This agent may also be particularly useful in the so-called high-absorber, low-synthesizer groups, in which subjects respond poorly to statins with little or no change in LDL-C. The Study of Heart and Renal Protection (SHARP) trial notwithstanding, which examined ezetimibe in combination with low-dose simvastatin against placebo only in those with advanced kidney disease,[93] there is no trial evidence of significant CV benefit with ezetimibe. The Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) Versus Simvastatin (IMPROVE-IT) trial assessed the incremental benefit of ezetimibe over statin therapy with respect to clinical outcomes in patients with ACS and compared simvastatin to simvastatin plus ezetimibe; this trial has completed and is due to report. Colesevelam is a bile acid absorption inhibitor that can be used as monotherapy or in combination therapy with statins. As the bile acid pool becomes depleted, the hepatic enzyme cholesterol 7-α-hydroxylase is upregulated, which increases the conversion of cholesterol to bile acids. This causes an increased demand for cholesterol in the liver cells, resulting in the dual effect of decreasing transcription and activity of the cholesterol biosynthetic enzyme HMG-CoA reductase and increasing the number of hepatic LDL receptors. These

compensatory effects result in increased clearance of LDL-C from blood, resulting in decreased serum LDL-C levels. The average LDL-C reduction is on the order of 18% with a rise in HDL-C of 3%.[94] Common adverse effects include flatulence and constipation, and a less common adverse effect is elevation of triglycerides. Few data are available to assess the impact of colesevelam on mortality and morbidity, but it maybe a useful adjunctive therapy given its favorable tolerability profile, glucose-lowering effect, and minimal propensity for drug-drug interactions.

Glitazones

Glitazones are a class of agents that stimulate the peroxisome proliferator-activated receptor γ (PPAR-γ), improve glycemic control, and have favorable effects on dyslipidemia, particularly in reducing triglycerides and raising HDL-C levels.

The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE) was a placebo-controlled trial that assessed the benefit of the PPAR-γ agonist pioglitazone in subjects with stable type 2 diabetes with evidence of macrovascular disease.[95] Compared with placebo, pioglitazone was associated with an 11.4% versus 1.8% reduction in triglycerides ($P < .0001$). Significantly, pioglitazone raised HDL-C levels by 19%, compared with 10.1% in the placebo group ($P < .0001$), and it reduced the LDL/HDL ratio by 9.5%, compared with 4.2% ($P < .0001$). The primary end point of mortality, nonfatal MI, stroke, ACS, coronary or peripheral arterial revascularization, and above-the-knee amputation tended to be lower in patients allocated to pioglitazone (HR, 0.9; $P = .095$). The secondary end point of mortality, nonfatal MI, and stroke was reduced by 16% among patients allocated to pioglitazone ($P = .027$). Pioglitazone slows progression of the surrogate marker, carotid intima media thickness, independently of improvements in hyperglycemia, insulin resistance, dyslipidemia, and systemic inflammation, which suggests a possible direct vascular effect.[96]

A meta-analysis of 16,390 individuals in pioglitazone trials found an 18% reduction in risk of death, MI, or stroke (95% CI, 0.72 to 0.94) but a 41% (95% CI, 1.141 to 1.76) increased risk of heart failure.[97] In the Efficacy Study of Pioglitazone Compared to Glimepiride on Coronary Atherosclerotic Disease Progression in Subjects With Type 2 Diabetes Mellitus (PERISCOPE), the rate of progression of atherosclerosis was lower in pioglitazone-treated subjects compared with those receiving glimepiride.[98] Whereas the difference in Hb_{A1c} in favor of pioglitazone was 0.19% lower, HDL-C was 4.6 mg/dL higher, and TG was 19.6 mg/dL lower. Thus much of the favorable effect of pioglitazone on atheroma progression is likely related to its beneficial effects on lipids, given the modest differences in Hb_{A1c}.

The favorable data for pioglitazone are distinctly contradictory to the safety data for rosiglitazone, which was called into consideration by a meta-analysis of randomized trials that suggested an increased risk of MI. In the most recent iteration of 56 trials that comprised 35,531 patients, rosiglitazone significantly increased the risk of MI by 28% (95% CI, 1.02 to 1.63) but had no effect on CV mortality (OR, 1.03; 95% CI, 0.78 to 1.36).[99] Rosiglitazone has been removed from the market in Europe, and in the United States, it has been put under strict restriction to be used only if all other antidiabetic medications have failed.

NOVEL TARGETS FOR THERAPY

Microsomal Triglyceride Transfer Protein Inhibitors

Microsomal triglyceride transfer protein inhibitors are a new class of approved drugs that reduce LDL-C through the inhibition of VLDL production. Microsomal transfer protein (MTP) is a key component of the pathway that mediates chylomicron and VLDL formation by facilitating transfer of lipids into apo B-100 or apo B-48 in the liver and intestine. Inherited MTP deficiency is associated with the rare condition abetalipoproteinemia. The finding of markedly low levels of apo B and serum cholesterol in patients with abetalipoproteinemia promoted interest in MTP inhibition as a novel therapeutic target. To date, the only compound currently viable for human clinical use is lomitapide. Published results are only available for small numbers of patients in phase I and II studies, and clinical outcomes data are as yet lacking.[100] Reductions of LDL-C levels of between 14% and 65% have been demonstrated, and this effect is additive with other lipid-lowering agents such as atorvastatin and ezetimibe. Commonly seen side effects are predominately gastrointestinal in nature, likely owing to raised enterocyte TG levels. Lomitapide is CYP3A4 metabolized, hence caution should be taken when the drug is coprescribed with simvastatin or warfarin. Lomitapide is currently licensed by the FDA for adjunctive treatment of FH.

PCSK-9 Inhibition

PCSK-9 is a glycoprotein that is expressed at its highest levels in the liver, intestine, and kidney. In humans, this protein degrades the LDL receptor, thus preventing the clearance of LDL-C or apo B–containing lipoproteins from the liver; this leads to higher levels of circulating LDL-C. Nonfunctioning mutations in the *PCSK9* gene (prevalence of ~2% to 3%) lead to lower circulating levels of LDL-C and, in turn, to a lower risk of CAD in black and northern European populations.[101,102] These individuals have lifelong lower LDL-C levels that range from 28% in blacks to 12% in northern Europeans. Notably, the observed risk of CAD was much greater than would have been expected for the degree of LDL-C reduction (88% and 28% in blacks and northern Europeans, respectively). Statins lead to an increase in the expression of PCSK-9 in a dose-dependent fashion, which perhaps explains why doubling the dose only affords a further 6% reduction in LDL-C. Since the discovery of *PCSK9* in 2003, the pace of development and testing of PCSK-9 inhibitors has been rapid. Multiple agents are being evaluated in phase I through III trials, both as monotherapy and in combination with statin or ezetimibe therapy (Table 12-4).

The Open Label Study of Long-Term Evaluation Against LDL-C (OSLER; $n = 1104$) has provided promising results.[103] Participants who received the anti–PCSK-9 monoclonal antibody AMG 145 on a four-times weekly basis demonstrated an LDL-C reduction of over 50% at 1 year with a favorable safety and tolerability profile. Those who discontinued the agent returned to baseline levels of LDL-C. AMG 145 also caused a substantial reduction in LDL-C in those with FH.[104] Thus far, the adverse effect profile appears similar to that of a placebo.[105] AMG 145 has also been demonstrated to significantly lower LDL-C in a traditionally difficult-to-treat group of patients, those with homozygous hypercholesterolemia with defective (but not in those with negative) LDL receptor activity.[106]

In the largest evaluation of PCSK-9 inhibitors to date, the Effect of Evolocumab or Ezetimibe Added to Moderate- or High-Intensity Statin Therapy on LDL-C Lowering in Patients With Hypercholesterolemia (LAPLACE-2; $n = 2067$), evolocumab added to a moderate- or high-intensity statin regimen in a primary hypercholesterolemia and mixed dyslipidemia population resulted in substantial reductions in LDL-C levels when compared against placebo (Fig. 12-15).[107] The addition of evolocumab to either moderate- or high-intensity statins resulted in 86% to 94% of patients achieving LDL-C levels of less than 70 mg/dL within 12 weeks. Further follow-up clinical outcome studies are ongoing.

An added benefit of PCSK-9 inhibition demonstrated in LAPLACE–TIMI 57 (LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy) appears to be Lp(a) reduction by almost a third.[108] Given that most other agents either have failed to affect clinical outcomes through Lp(a) reduction, have little effect, or raise Lp(a), this is potentially an important therapeutic avenue for affecting this key lipid fraction.

Impressive reductions have been seen with the monoclonal agent alirocumab, which is currently being extensively investigated.[109] The global phase III ODYSSEY program is expected to enroll more than 23,000 patients and currently includes 14 clinical trials of alirocumab both in combination with other lipid-lowering agents and as monotherapy. The trial populations are similar to previous trials with other agents, and results will be comparable. The primary phase III study end

TABLE 12-4 Overview of PCSK-9 Inhibition Phase III Development Programs

Trial Type	Alirocumab Trials	*N*	Duration (Mo)	Patient Exposure (Yr)	Min LDL-C Levels (mg/dL)	Evolocumab Trials	*N*	Duration (Mo)	Patient Exposure (Yr)	Min LDL-C Levels	Bococizumab Trials	N	Duration (Mo)	Patient Exposure (Yr)	Min LDL-C Levels (mg/dL)
HeFH/HoFH	ODYSSEY FH I/II[110]	471/250	18	496/250.5	≥100	RUTHERFORD-2 (FH)[118]	300	3	46	≥100	SPIRE-HF[127]	300	12	200	≥70
	ODYSSEY HIGH FH[110]	105	18	106.5	≥160	TAUSSIG (FH/HoFH)[119]	310	60	TBD	≥100					
						TESLA (HoFH)[120]	58	3	TBD	≥130					
Combination therapy	ODYSSEY COMBO I/2[111]	306/606	12/24	210/960	≥70	LAPLACE-2[121]	1700	3	231	≥80	SPIRE-HR[128]	600	18	600	≥70
	ODYSSEY OPTIONS I/II[112]	350/300	6	50	≥70						SPIRE-LDL[129]	1600	18	1600	≥70
Monotherapy	ODYSSEY MONO[113]	100	6	25.5	≥100	MENDEL-2[122]	600	3	92	≥100	?				
Statin intolerance	ODYSSEY ALTERNATIVE[114]	250	6	50	≥70	GAUSS-2[123]	300	3	46	None	PLANNED				
						GAUSS-3[124]	500	3	?	?					
LTS	ODYSSEY LONG-TERM[115]	2100	18	2340	≥70	DESCARTES[125]	905	12	602	≥75	SPIRE-LL[130]	939	12	626	>100
						OSLER	3515	52+	TBD	TBD					
						Open label[126]									
Q4W	ODYSSEY CHOICE I[116]	700	12	500	≥70	Almost all of the evolocumab studies have a Q4W dosing regimen									
	ODYSSEY CHOICE II[117]	200	6	150	≥70										
	Total number of patients	4892	4538 Patient-years in double-blind placebo-controlled trials			Total number of patients	7820	1017 Patient-years in double-blind placebo controlled trials			Total number of patients	3439	~3000 Patient-years (assumes 2 : 1 randomization, final number likely to be larger because additional trials are anticipated)		

FH, Familial hypercholesterolemia; *He,* heterozygous; *Ho,* homozygous; *LDL-C,* low-density lipoprotein cholesterol; *LTS,* long term study; *Q4W,* administered every 4 weeks.

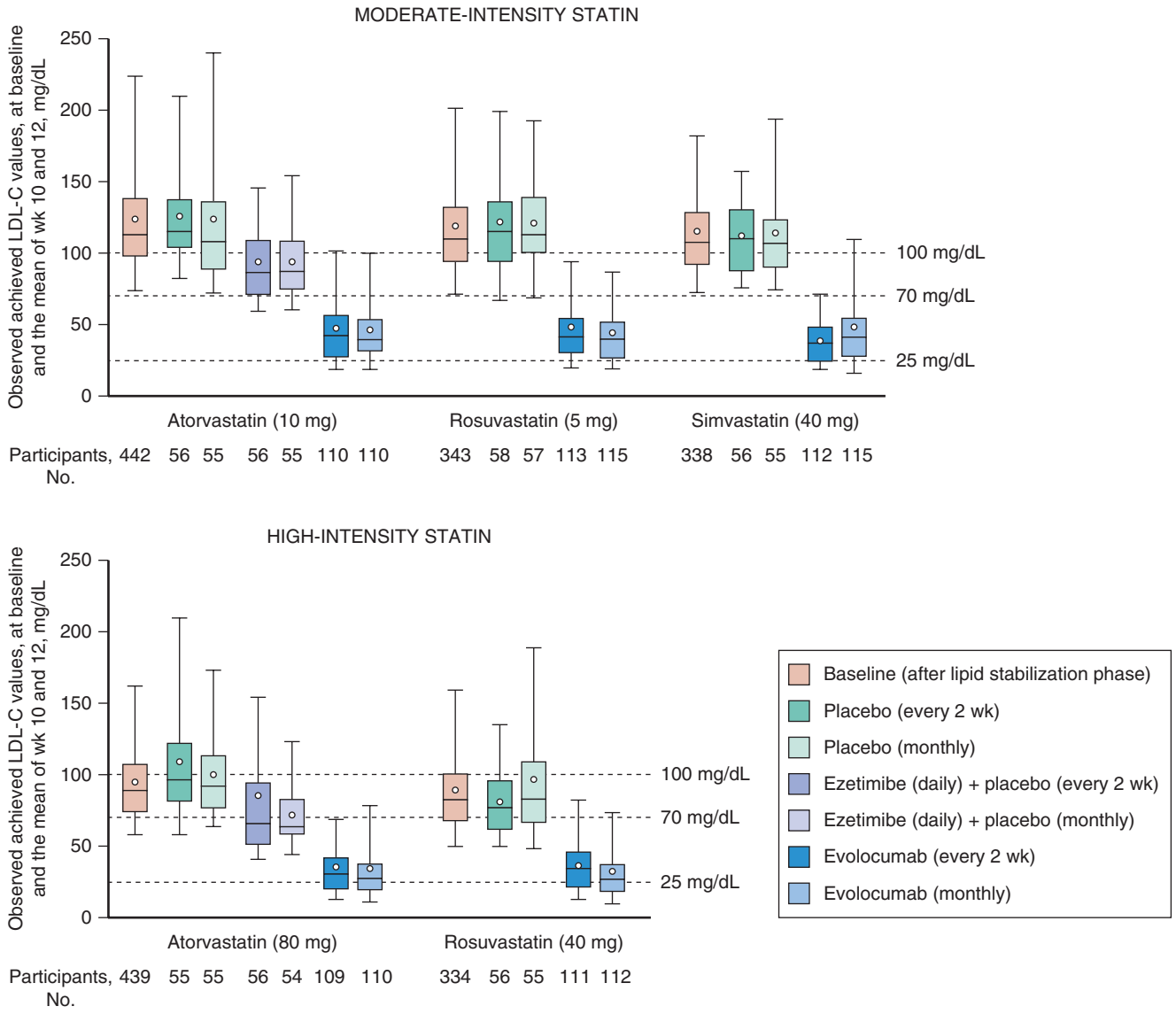


FIGURE 12-15 Summary statistics for baseline and mean of weeks 10 and 12 low-density lipoprotein cholesterol (LDL-C) values with evolocumab plus statin therapy. (Data from Robinson JG, Nedergaard BS, Rogers WJ, et al: Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA* 311[18]:1870-1882, 2014.)

point is the percent mean reduction in LDL-C at 24 weeks, giving measures of efficacy and safety. In addition, several other lipid markers are being assessed. Other approaches to inhibition of PCSK-9 under investigation include use of inhibitory adnectins and small interfering RNAs.[131]

Antisense to Apolipoprotein B

Mipomersen is an antisense oligonucleotide designed to reduce apo B-100 synthesis by binding to the messenger ribonucleic acid (mRNA) for apo B-100, which results in subsequent degradation by ribonuclease H and a reduction in apo B-100 and thus in LDL-C.

A number of small phase III trials of mipomersen have reported safety and efficacy data in different patient cohorts. Homozygous and heterozygous FH patients on lipid-lowering therapy experience LDL-C reductions of 24.7% and 28%, respectively, when receiving mipomersen.[132,133] In patients with mild to moderate hypercholesterolemia, mipomersen monotherapy was associated with LDL-C concentration reductions of up to 61% at the highest dose.[134] Patients with severe hypercholesterolemia with CAD or at high risk of CAD who were already receiving maximally tolerated lipid-lowering therapy exhibited LDL-C reductions of 36.9% with mipomersen.[135] Hard clinical outcomes data with mipomersen, either as monotherapy or adjunctive therapy, are still awaited; however, these initial data provide an important proof of concept for LDL-C modulation using a novel approach. Common adverse effects with mipomersen include injection site reactions, flulike symptoms, and elevations in alanine transferase levels that return to normal after drug cessation.

Thyroid Hormone Analogues

In individuals with hypothyroidism, thyroxine reduces LDL-C levels by increasing the expression of the LDL receptor. The SRB1 receptor in the liver increases the clearance of cholesterol and its excretion in bile. Eprotirome is a thyroid hormone analogue that has minimal uptake in extrahepatic tissues and a greater affinity for the T3 β-receptor

in the liver, compared with the T3 α-receptor in the heart, which modulates the cardiac effects of T3.

Three phase III studies using this agent have been conducted. In a 12-week dose-ranging trial, this compound reduced LDL-C from 3.6 mmol/L to 2.4 mmol/L in statin-treated subjects at the highest dose.[136] Similar proportional reductions were observed in apo B, TG, and Lp(a). In primary hypercholesterolemia, eprotirome monotherapy was associated with serum LDL-C reductions of up to 31%.[137] Although no significant cardiac or bone adverse effects have been reported in human studies, the largest planned trial to date was terminated early after reports of cartilage damage in canines.[138] Significant elevations in hepatic enzymes of three to seven times the ULN were seen in this human trial at 6 weeks. Other thyromimetic agents, such as sobetirome, are also currently being explored.

CONCLUSION

All patients with CAD benefit from statin therapy, with no apparent threshold below which benefit is absent. Intensive statin therapy reduces cardiovascular events and atherosclerotic disease progression compared with standard therapy and therefore should be considered the standard of care for patients with CAD. In addition to important reductions of LDL-C levels, intensive statin therapy reduces inflammation, which appears to be particularly important with regard to the early benefits observed in patients with ACS and perhaps makes significant contributions thereafter to long-term risk reduction. Beyond statin therapy, data for other agents that favorably alter lipid profiles are emerging but await validation in large-scale outcomes studies.

REFERENCES

1. Kannel WB, Dawber TR, Friedman GD, et al: Risk factors in coronary heart disease: an evaluation of several serum lipids as predictors of coronary heart disease; the Framingham Study. *Ann Intern Med* 61:888–899, 1964.
2. Kannel WB, Castelli WP, Gordon T, McNamara PM: Serum cholesterol, lipoproteins, and the risk of coronary heart disease: the Framingham Study. *Ann Intern Med* 74(1):1–12, 1971.
3. Neaton JD, Wentworth D: Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med* 152(1):56–64, 1992.
4. Neaton JD, Blackburn H, Jacobs D, et al: Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med* 152(7):1490–1500, 1992.
5. Law MR, Wald NJ: Risk factor thresholds: their existence under scrutiny. *BMJ* 7(1):152–163, 2002.
6. Pischon T, Girman CJ, Sacks FM, et al: Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. *Circulation* 112(22):3375–3383, 2005.
7. Ridker PM, Rifai N, Cook NR, et al: Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA* 294(3):326–333, 2005.
8. Denke MA: Weighing in before the fight: low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol versus apolipoprotein B as the best predictor for coronary heart disease and the best measure of therapy. *Circulation* 112(22): 3368–3370, 2005.
9. Emerging Risk Factors Collaboration: Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA* 302(4):412–423, 2009.
10. The Emerging Risk Factors Collaboration: Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 302(18):1993, 2009.
11. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG: Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* 301(22):2331, 2009.
12. Clarke R, Peden JF, Hopewell JC, et al: Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* 361(26):2518–2528, 2009.
13. National Institutes of Health Consensus Development Conference Statement Lowering Blood Cholesterol. *Nutr Today* 20(1): 13–16, 1985.
14. American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 129(25 Suppl 2):S1–S45, 2013.
15. European Association for Cardiovascular Prevention and Rehabilitation, ESC Committee for Practice Guidelines (CPG) 2008-2010 and 2010-2012 Committees, et al: ESC/EAS Guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 32:1769–1818, 2011.
16. Ray KK, Kastelein JJP, Boekholdt SM, et al: The ACC/AHA 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the uncertain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011. *Eur Heart J* 35(15): 960–968, 2014.
17. Pencina MJ, Navar-Boggan AM, D'Agostino RB, Sr, et al: Application of new cholesterol guidelines to a population-based sample. *N Engl J Med* 370(15):1422–1431, 2014.
18. The Lipid Research Clinics Coronary Primary Prevention Trial results: I. Reduction in incidence of coronary heart disease. *JAMA* 251(3):351–364, 1984.
19. Stamler J: The coronary drug project—findings with regard to estrogen, dextrothyroxine, clofibrate and niacin. *Adv Exp Med Biol* 82:52–75, 1977.
20. Canner PL, Berge KG, Wenger NK, et al: Fifteen-year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol* 8(6):124–155, 1986.
21. Carlson LA, Danielson M, Ekberg I, Klintemar B: Reduction of myocardial reinfarction by the combined treatment with clofibrate and nicotinic acid. *Atherosclerosis* 28(1):81–86, 1977.
22. Frick MH, Heinonen OP, Huttunen JK, et al: Efficacy of gemfibrozil in dyslipidaemic subjects with suspected heart disease. An ancillary study in the Helsinki Heart Study frame population. *Ann Med* 25(1):41–45, 1993.
23. Rubins HB, Robins SJ, Collins D, et al: Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 341(6):410–418, 1999.
24. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 344(8934):1383–1399, 1994.
25. Sacks FM, Pfeffer MA, Moye LA, et al: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 335(14):1001–1009, 1996.
26. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 339(19):1349–1357, 1998.
27. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 360(9326):7–22, 2002.
28. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 361(9374):2005–2016, 2003.
29. Cholesterol Treatment Trialists Collaborators: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 366(9493):1267–1278, 2005.
30. Schwartz GG, Olsson AG, Ezekowitz MD, et al: Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes: The MIRACL Study: A Randomized Controlled Trial. *JAMA* 285(13):1711–1718, 2001.
31. Cannon CP, Braunwald E, McCabe CH, et al: Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 350(15):1495–1504, 2004.
32. de Lemos JA, Blazing MA, Wiviott SD, et al: Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 292(11): 1307–1316, 2004.
33. Wiviott SD, de Lemos JA, Cannon CP, et al: A tale of two trials: a comparison of the post-acute coronary syndrome lipid-lowering trials A to Z and PROVE IT-TIMI 22. *Circulation* 113(11):1406–1414, 2006.
34. Grundy SM, Cleeman JI, Merz CN, et al: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 110(2):227–239, 2004.
35. LaRosa JC, Grundy SM, Waters DD, et al: Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 352(14):1425–1435, 2005.
36. Pedersen TR, Faergeman O, Kastelein JJ, et al: High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 294(19):2437–2445, 2005.
37. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group: Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet* 376(9753):1658–1669, 2010.
38. Cannon CP, Steinberg BA, Murphy SA, et al: Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol* 48(3):438–445, 2006.
39. Scirica BM, Morrow DA, Cannon CP, et al: Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the PROVE IT-TIMI 22 study. *J Am Coll Cardiol* 47(11):2326–2331, 2006.
40. Murphy SA, Cannon CP, Wiviott SD, et al: Effect of intensive lipid-lowering therapy on mortality after acute coronary syndrome (a Patient-Level Analysis of the Aggrastat to Zocor and Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22 Trials). *Am J Cardiol* 100(7):1047–1051, 2007.
41. Murphy SA, Cannon CP, Wiviott SD, et al: Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy compared with moderate lipid-lowering statin therapy after acute coronary syndromes. *J Am Coll Cardiol* 54(25):2358–2362, 2009.
42. Cholesterol Treatment Trialists' Collaboration: Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 376(9753):1670–1681, 2010.
43. Ray KK, Cannon CP: The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes. *J Am Coll Cardiol* 46(8): 1425–1433, 2005.
44. Ray KK, Cannon CP, McCabe CH, et al: Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 Trial. *J Am Coll Cardiol* 46(8):1405–1410, 2005.
45. Ray KK, Cannon CP, McCabe CH, et al: Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol* 46(8):1405–1410, 2005.
46. Hulten E, Jackson JL, Douglas K, et al: The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. *Arch Intern Med* 166(17):1814–1821, 2006.
47. Ballantyne CM: Clinical trial endpoints: angiograms, events, and plaque instability. *Am J Cardiol* 82(6):5M–11M, 1998.
48. Nissen SE: Effect of intensive lipid lowering on progression of coronary atherosclerosis: evidence for an early benefit from the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial. *Am J Cardiol* 96(5A):61F–68F, 2005.
49. Nissen SE, Nicholls SJ, Sipahi I, et al: Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 295(13):1556–1565, 2006.
50. Nicholls SJ, Ballantyne CM, Barter PJ, et al: Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med* 365(22):2078–2087, 2011.
51. Nicholls SJ, Hsu A, Wolski K, et al: Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. *J Am Coll Cardiol* 55(21):2399–2407, 2010.
52. Wiviott SD, Cannon CP, Morrow DA, et al: Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy: a PROVE IT-TIMI 22 substudy. *J Am Coll Cardiol* 46(8):1411–1416, 2005.
53. Ridker PM, Danielson E, Fonseca FA, et al: Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 359(21):2195–2207, 2008.
54. Morrow DA, de Lemos JA, Sabatine MS, et al: Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor Trial. *Circulation* 114(4):281–288, 2006.
55. Gotto AM, Whitney E, Stein EA, et al: Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Circulation* 101(5):477–484, 2000.

56. Simes RJ, Marschner IC, Hunt D, et al: Relationship between lipid levels and clinical outcomes in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial: to what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels? *Circulation* 105(10):1162–1169, 2002.
57. Kastelein JJ, van der Steeg WA, Holme I, et al: Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. *Circulation* 117(23):3002–3009, 2008.
58. Tsimikas S, Brilakis ES, Miller ER, et al: Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. *N Engl J Med* 353(1):46–57, 2005.
59. Tsimikas S, Witztum JL, Miller ER, et al: High-dose atorvastatin reduces total plasma levels of oxidized phospholipids and immune complexes present on apolipoprotein B-100 in patients with acute coronary syndromes in the MIRACL trial. *Circulation* 110(11):1406–1412, 2004.
60. Tsimikas S, Duff GW, Berger PB, et al: Pro-inflammatory interleukin-1 genotypes potentiate the risk of coronary artery disease and cardiovascular events mediated by oxidized phospholipids and lipoprotein(a). *J Am Coll Cardiol* 63(17):1724–1734, 2014.
61. Ray KK: Interleukin-1 revisited. *J Am Coll Cardiol* 63(17):1735–1738, 2014.
61a. Ridker PM, Thuren T, Zalewski A, et al: Interleukin-1β inhibition and the prevention of recurrent cardiovascular events: rationale and design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). *Am Heart J* 162(4):597–605, 2011.
62. The STABILITY Investigators: Darapladib for preventing ischemic events in stable coronary heart disease. *N Engl J Med* 370(18):1702–1711, 2014.
62a. AIM-HIGH Investigators, Boden WE, Probstfield JL, et al: Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 365(24):2255–2267, 2011.
62b. HPS2-THRIVE Collaborative Group, Landray MJ, Haynes R, et al: Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* 371(3):203–212, 2014.
63. Nissen SE, Tsunoda T, Tuzcu EM, et al: Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA* 290(17):2292–2300, 2003.
64. Effects of rHDL on Atherosclerosis–Safety and Efficacy (ERASE) Investigators: Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. *JAMA* 297(15):1675–1682, 2007.
65. Tardif JC: Emerging high-density lipoprotein infusion therapies: fulfilling the promise of epidemiology? *J Clin Lipidol* 4(5):399–404, 2010.
66. Nicholls SJ, Gordon A, Johansson J, et al: Efficacy and safety of a novel oral inducer of apolipoprotein a-I synthesis in statin-treated patients with stable coronary artery disease a randomized controlled trial. *J Am Coll Cardiol* 57(9):1111–1119, 2011.
67. Nicholls SJ, Chapman MJ: ASSURE: Effect of an Oral Agent Inducing Apo A-I Synthesis on Progression of Coronary Atherosclerosis: Results of the ASSURE Study, 2013 Sep 2. Available from: <http://www.escardio.org/congresses/esc-2013/congress-reports/Pages/708-ASSURE.aspx#presenter>.
68. Tardif JC, Ballantyne CM, Barter P, et al: Effects of the high-density lipoprotein mimetic agent CER-001 on coronary atherosclerosis in patients with acute coronary syndromes: a randomized trial. *Eur Heart J* 35(46):3277–3286, 2014.
69. Barter PJ, Caulfield M, Eriksson M, et al: Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 357(21):2109–2122, 2007.
70. Nicholls SJ, Tuzcu EM, Brennan DM, et al: Cholesteryl ester transfer protein inhibition, high-density lipoprotein raising, and progression of coronary atherosclerosis: insights from ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation). *Circulation* 118(24):2506–2514, 2008.
71. Vergeer M, Bots ML, van Leuven SI, et al: Cholesteryl ester transfer protein inhibitor torcetrapib and off-target toxicity: a pooled analysis of the rating atherosclerotic disease change by imaging with a new CETP inhibitor (RADIANCE) trials. *Circulation* 118(24):2515–2522, 2008.
72. Krishna R, Anderson MS, Bergman AJ, et al: Effect of the cholesteryl ester transfer protein inhibitor, anacetrapib, on lipoproteins in patients with dyslipidaemia and on 24-h ambulatory blood pressure in healthy individuals: two double-blind, randomised placebo-controlled phase I studies. *Lancet* 370(9603):1907–1914, 2007.
73. Bloomfield D, Carlson GL, Sapre A, et al: Efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib as monotherapy and coadministered with atorvastatin in dyslipidemic patients. *Am Heart J* 157(2):352–360, e2, 2009.
74. Cannon CP, Shah S, Dansky HM, et al: Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med* 363(25):2406–2415, 2010.
75. Gotto AM, Cannon CP, Li XS, et al: Evaluation of lipids, drug concentration, and safety parameters following cessation of treatment with the cholesteryl ester transfer protein inhibitor anacetrapib in patients with or at high risk for coronary heart disease. *Am J Cardiol* 113(1):76–83, 2014.
76. Lüscher TF, Taddei S, Kaski J-C, et al: Vascular effects and safety of dalcetrapib in patients with or at risk of coronary heart disease: the dal-VESSEL randomized clinical trial. *Eur Heart J* 33(7):857–865, 2012.
77. Fayad ZA, Mani V, Woodward M, et al: Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. *Lancet* 378(9802):1547–1559, 2011.
78. Schwartz GG, Olsson AG, Abt M, et al: Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 367(22):2089–2099, 2012.
79. Ray KK, Ditmarsch M, Kallend D: The effect of cholesteryl ester transfer protein inhibition on lipids, lipoproteins, and markers of HDL function after an acute coronary syndrome: the dal-ACUTE randomized trial. *Eur Heart* 35(27):1792–1800, 2014.
80. Khera AV, Cuchel M, la Llera-Moya de M, et al: Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med* 364(2):127–135, 2011.
81. Nicholls SJ, Brewer HB, Kastelein JJ, et al: Effects of the CETP inhibitor evacetrapib administered as monotherapy or in combination with statins on HDL and LDL cholesterol: a randomized controlled trial. *JAMA* 306(19):2099–2109, 2011.
82. Teramoto T, Takeuchi M, Morisaki Y, et al: Efficacy, safety, tolerability, and pharmacokinetic profile of evacetrapib administered as monotherapy or in combination with atorvastatin in Japanese patients with dyslipidemia. *Am J Cardiol* 113(12):2021–2029, 2014.
83. Birjmohun R, Hutten B, Kastelein J, Stroes E: Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 45(2):185–197, 2005.
84. Taylor AJ, Sullenberger LE, Lee HJ, et al: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: A double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation* 110(23):3512–3517, 2004.
85. Villines TC, Stanek EJ, Devine PJ, et al: The ARBITER 6-HALTS Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis): final results and the impact of medication adherence, dose, and treatment duration. *J Am Coll Cardiol* 55(24):2721–2726, 2010.
86. Lee JM, Robson MD, Yu LM, et al: Effects of high-dose modified-release nicotinic acid on atherosclerosis and vascular function: a randomized, placebo-controlled, magnetic resonance imaging study. *J Am Coll Cardiol* 54(19):1787–1794, 2009.
87. AIM-HIGH Investigators: Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 365(24):2255–2267, 2011.
88. HPS2-THRIVE Collaborative Group: HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J* 34(17):1279–1291, 2013.
89. Keech A, Simes RJ, Barter P, et al: Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 366(9500):1849–1861, 2005.
90. ACCORD Study Group: Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 362(17):1563–1574, 2010.
91. Jun M, Foote C, Lv J, et al: Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet* 375(9729):1875–1884, 2010.
92. Colhoun HM, Betteridge DJ, Durrington PN, et al: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 364(9435):685–696, 2004.
93. Baigent C, Landray MJ, Reith C, et al: The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomized placebo-controlled trial. *Lancet* 377(9784):2181–2192, 2011.
94. Davidson MH, Donovan JM, Misir S, Jones MR: A 50-week extension study on the safety and efficacy of colesevelam in adults with primary hypercholesterolemia. *Am J Cardiovasc Drugs* 10(5):305–314, 2010.
95. Dormandy JA, Charbonnel B, Eckland DJ, et al: Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 366(9493):1279–1289, 2005.
96. Saremi A, Schwenke DC, Buchanan TA, et al: Pioglitazone slows progression of atherosclerosis in prediabetes independent of changes in cardiovascular risk factors. *Arterioscler Thromb Vasc Biol* 33(2):393–399, 2013.
97. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE: Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus. *JAMA* 298(10):1180, 2007.
98. Nissen SE, Nicholls SJ, Wolski K, et al: Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes. *JAMA* 299(13):1561, 2008.
99. Nissen SE, Wolski K: Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med* 170(14):1191–1201, 2010.
100. Samaha FF, McKenney J, Bloedon LT, et al: Inhibition of microsomal triglyceride transfer protein alone or with ezetimibe in patients with moderate hypercholesterolemia. *Nat Clin Pract Cardiovasc Med* 5(8):497–505, 2008.
101. Cohen JC, Boerwinkle E, Mosley TH, Jr, Hobbs HH: Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 354(12):1264–1272, 2006.
102. Benn M, Nordestgaard BG, Grande P, et al: PCSK9 R46L, low-density lipoprotein cholesterol levels, and risk of ischemic heart disease. *J Am Coll Cardiol* 55(25):2833–2842, 2010.
103. Koren MJ, Giugliano RP, Raal FJ, et al: Efficacy and safety of longer-term administration of evolocumab (AMG 145) in patients with hypercholesterolemia: 52-week results from the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) randomized trial. *Circulation* 129(2):234–243, 2014.
104. Raal F, Scott R, Somaratne R, et al: Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. *Circulation* 126(20):2408–2417, 2012.
105. Dias CS, Shaywitz AJ, Wasserman SM, et al: Effects of AMG 145 on low-density lipoprotein cholesterol levels: results from 2 randomized, double-blind, placebo-controlled, ascending-dose phase 1 studies in healthy volunteers and hypercholesterolemic subjects on statins. *J Am Coll Cardiol* 60(19):1888–1898, 2012.
106. Stein EA, Honarpour N, Wasserman SM, et al: Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia. *Circulation* 128(19):2113–2120, 2013.
107. Robinson JG, Nedergaard BS, Rogers WJ, et al: Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA* 311(18):1870–1882, 2014.
108. Desai NR, Kohli P, Giugliano RP, et al: AMG145, a monoclonal antibody against proprotein convertase subtilisin kexin type 9, significantly reduces lipoprotein(a) in hypercholesterolemic patients receiving statin therapy: an analysis from the LDL-C Assessment with Proprotein Convertase Subtilisin Kexin Type 9 Monoclonal Antibody Inhibition Combined with Statin Therapy (LAPLACE)-Thrombolysis in Myocardial Infarction (TIMI) 57 trial. *Circulation* 128(9):962–969, 2013.
109. Roth EM, McKenney JM, Hanotin C, et al: Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. *N Engl J Med* 367(20):1891–1900, 2012.
110. Kastelein JJ, Robinson JG, Farnier M, et al: Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia not adequately controlled with current lipid-lowering therapy: design and rationale of the ODYSSEY FH studies. *Cardiovasc Drugs Ther* 28(3):281–289, 2014.
111. Colhoun HM, Robinson JG, Farnier M, et al: Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials. *BMC Cardiovasc Disord* 14:121, 2014.
112. Robinson JG, Colhoun HM, Bays HE, et al: Efficacy and safety of alirocumab as add-on therapy in high-cardiovascular-risk patients with hypercholesterolemia not adequately controlled with atorvastatin (20 or 40 mg) or rosuvastatin (10 or 20 mg): design and rationale of the ODYSSEY OPTIONS Studies. *Clin Cardiol* 37(10):597–604, 2014.
113. Roth EM, Taskinen MR, Ginsberg HN, et al: Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized Phase 3 trial. *Int J Cardiol* 176(1):55–61, 2014.
114. Moriarty PM, Jacobson TA, Bruckert E, et al: Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. *J Clin Lipidol* 8(6):554–561, 2014.
115. Robinson JG, Farnier M, Krempf M, et al: Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 372(16):1489–1499, 2015.
116. Study to Evaluate the Efficacy and Safety of an Every Four Weeks Treatment Regimen of Alirocumab (REGN727/ SAR236553) in Patients With Primary Hypercholesterolemia (ODYSSEY CHOICE 1). Available from: <https://clinicaltrials.gov/ct2/show/NCT01926782?term=ODYSSEY+CHOICE&rank=2>.
117. Phase III Study To Evaluate Alirocumab in Patients With Hypercholesterolemia Not Treated With a Statin (ODYSSEY CHOICE II). Available from: <https://clinicaltrials.gov/ct2/show/NCT02023879?term=ODYSSEY+CHOICE&rank=1>.
118. Raal F, Scott R, Somaratne R, et al: Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. *Circulation* 126(20):2408–2417, 2012.
119. Trial Assessing Long Term USe of PCSK9 Inhibition in Subjects With Genetic LDL Disorders (TAUSSIG). Available from: <https://clinicaltrials.gov/ct2/show/NCT01624142?term=TAUSSIG&rank=3>.

120. Effect of CER-001 on Plaque Volume in Homozygous Familial Hypercholesterolemia (HoFH) Subjects (MODE). Available from: <https://clinicaltrials.gov/ct2/show/NCT01412034?term=TESLA+%28HoFH%29&rank=1>.
121. Robinson JG, Nedergaard BS, Rogers WJ, et al: Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA* 311(18): 1870–1882, 2014.
122. Koren MJ, Lundqvist P, Bolognese M, et al: Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. *J Am Coll Cardiol* 63(23):2531–2540, 2014.
123. Stroes E, Colquhoun D, Sullivan D, et al: Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol* 63(23):2541–2548, 2014.
124. Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-3. Available from: <https://clinicaltrials.gov/ct2/show/NCT01984424?term=Goal+Achievement+After+Utilizing+an+Anti-PCSK9&rank=2>.
125. Blom DJ, Hala T, Bolognese M, et al: A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med* 370(19):1809–1819, 2014.
126. Open Label Study of Long Term Evaluation Against LDL-C Trial (OSLER). Available from: <https://clinicaltrials.gov/ct2/show/NCT01439880?term=osler&rank=3>.
127. A 52 Week Study To Assess The Use Of Bococizumab (PF-04950615; RN316) In Subjects With Heterozygous Familial Hypercholesterolemia (SPIRE-FH). Available from: <https://clinicaltrials.gov/ct2/show/NCT01968980?term=SPIRE-HF&rank=1>.
128. Randomized Clinical Trial Of Bococizumab (PF-04950615; RN316) In Subjects With Hyperlipidemia Or Mixed Dyslipidemia At Risk Of Cardiovascular Events (SPIRE-HR). Available from: <https://clinicaltrials.gov/ct2/show/NCT01968954?term=SPIRE-HR&rank=1>.
129. Randomized Clinical Trial of Bococizumab (PF-04950615; RN316) in Subjects With Hyperlipidemia or Mixed Dyslipidemia at Risk of Cardiovascular Events (SPIRE-LDL). Available from: <https://clinicaltrials.gov/ct2/show/NCT01968967?term=SPIRE-LDL&rank=1>.
130. Randomized Clinical Trial of Bococizumab (PF-04950615; RN316) in Subjects With Primary Hyperlipidemia or Mixed Dyslipidemia At Risk Of Cardiovascular Events (SPIRE-LL). Available from: <https://clinicaltrials.gov/ct2/show/NCT02100514?term=SPIRE-LL&rank=1>.
131. Seidah NG, Awan Z, Chrétien M, Mbikay M: PCSK9: a key modulator of cardiovascular health. *Circ Res* 114(6):1022–1036, 2014.
132. Stein EA, Dufour R, Gagne C, et al: Apolipoprotein B synthesis inhibition with mipomersen in heterozygous familial hypercholesterolemia: results of a randomized, double-blind, placebo-controlled trial to assess efficacy and safety as add-on therapy in patients with coronary artery disease. *Circulation* 126(19):2283–2292, 2012.
133. Raal FJ, Santos RD, Blom DJ, et al: Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomized, double-blind, placebo-controlled trial. *Lancet* 375(9719):998–1006, 2010.
134. Akdim F, Tribble DL, Flaim JD, et al: Efficacy of apolipoprotein B synthesis inhibition in subjects with mild-to-moderate hyperlipidaemia. *Eur Heart J* 32(21):2650–2659, 2011.
135. Thomas GS, Cromwell WC, Ali S, et al: Mipomersen, an apolipoprotein B synthesis inhibitor, reduces atherogenic lipoproteins in patients with severe hypercholesterolemia at high cardiovascular risk: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 62(23):2178–2184, 2013.
136. Ladenson PW, Kristensen JD, Ridgway EC, et al: Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. *N Engl J Med* 362(10):906–916, 2010.
137. Angelin B, Kristensen JD, Eriksson M, et al: Reductions in serum levels of LDL cholesterol, apolipoprotein B, triglycerides and lipoprotein(a) in hypercholesterolaemic patients treated with the liver-selective thyroid hormone receptor agonist eprotirome. *J Intern Med* 277:331–342, 2015.
138. Sjouke B, Langslet G, Ceska R, et al: Eprotirome in patients with familial hypercholesterolaemia (the AKKA trial): a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Diabetes Endocrinol* 2(6):455–463, 2014.

Thrombolytic Intervention

13

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KEY POINTS

- Thrombolytic therapy remains the preferred reperfusion strategy in patients with ST-elevation myocardial infarction (STEMI) who present within 12 hours of symptom onset when timely primary percutaneous coronary intervention (PCI) is not available and no contraindications to thrombolysis are present.
- Adjunctive antiplatelet and antithrombotic therapies are critical to the maintenance of epicardial vessel patency and to the reduction of downstream microvascular obstruction in patients treated with thrombolytics, and they offer proven survival benefits.
- The routine use of thrombolytics as adjunctive therapy in primary PCI is not supported by clinical evidence and should generally be avoided.
- Early routine coronary angiography and PCI following primary thrombolytic therapy for STEMI should be performed in all high-risk patients, and it should be considered in all patients following successful thrombolysis.
- Despite the growing availability of primary PCI, thrombolytic therapy will be the most common and important reperfusion strategy for STEMI given the growing burden of cardiovascular disease worldwide, particularly in developing nations.

Atherosclerotic plaque rupture with subsequent thrombus formation through an intricate series of interactions among the coronary artery endothelium, exposed subendothelium, circulating platelets, and coagulation factors that lead to occlusion of an epicardial coronary artery are the pathophysiologic underpinnings of STEMI. The "open artery" hypothesis postulates that early reperfusion of the occluded artery translates into myocardial salvage and ultimately improved survival, and this is the basis of reperfusion therapy. The evidence for the benefit of thrombolytic therapy as a reperfusion strategy in STEMI is indisputable. Pivotal placebo-controlled randomized trials of patients with STEMI from the 1980s, beginning with the *Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico* (GISSI) study and the Second International Study of Infarct Survival (ISIS-2), proved the value of early thrombolysis by reducing mortality by approximately 30% (Table 13-1).[1] These studies catalyzed the acceptance of thrombolysis as standard therapy for reperfusion in patients with acute myocardial infarction (AMI) and ushered in the *thrombolytic era*, a term that characterizes the revolution in attitude among the medical community toward this disease. Although primary PCI has superseded thrombolysis as the preferred reperfusion strategy in most instances, the recently updated American College of Cardiology Foundation/American Heart Association (ACCF/AHA) STEMI guidelines continue to favor thrombolytic therapy over primary PCI as the primary reperfusion strategy in patients who (1) present within 12 hours of symptom onset, (2) have no invasive option (i.e., a catheterization laboratory is unavailable, vascular access issues are present) or face a delay of more than 120 minutes from first medical contact to primary PCI, (3) are not in cardiogenic shock, and (4) have no contraindications to thrombolytic therapy (Table 13-2).[2] However, because of concerns about bleeding complications, incomplete patency, and early reocclusion rates with thrombolytic therapy—combined with the fact that more primary PCIs are safely and successfully being performed at smaller hospitals without on-site cardiac surgery back-up—thrombolytic therapy has been surpassed by primary PCI as the treatment modality for STEMI associated with better clinical outcomes (Fig. 13-1).[3-6] Whereas PCI has evolved into the preferred reperfusion strategy, particularly at high-volume experienced centers, it is not universally available. Despite a 44% relative increase in the number of PCI-capable hospitals in the United States from 2001 to 2006, only 79.9% of the U.S. population lived within a 60-minute drive of a PCI-capable hospital in 2006.[7] Moreover, data from the National Registry of Myocardial Infarction (NRMI-3/4) suggest that door-to-balloon times remain poor, with a median time of 180 minutes for patients transferred from one hospital to another for primary PCI, even within the framework of the current STEMI guidelines; this indicates that a substantial number of patients still experience an inordinate delay in mechanical reperfusion therapy in current practice.[8] This was further evidenced by a cohort study of 68,439 patients who presented to PCI-capable hospitals with STEMI between 1999 and 2002, which suggested that most STEMI patients received reperfusion therapy (68.7% PCI and 54.2% fibrinolysis) during off hours (weekdays 5 PM to 7 AM and weekends) and that these patients experienced significant delays in PCI but not in thrombolytic therapy.[9] Moreover, De Luca and colleagues[10] showed that every 30 minutes of delay in primary PCI results in a 7.5% increase in 1-year mortality. Therefore thrombolytic therapy remains an important tool in the therapeutic armamentarium for treating STEMI, albeit with significant limitations. This chapter reviews the historic basis of thrombolytic intervention, summarizes current thrombolytic agents and adjunctive therapies, and highlights the evidence for its current role in reperfusion therapy for STEMI, laying the groundwork for future progress in this field.

THROMBOLYTIC AGENTS

Thrombolytic therapy was born in 1933, when Tillett and Garner[11] described the fibrinolytic activity of β-hemolytic streptococci, which led to the first therapeutic attempt by Tillett and Sherry[12] in 1948 to dissolve a fibrinous pleural effusion. Over 20 years later, in 1971, the results of the first randomized controlled trial demonstrating the benefit of thrombolytic therapy using streptokinase in AMI were published.[13] In 1981, Rentrop and colleagues[14] showed that intracoronary streptokinase was effective in the lysis of coronary thrombi with the use of coronary angiography, and Markis and coworkers[15] demonstrated myocardial salvage with the same therapy, thus providing proof of the validity of the concept. Shortly thereafter, human tissue plasminogen activator (tPA) was isolated from a melanoma cell line[16] and was demonstrated to be effective in reducing mortality in AMI.[17] Current thrombolytic therapy comprises a class of agents known as *plasminogen activators*, which directly or indirectly convert the proenzyme plasminogen into plasmin. Plasmin is a nonspecific serine protease that catalyzes the degradation of fibrin, fibrinogen, prothrombin, and factors V and VII, thus disrupting the coagulation cascade and thrombus generation.[18] Plasminogen activators include the fibrin-specific agents such as *alteplase* (tissue-type plasminogen activator [t-PA]), *single-chain urokinase plasminogen activator* (scu-PA), *tenecteplase* (TNK), and *staphylokinase* (SAK)—which enzymatically convert plasminogen into plasmin—as well as the non–fibrin-specific agents such as *streptokinase*, *anistreplase* (anisoylated plasminogen

TABLE 13-1 Summary of Initial Randomized Clinical Trials for Thrombolytic Therapy in ST-Elevation Myocardial Infarction

Trial (*N*)	No. of Sites	Agent	Dose/Duration	Enrollment Dates	Placebo/Blinding	Age Criteria (y)	Symptom Duration (hr)
GISSI-1 (11,806)	176	SK	1.5 MU/1 hr	2/84–6/85	No	All	<12
ISIS-2 (17,187)	417	SK	1.5 MU/1 hr	3/85–12/87	Yes	All	<24
AIMS (1258)	39	APSAC	30 U/5 min	9/85–10/87	Yes	<75	<6
ASSET (5011)	52	tPA	100 mg/3 hr	11/86–2/88	Yes	<75	<6

Modified from Table 2 in Kiernan TJ, Gersh BJ: Thrombolysis in acute myocardial infarction: current status. *Med Clin North Am* 91(4):617-637, 2007.
AIMS, Anistreplase Intervention Mortality Study; *APSAC,* anisoylated plasminogen streptokinase activator complex; *ASSET,* Anglo-Scandinavian Study of Early Thrombolysis; *GISSI-1,* Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; *ISIS-2,* Second International Study of Infarct Survival; *MU,* million units; *SK,* streptokinase; *tPA,* tissue plasminogen activator.

TABLE 13-2 Contraindications to Thrombolytic Therapy in Patients With ST-Elevation Myocardial Infarction*

ABSOLUTE CONTRAINDICATIONS

1. Any prior intracerebral hemorrhage
2. Known structural cerebral vascular lesion (e.g., arteriovenous malformation)
3. Known malignant intracranial neoplasm (primary or metastatic)
4. Ischemic stroke within 3 months, except acute ischemic stroke within 4.5 hours
5. Suspected aortic dissection
6. Active bleeding or bleeding diathesis (excluding menses)
7. Significant closed-head or facial trauma within 3 months
8. Intracranial or intraspinal surgery within 2 months
9. Severe uncontrolled hypertension (unresponsive to emergency therapy)
10. For streptokinase, prior treatment within the previous 6 months

RELATIVE CONTRAINDICATIONS

1. History of chronic, severe, poorly controlled hypertension
2. Systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg on presentation
3. History of ischemic stroke more than 3 months prior
4. Dementia
5. Known intracranial pathology other than those in absolute contraindications
6. Traumatic or prolonged (>10 min) cardiopulmonary resuscitation
7. Major surgery within the prior 3 weeks
8. Internal bleeding within the prior 2 to 4 weeks
9. Noncompressible vascular punctures
10. Pregnancy
11. Active peptic ulcer
12. Oral anticoagulant therapy

From Table 6 in O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 61(40):e78-e140, 2013.
*This table should be used only for assistance in clinical decision making and may not be all inclusive.

streptokinase activator complex [APSAC]), and *urokinase*. *Reteplase* (recombinant plasminogen activator [r-PA]) and *lanoteplase* (novel plasminogen activator [n-PA]) have intermediate fibrin specificity. Currently, four thrombolytic agents are approved for use by the U.S. Food and Drug Administration (FDA) and are used most commonly worldwide: *streptokinase*, *alteplase*, *reteplase*, and *tenecteplase*. The last three agents were developed via recombinant deoxyribonucleic acid (DNA) technology to improve fibrin specificity and to increase the duration of activity to enable bolus dosing.[18] The major thrombolytic agents are briefly reviewed with regard to mechanism of action and thrombolytic profile (Table 13-3). Several novel fibrin-specific agents, *monteplase* (MT-PA), *palmiteplase* (YM866), and *amediplase* (K[2] tu-PA)—as well as a novel thrombin-activated plasminogen analogue, BB-10153, which would theoretically be activated only at the site of a developing thrombus—were evaluated in preclinical studies and small-scale human trials, but the efficacy of these agents has yet to be evaluated in larger phase III studies.

MAJOR HISTORICAL COMPARATIVE THROMBOLYTIC TRIALS

The GISSI-2/International trial with 20,891 patients with STEMI within 6 hours of symptom onset randomly assigned to either alteplase or streptokinase demonstrated no difference in mortality between streptokinase and alteplase with or without subcutaneous heparin (intravenous [IV] heparin was rarely used in this trial) but showed a higher rate of ischemic stroke in the alteplase group.[19] The ISIS-3 trial with 41,299 patients randomized to alteplase, streptokinase, or anistreplase demonstrated equivalence in mortality reduction among the three agents but found that streptokinase was associated with the lowest overall rates of stroke (1.1%) and intracerebral hemorrhage (0.3%).[20] IV heparin was not used in this trial; however, it has been borne out collectively through other studies of the fibrin-specific plasminogen activators that adjunctive heparin, although not critical to achieve thrombolysis, is important to sustain infarct vessel patency through the avoidance of recurrent thrombosis. The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries I (GUSTO-I) trial with 41,021 patients promulgated the benefit of "accelerated" alteplase plus IV heparin in STEMI, leading to a 15% relative and 1% absolute reduction in mortality (or 1 life saved per 100 patients treated).[21] This study included an angiographic component, which led to the major finding that early and complete infarct vessel patency was tightly linked to a reduction in mortality.[22] The Reteplase (r-PA) Angiographic Phase I International Dose-Finding Study (RAPID-I) suggested a nonsignificant 30-day mortality benefit with reteplase compared with alteplase (1.9% vs. 3.9%), and the RAPID-II trial showed a significant improvement in coronary artery patency defined as thrombolysis in myocardial infarction (TIMI) grade 2 flow within 90 minutes that favored reteplase over alteplase (85.2% vs. 77.2%, $P = .03$).[23,24] The GUSTO-III trial involved 15,021 patients but failed to show true equivalence of reteplase to "accelerated" alteplase, although it demonstrated a trend toward equivalence, especially for death and disabling stroke. These findings, combined with the more convenient double-bolus administration, rendered reteplase a viable option for thrombolysis.[25] The Assessment of the Safety and Efficacy of a New Thrombolytic 2 (ASSENT-2) trial of 16,949 patients randomized to receive either tenecteplase or alteplase found similar mortality rates, but the highly fibrin-specific tenecteplase was notable for significantly less bleeding compared with alteplase.[26] Although this result was tempered by a relatively high rate of intracerebral hemorrhage in both groups, lower rates of overall bleeding (26.1% vs. 28.4%, $P < .0003$) and blood transfusions (4.3% vs. 5.5%, $P = .0002$) were observed with tenecteplase compared with alteplase. Currently, thrombolytic agent selection at most hospitals in the United States is guided by hospital formulary and drug availability given the lack of any striking differences in the efficacy or safety of the approved thrombolytics.

TIMING OF THROMBOLYTIC THERAPY

Early Treatment

The degree of myocardial salvage following AMI is clearly related to timely reperfusion, reinforcing the "time is myocardium" principle

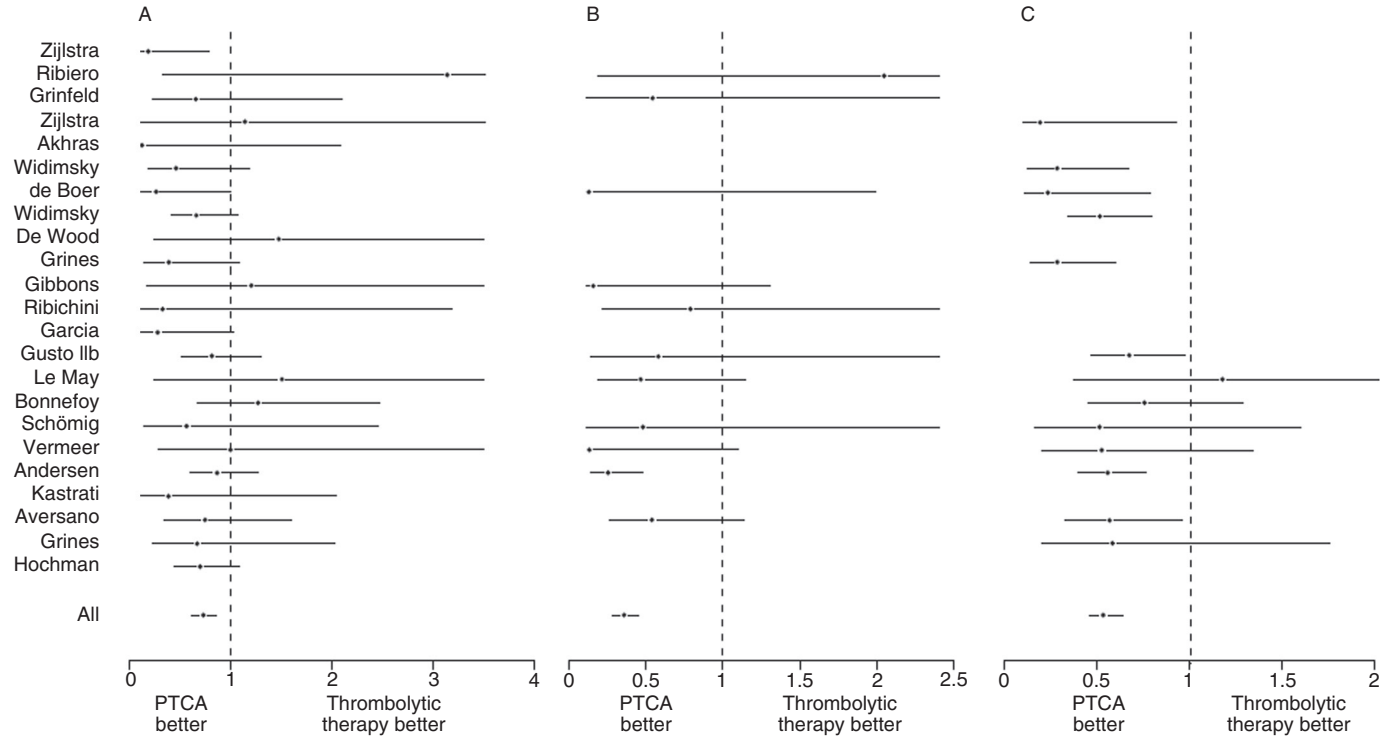


FIGURE 13-1 Odds ratios (95% confidence interval) of short-term death (**A**), nonfatal reinfarction (**B**), and combined death, nonfatal reinfarction, and stroke (**C**) for patients treated with percutaneous coronary intervention (also known as percutaneous transluminal coronary angioplasty [PTCA]) versus thrombolytic therapy for ST-elevation myocardial infarction. (From Keeley EC, Boura JA, Grines CL: Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 361[9351]:13-20, 2003.)

TABLE 13-3 Characteristics of Thrombolytic Agents

	Streptokinase	Tenecteplase	Alteplase	Reteplase
Source	Group C streptococci	Recombinant, human	Recombinant, human	Recombinant, human mutant tPA
Molecular weight (kDa)	47	57*	63 to 70	39
Fibrin specificity	No	Yes	Yes	Yes
Metabolism	Hepatic	Hepatic	Hepatic	Renal
Half-life (min)	18 to 23	20 to 24	3 to 4	14
Mode of action	Activator complex	Direct	Direct	Direct
Antigenicity	Yes	No	No	No
Estimated hospital cost per dose (USD)†	$300/1.5 MU	$2200	$2200/100 mg	$2200/20 MU

Modified from Granger CB, Califf RM, Topol EJ: Thrombolytic therapy for acute myocardial infarction. A review. *Drugs* 44(3):293-325, 1992.
*Turcasso NM, Nappi JM: Tenecteplase for treatment of acute myocardial infarction. *Ann Pharmacother* 35(10):1233-1240, 2001.
†Costs list U.S. prices of usual dose.
MU, Million units; *tPA,* tissue plasminogen activator; USD, United States dollars.

with the 2- to 3-hour time point representing the critical window to minimize morbidity and mortality from this disease process (Fig. 13-2).[27,28] A meta-analysis of six randomized controlled trials of prehospital and in-hospital thrombolysis for AMI that included 6434 patients showed reduced time to thrombolysis (104 vs. 162 min, $P = .007$) and reduced all-cause hospital mortality (odds ratio [OR], 0.83; 95% confidence interval [CI] 0.70 to 0.98) with prehospital fibrinolysis.[29] Subsequent randomized trials have reproduced these findings in populations in the United States and in Europe and have demonstrated the feasibility of safe and effective prehospital fibrinolysis administered by paramedics.[30-32] Current ACCF/AHA guidelines for STEMI management recognize the potential benefit of prehospital fibrinolysis by appropriately trained personnel,[2] but logistical challenges that include implementation of systems for rapid prehospital diagnosis and training of personnel in the appropriate administration of thrombolytic agents and adjunctive therapies have limited the widespread acceptance and adoption of prehospital fibrinolysis.[33,34] Therefore the 2013 update to the ACCF/AHA guidelines for STEMI management endorses the need for further research regarding the implementation of prehospital thrombolysis but stops short of recommending its use.[2]

There appears to be an early and sustained difference in favor of primary PCI versus thrombolysis as a function of time to reperfusion. A pooled analysis of 22 randomized clinical trials that included 6763 patients with STEMI who presented within 12 hours of symptom onset showed a 37% reduction in 30-day mortality (adjusted OR 0.63; 95% CI, 0.42 to 0.84) in patients randomized to primary PCI compared with

those randomized to thrombolysis regardless of presentation delay up to 12 hours or a PCI-related delay up to 2 hours (Fig. 13-3).[5] Furthermore, the absolute mortality reduction in the PCI group increased from 1.3% in those who presented within an hour after symptom onset to 4.2% for those who presented 6 to 12 hours after symptom onset. Primary PCI is also superior to both prehospital and in-hospital thrombolysis with regard to 30-day mortality, 1-year mortality, reinfarction, and myocardial salvage.[35,36] In addition, long-term follow up of the Swedish Early Decision Reperfusion Strategy (SWEDES) trial showed that the benefit of primary PCI over fibrinolysis with respect to cardiac death or recurrent AMI persisted out to 5 years (hazard ratio [HR] 0.40; 95% CI, 0.19 to 0.82).[37] Even if transfer to another facility is required, the benefit of PCI over thrombolysis with regard to the combined reduction in death, reinfarction, and disabling stroke at 30 days (driven primarily by reinfarction) is sustained in those patients with STEMI who present within 12 hours of symptom onset.[3,38] Furthermore, in the referral hospital substudy of the Danish Trial in Acute Myocardial Infarction 2 (DANAMI-2), patients with STEMI transferred to a PCI-capable hospital for primary PCI within 120 minutes had improvements in reinfarction (13% vs. 18.5%, HR 0.66; 95% CI, 0.49 to 0.89) and mortality (26.7% vs. 33.3%, HR 0.78; 95% CI, 0.63 to 0.97) out to 8 years of follow-up.[39] However, the net benefit of primary PCI over thrombolysis may be neutralized if the door-to-balloon (DTB) time for PCI is 60 minutes longer than door-to-needle (DTN) time for thrombolysis, given that every 30-minute delay in the interval from symptom onset to balloon inflation is associated with a 7.5% increased risk of death at 1 year.[10] Hence the 2013 ACCF/AHA STEMI guidelines recommend that in-hospital thrombolytic therapy should be administered to those patients who present to a non–PCI-capable hospital within 12 hours of symptom onset *if* transfer for primary PCI (the preferred reperfusion strategy) cannot be completed in a timely fashion—that is, time from arrival at the non–PCI-capable hospital to leaving for the PCI-capable hospital (door-in-door-out [DIDO] time) of 30 minutes or less or anticipated first medical contact to device time of 120 minutes of less—and there is no evidence of severe heart failure or cardiogenic shock (Fig. 13-4).[2]

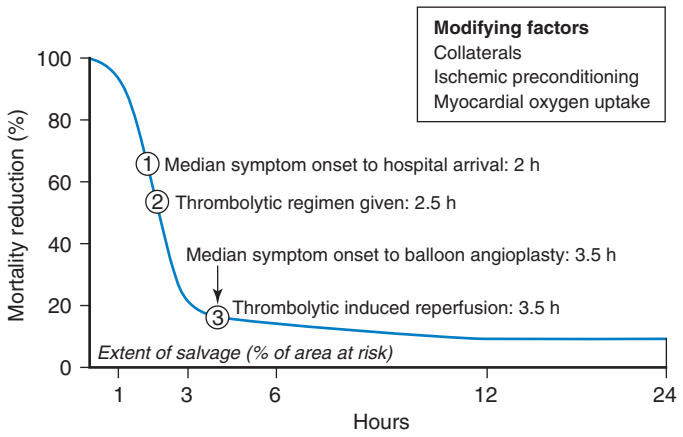


FIGURE 13-2 Mortality reduction as a function of time with reperfusion therapy and the potential for myocardial salvage. This illustrates that unless patients present very early in the course of an ST-elevation myocardial infarction, thrombolysis before percutaneous coronary intervention would have little benefit. (Adapted from Stone GW, Gersh BJ: Facilitated angioplasty: paradise lost. *Lancet* 367[9510]:543-546, 2006.)

In 30% to 40% of patients who fail thrombolysis (<70% ST-segment resolution at 90 min or ongoing chest pain), rescue PCI should be performed, given the benefit of this strategy (Fig. 13-5).[40-42] Accumulating evidence also supports the benefit of performing routine cardiac catheterization and PCI within 24 hours or earlier regardless of the success of thrombolysis (Fig. 13-6).[43-46] This pharmacoinvasive approach is discussed in more detail later in this chapter; the facilitated PCI approach, with early administration of a thrombolytic agent in anticipation of mechanical revascularization, is also discussed later in this chapter and also in Chapter 20, Percutaneous Coronary Intervention in Acute ST-Segment Elevation Myocardial Infarction.

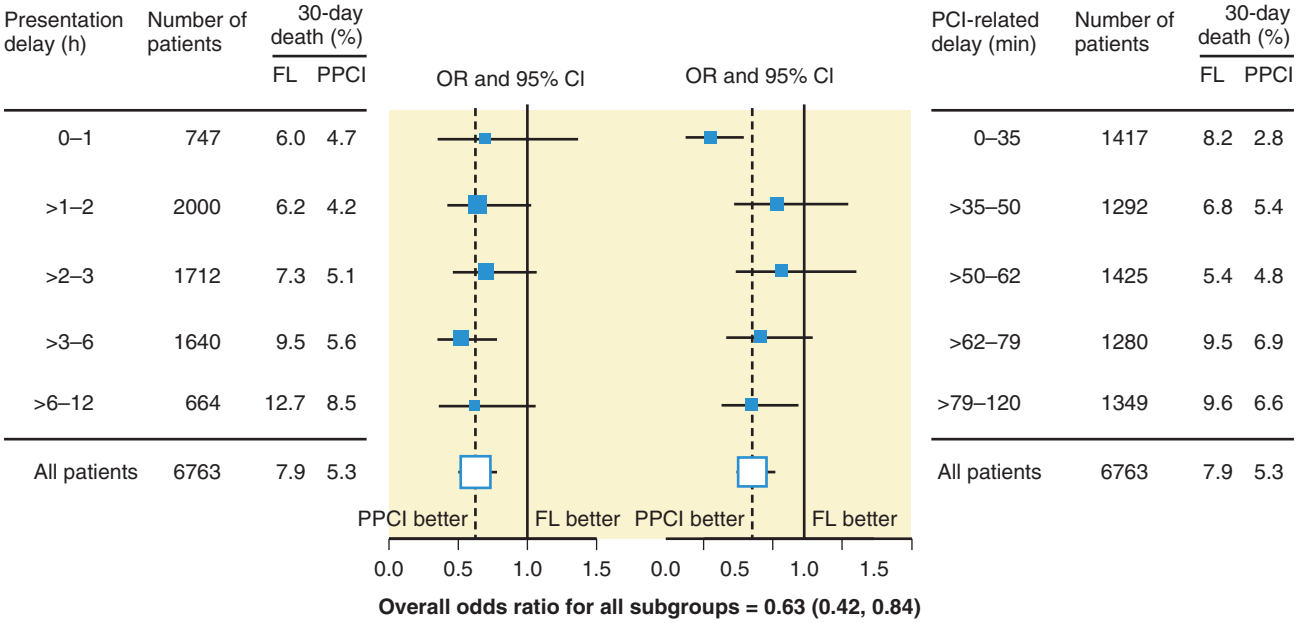


FIGURE 13-3 Odds ratios (ORs) for 30-day death in a pooled analysis of 22 randomized trials of primary percutaneous coronary intervention (PPCI) compared with fibrinolysis (FL) according to presentation delay (*left panel*) and PCI-related delay (*right panel*). CI, Confidence interval. (From the Primary Coronary Angioplasty vs. Thrombolysis Group: Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J* 27[7]:779-788, 2006.)

Late Treatment

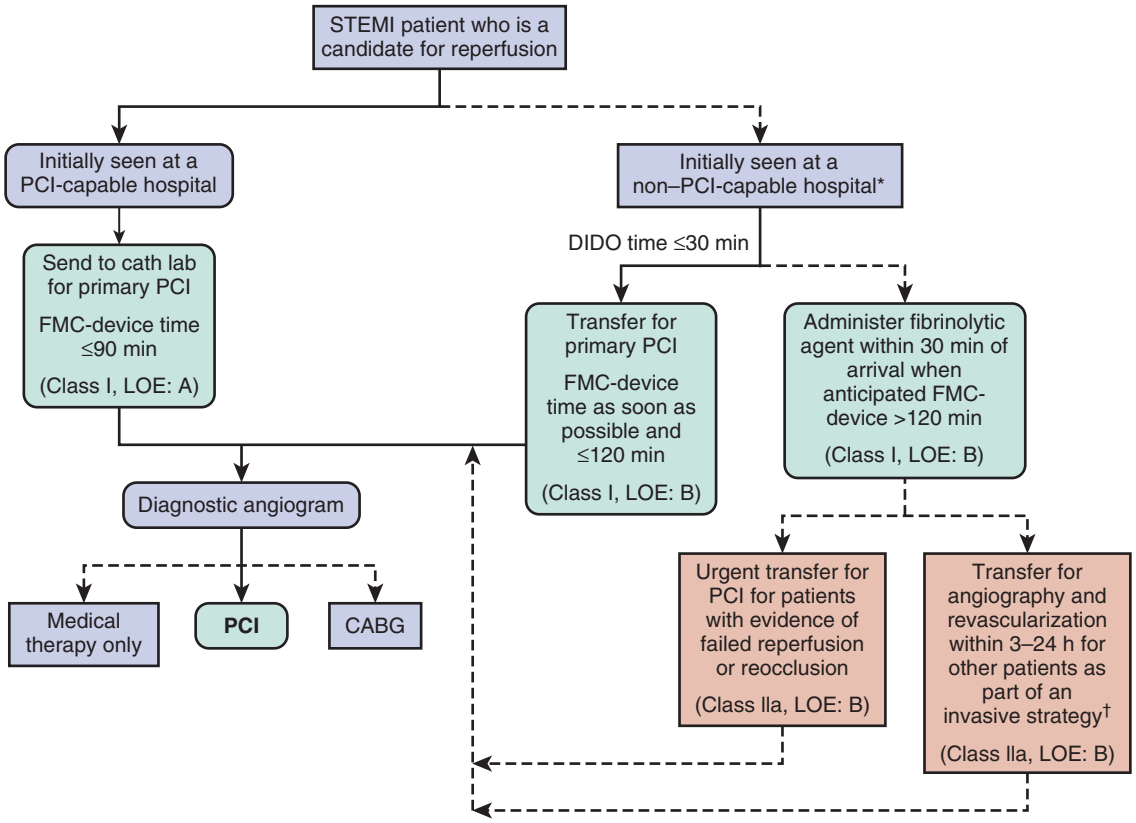
Large mega-trials have suggested that most of the benefit of thrombolytic therapy is largely confined to the first 12 hours following symptom onset and that many of the complications, such as serious bleeding and latent myocardial rupture, occur with late thrombolysis. Two specific trials, the *Estudio Multicentrico Estreptoquinasa Republica Americas Sud* (EMERAS [South American Multicenter Streptokinase Study])[47] and the Late Assessment of Thrombolytic Efficacy (LATE) trial,[48] addressed the issue of late thrombolysis and showed no demonstrable survival benefit beyond the 12-hour mark with streptokinase or alteplase, respectively, with excessive serious bleeding complications in the latter trial. The Fibrinolytic Therapy Trialists' Collaboration performed a pooled analysis of 52,892 patients enrolled into eight placebo-controlled trials (excluding LATE) and showed significant benefit up to but not beyond 12 hours from symptom onset.[49] The available data provide cogent evidence that there is a "golden" first hour and a "dim" twelfth hour after symptom onset, which illustrates the narrow therapeutic window for thrombolytic therapy (Fig. 13-7). Health care systems should develop and implement plans to minimize the delays in patient triage and facilitate timely initiation of reperfusion therapy.

ADJUNCTIVE THERAPIES

One of the remaining challenges of contemporary reperfusion therapy is to achieve tissue-level perfusion rather than simply restoring the patency of the infarct-related epicardial coronary artery. Microcirculatory reperfusion after thrombolysis is critical, and strategies to reduce platelet aggregation, maintain endothelial integrity, and prevent the downstream effects of an embolized thrombus and atherosclerotic debris through the use of potent anticoagulant, antithrombotic, and antiplatelet agents have led to several important clinical trials. To that end, adjunctive therapies aimed at improving epicardial and microcirculatory patency while preserving myocardial function are discussed below.

Aspirin

The standard adjuvant pharmacotherapy for all patients with AMI undergoing thrombolysis should include a loading dose of 162 to 325 mg of aspirin in the absence of a documented allergy.[2,20,50,51] The benefit of aspirin therapy in ISIS-2 resulted in 25 lives saved per 1000 patients treated, as well as 10 prevented nonfatal reinfarctions and 3 strokes prevented per 1000 patients treated.[52] These findings appeared



*Patients with cardiogenic shock or severe heart failure initially seen at a non-PCI-capable hospital should be transferred for cardiac catheterization and revascularization as soon as possible irrespective of time delay from MI onset (class I, level of evidence B).
†Angiography and revascularization should not be performed within the first 2 to 3 hours after administration of fibrinolytic therapy.

FIGURE 13-4 Reperfusion therapy for patients with ST-elevation myocardial infarction (STEMI). The bold arrows and boxes are the preferred strategies. Performance of percutaneous coronary intervention (PCI) is dictated by an anatomically appropriate culprit stenosis. *CABG,* Coronary artery bypass graft; *DIDO,* door-in-door-out; *FMC,* first medical contact; *LOE,* level of evidence. (From O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 61[4]:e78-e140, 2013.)

to be durable at 10 years of follow-up, making the duration of aspirin therapy in this setting indefinite.[53] Furthermore, in the CURRENT-OASIS 7 trial,[54] a maintenance dose of 81 mg/day was noninferior to 300 to 325 mg/day with regard to a composite of cardiovascular (CV) death, MI, or stroke at 30 days in patients with acute coronary syndromes (ACSs) undergoing early PCI. On the basis of this study and others, the 2013 ACCF/AHA STEMI guidelines give a class IIa recommendation to an aspirin maintenance dose of 81 mg/day instead of higher doses.[2]

Thienopyridines

A loading dose of 300 mg of clopidogrel (75 mg in patients ≥75 years of age) at or before the time of thrombolysis followed by 75 mg daily for a minimum of 1 year is standard adjuvant therapy (along with aspirin) in STEMI patients treated with thrombolytics, and it probably works by maintaining infarct artery patency after thrombolysis.[2] In the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)[55] of 45,852 patients, clopidogrel was shown to significantly reduce death (7.5% vs. 8.1%, $P = .03$; Fig. 13-8) and the combined end point of death, reinfarction, and stroke (9.2% vs. 10.1%, $P = .002$) when given to aspirin-treated patients before thrombolytic therapy for STEMI (Fig. 13-9). The Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)–TIMI 28 trial[56] also supported the benefit of clopidogrel pretreatment before thrombolysis in patients aged 75 years or younger with STEMI and demonstrated reduced rates of death and recurrent MI or ischemia at 30 days (Figs. 13-10 and 13-11) and significant improvement in coronary blood flow at 48 hours with no excess bleeding with clopidogrel. Furthermore, in the subset of patients undergoing PCI within 2 to 8 days after thrombolysis, pretreatment with clopidogrel (300 mg loading dose followed by 75 mg daily thereafter) at the time of thrombolysis compared with placebo significantly reduced the combined end point of CV death, MI, and stroke through 30 days (7.5% vs. 12%, $P = .001$) with no significant increase in bleeding.[57] The Harmonizing Outcomes With Revascularization and Stents in Acute

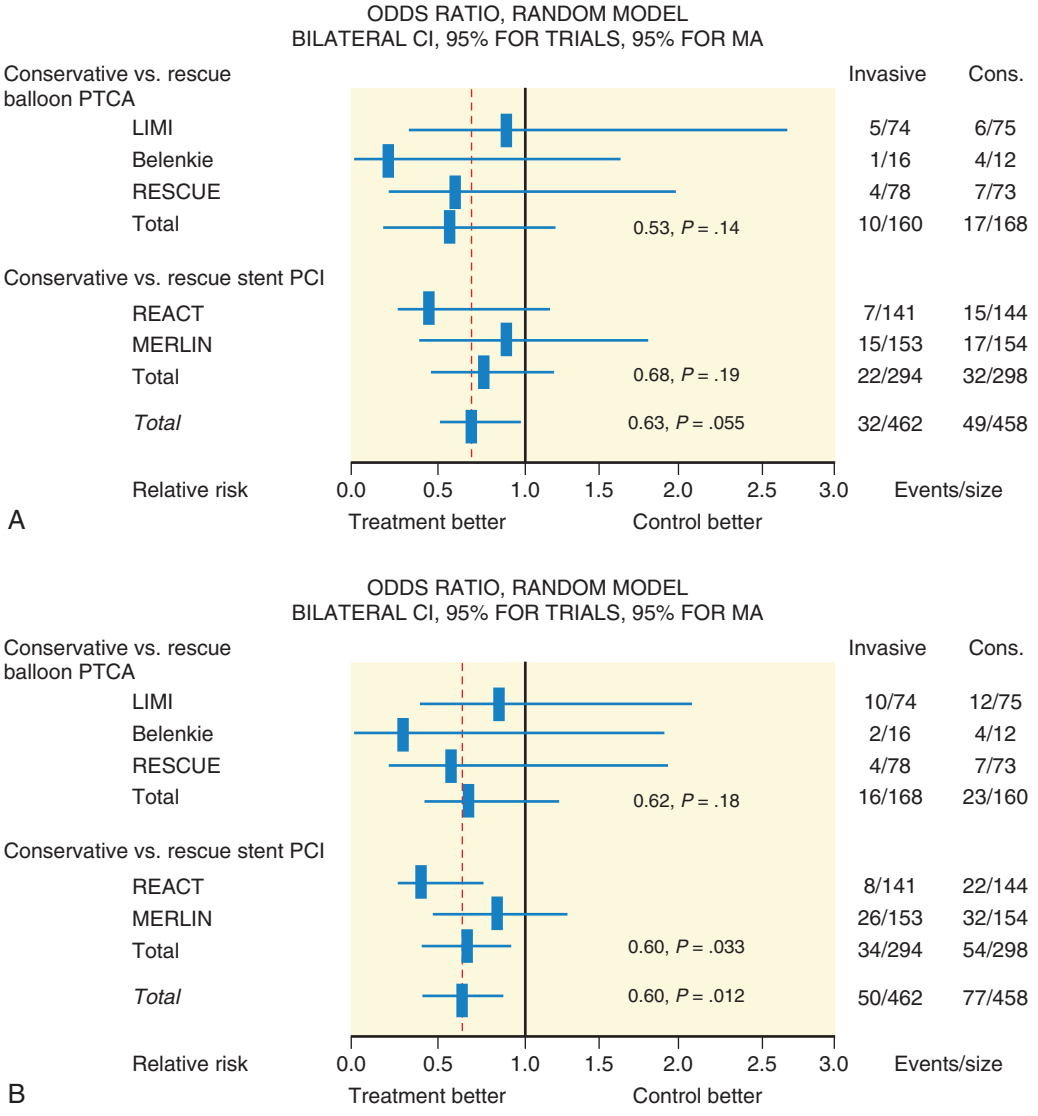


FIGURE 13-5 Odds ratios for death (**A**) and death or reinfarction (**B**) with rescue percutaneous coronary intervention (PCI) versus conservative (Cons.) management of ST-elevation myocardial infarction at 30 days. *CI,* Confidence interval; *LIMI,* Limburg Myocardial Infarction Trial; *MA,* meta-analysis; *MERLIN,* Middlesborough Early Revascularization to Limit Infarction; *PTCA,* percutaneous transluminal coronary angioplasty; *REACT,* Rescue Angioplasty Versus Conservative Therapy or Repeat Thrombolysis Trial; *RESCUE,* Randomized Evaluation of Salvage Angioplasty with Combined Utilization of Endpoints. (From Collet JP, Montalescot G, Le May M, et al: Percutaneous coronary intervention after fibrinolysis: a multiple meta-analyses approach according to the type of strategy. *J Am Coll Cardiol* 48[7]:1326-1335, 2006.)

Myocardial Infarction (HORIZONS-AMI)[58] and Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions (CURRENT–OASIS 7)[54] trials have demonstrated the efficacy and safety of a 600-mg loading dose of clopidogrel in the treatment of ACS managed with an invasive reperfusion strategy, but no studies to date have evaluated this dosing strategy in combination with thrombolytic therapy.

Prasugrel, a novel thienopyridine $P2Y_{12}$ receptor antagonist with more potent platelet inhibition and possibly less resistance to platelet inhibition was shown to reduce the rate of CV death, nonfatal MI, and nonfatal stroke at 1 year compared with clopidogrel (9.9% vs. 12.1%, $P < .001$) in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel (TRITON)–TIMI 38 trial,[59] which included 13,608 patients with moderate- to high-risk ACS managed with PCI. Higher rates of bleeding were also observed with prasugrel compared with clopidogrel (2.4% vs. 1.8%, $P = .03$), and no difference in mortality was observed. However, this study suggested a net harm among patients with a history of cerebrovascular disease, those aged 75 years and older, and in patients weighing less than 60 kg. Although the FDA has approved prasugrel for use in the management of ACS with PCI, it remains to be seen whether prasugrel will demonstrate sufficient benefit and safety to be useful as adjunctive therapy with thrombolysis.

Ticagrelor is a novel nonthienopyridine $P2Y_{12}$ receptor antagonist that reversibly inhibits adenosine diphosphate (ADP)–stimulated platelet activation with more rapid and potent activity than clopidogrel in preclinical studies.[60] The Platelet Inhibition and Patient Outcomes (PLATO) study,[61] a randomized controlled trial that included 18,624 patients, showed a benefit of ticagrelor compared with clopidogrel in the management of ACS with PCI, with a reduction in vascular death, MI, and stroke at 12 months (9.8% vs. 11.7%, $P = .001$). There was no difference in overall bleeding, but a higher rate of nonprocedural

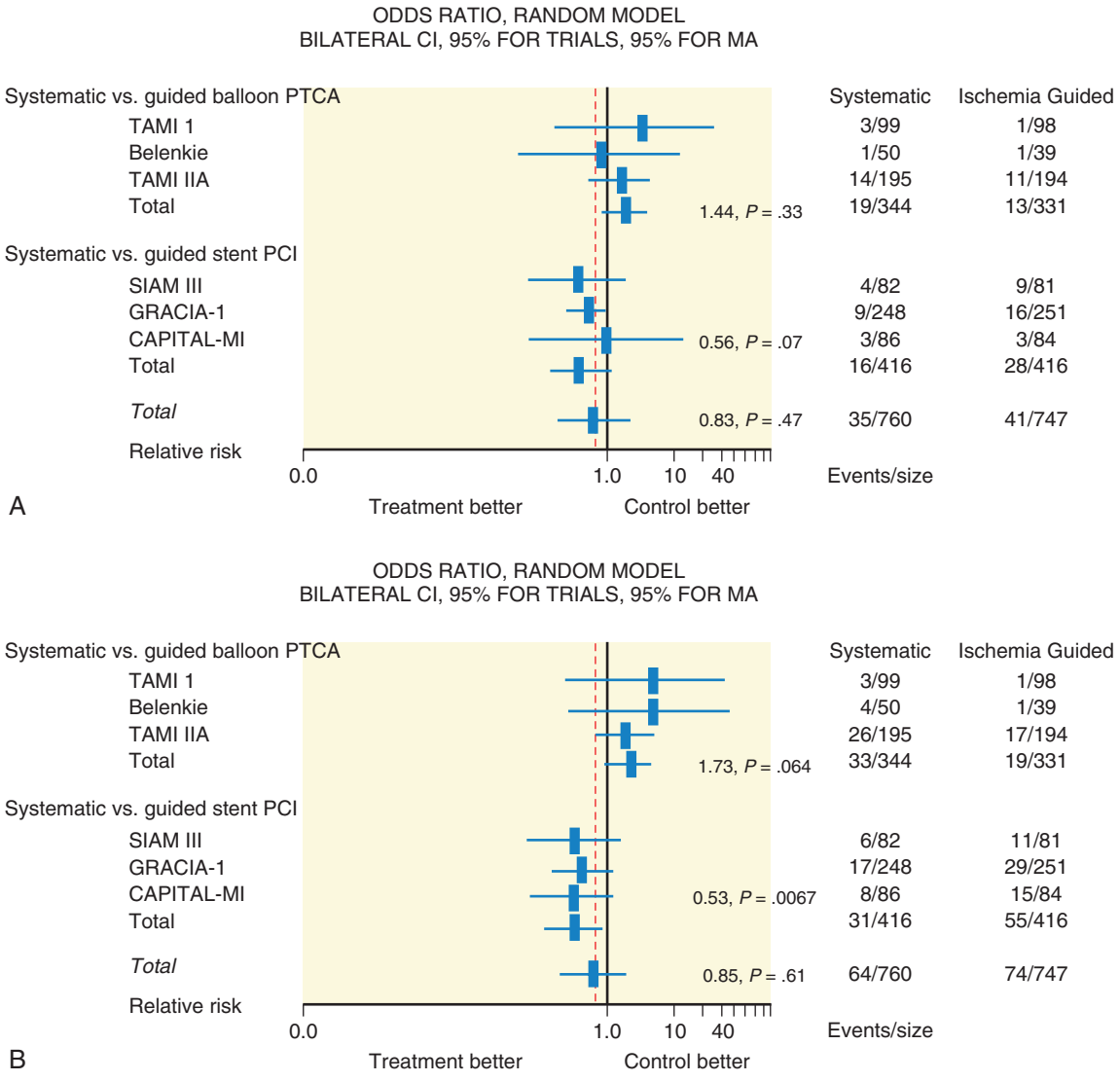


FIGURE 13-6 Odds ratios for death (**A**) and death or reinfarction (**B**) with systematic versus ischemia-guided percutaneous coronary intervention (PCI) after ST-elevation myocardial infarction. *CAPITAL-MI,* Combined Angioplasty and Pharmacologic Intervention Versus Thrombolytics Alone in Acute Myocardial Infarction; *CI,* confidence interval; *Cons.,* conservative; *GRACIA-1,* Randomized Trial Comparing Stenting Within 24 Hours of Thrombolysis Versus Ischemia-Guided Approach to Thrombolyzed Acute Myocardial Infarction With ST-Segment Elevation; *MA,* meta-analysis; *PTCA,* percutaneous transluminal coronary angioplasty; *SIAM,* Comparison of Invasive and Conservative Strategies After Treatment with Streptokinase in Acute Myocardial Infarction; *TAMI,* Thrombolysis and Angioplasty in Myocardial Infarction. (Collet JP, Montalescot G, Le May M, et al: Percutaneous coronary intervention after fibrinolysis: a multiple meta-analyses approach according to the type of strategy. *J Am Coll Cardiol* 48[7]:1326-1335, 2006.)

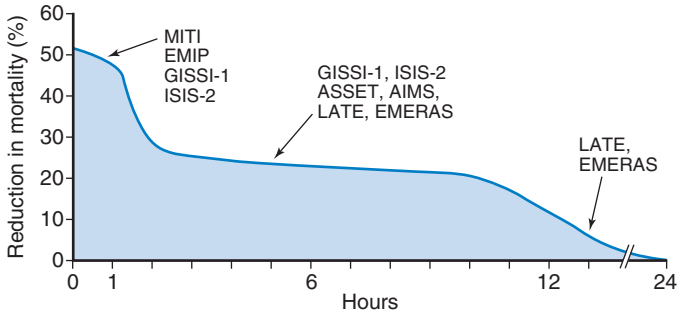
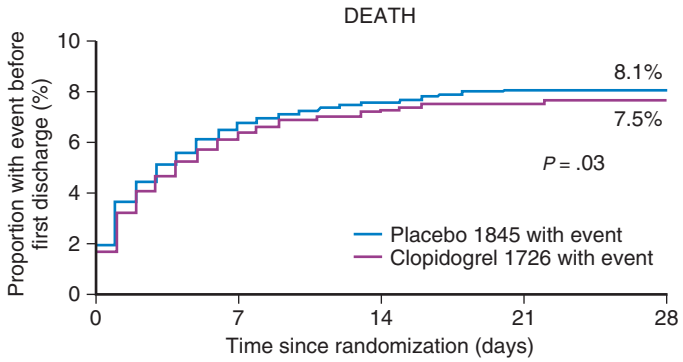


FIGURE 13-7 Percent mortality reduction derived from thrombolytic therapy as a function of time from symptom onset to initiation of therapy with clinical trials noted from which these data are extrapolated. A greater than 50% reduction in mortality is noted during the first "golden hour," after which the mortality benefit declines to a plateau of approximately 25% reduction until 12 hours, after which there is no apparent survival benefit with thrombolytic therapy. *AIMS,* Anistreplase Intervention Mortality Study; *ASSET,* Anglo-Scandinavian Study of Early Thrombolysis; *EMERAS,* Estudio Multicentrico Estreptoquinasa Republicas de America Del Sur; *EMIP,* European Myocardial Infarction Project; *GISSI-1,* Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; *ISIS-2,* Second International Study of Infarct Survival; *LATE,* Late Assessment of Thrombolytic Efficacy; *MITI,* Myocardial Infarction and Triage Intervention Project. (Lincoff AM, Topol EJ: The illusion of reperfusion. Does anyone achieve optimal reperfusion during acute myocardial infarction? *Circulation* 88[3]:1361-1374, 1993.)

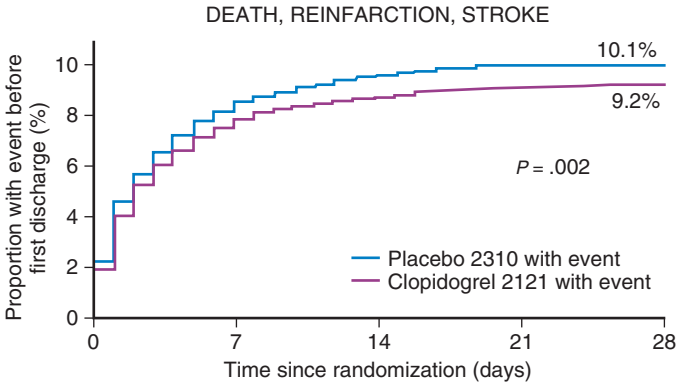


Days	0–6	7–13	14–20	21–28
No. of events:				
Clopidogrel	1403	223	69	31
Placebo	1487	246	89	23

FIGURE 13-8 Death rates from the COMMIT trial with the addition of clopidogrel to aspirin in 45,852 patients with ST-elevation myocardial infarction. (Chen ZM, Jiang LX, Chen YP, et al: Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 366[9497]:1607-1621, 2005.)

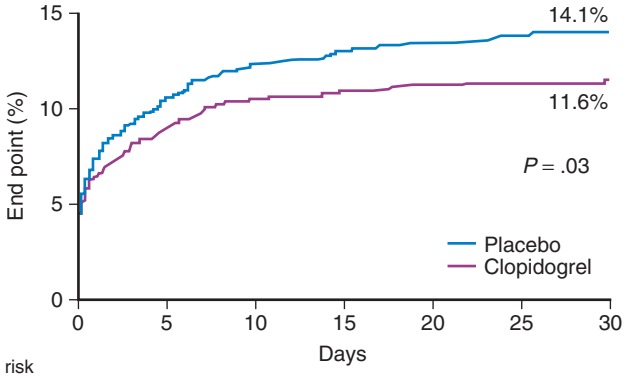
bleeding was observed with ticagrelor (4.5% vs. 3.8%, $P = .03$), which included intracerebral hemorrhage. Ticagrelor is now FDA approved for the treatment of ACS and to prevent stent thrombosis with PCI but has not been evaluated as an adjuvant therapy with thrombolysis.

Adjuvant therapy with the intravenous $P2Y_{12}$ receptor antagonist cangrelor has also been explored. The Safety, Tolerability, and Effect on Patency in Acute Myocardial Infarction (STEP-AMI) angiographic trial[62] of 92 patients with STEMI randomized patients to aspirin and heparin with either cangrelor, full-dose alteplase, or half-dose alteplase with one of three doses of cangrelor. Although stopped early by the sponsor because of a change in the priority of drug development,



Days	0–6	7–13	14–20	21–28
No. of events:				
Clopidogrel	1751	247	91	32
Placebo	1879	301	104	26

FIGURE 13-9 Combined end point of death, reinfarction, and stroke from the COMMIT trial with the addition of clopidogrel to aspirin in 45,852 patients with ST-elevation myocardial infarction. (Chen ZM, Jiang LX, Chen YP, et al: Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 366[9497]:1607-1621, 2005.)



No. at risk				
Placebo	1739	1529	1504	1494
Clopidogrel	1752	1569	1555	1550

FIGURE 13-10 Cumulative incidence of the combined end point of cardiovascular death, recurrent myocardial infarction, or recurrent ischemia leading to the need for urgent revascularization. (Sabatine MS, Cannon CP, Gibson CM, et al: Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 352[12]:1179-1189, 2005.)

cangrelor with half-dose alteplase appeared to result in a similar rate of complete reperfusion compared with full-dose alteplase. Whether cangrelor is more effective and/or safe than oral $P2Y_{12}$ receptor antagonists as an adjuvant to thrombolysis awaits further study.

No meaningful studies have compared ticlopidine with placebo as adjunctive therapy in STEMI patients undergoing thrombolysis. The Ticlopidine Versus Aspirin After Myocardial Infarction (STAMI)[63] trial did address the role of ticlopidine in secondary prevention of CV events in STEMI patients treated with thrombolysis but found no difference compared with aspirin monotherapy.

Heparin

In the absence of heparin-induced thrombocytopenia or known allergy to heparin, unfractionated heparin (UFH), low molecular-weight-heparin (LMWH), or fondaparinux should also be part of the standard

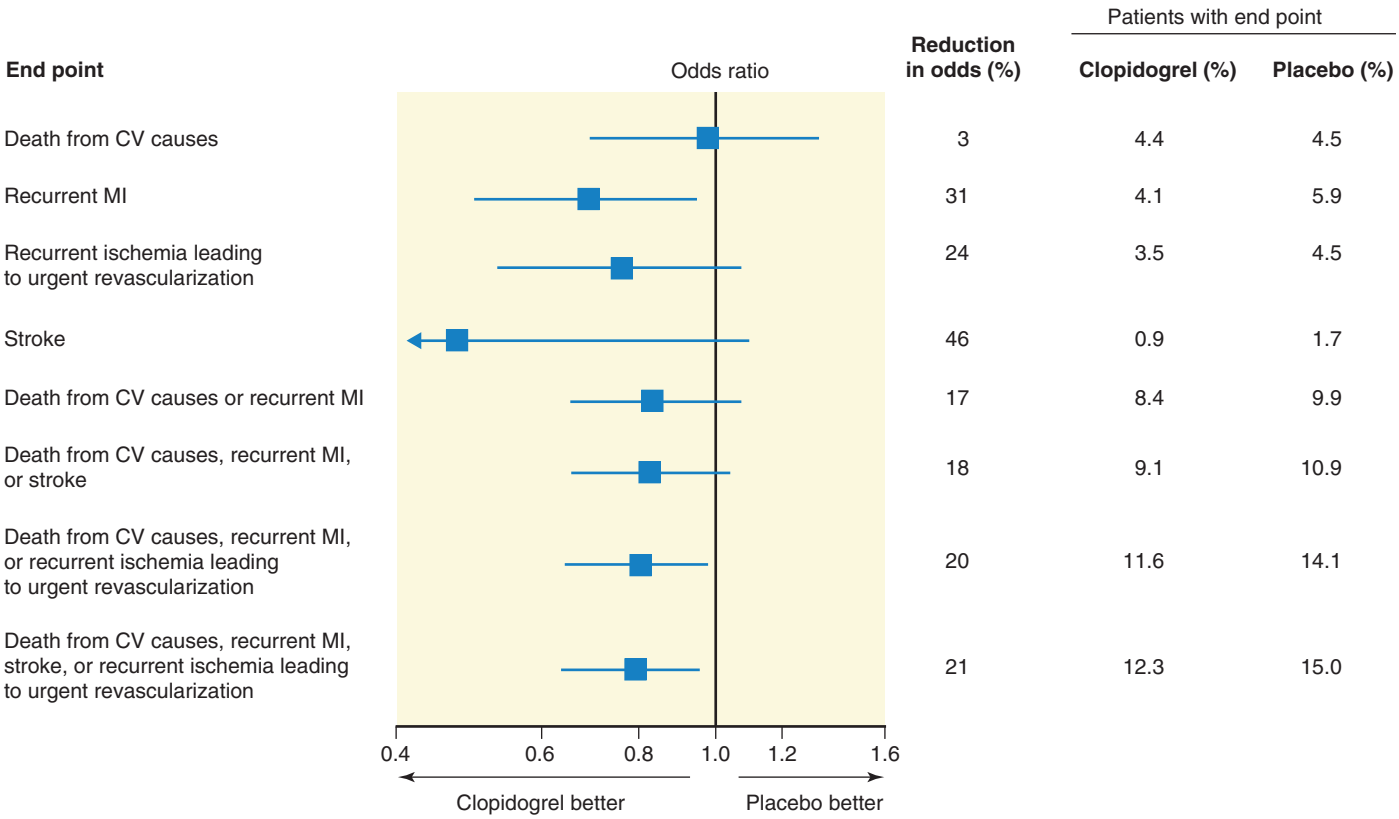


FIGURE 13-11 Odds ratios for individual and composite clinical end points through 30 days from the CLARITY–TIMI 28 trial. *CV,* Cardiovascular; *MI,* myocardial infarction. (Sabatine MS, Cannon CP, Gibson CM, et al: Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 352[12]:1179-1189, 2005.)

adjuvant pharmacotherapy for patients with AMI treated with thrombolysis, given the thrombin-mediated prothrombotic state created. All are given for a minimum of 48 hours and a maximum of 8 days or until revascularization. The ACCF/AHA STEMI guidelines recommend UFH given as a weight-adjusted IV bolus followed by an infusion titrated to keep the activated partial thromboplastin time (aPTT) between 1.5 and 2.0 times control (class I recommendation).[2]

LMWH is an alternative to UFH as adjunctive therapy for thrombolysis and is given as an IV bolus followed 15 minutes later by subcutaneous injection, with the dose adjusted according to age, weight, and renal function.[2] Several clinical trials have shown the noninferiority of LMWH compared with UFH with regard to death and nonfatal reinfarction. The ASSENT-3 trial[64] assessed two different combination strategies: (1) half-dose tenecteplase plus low-dose UFH and abciximab and (2) full-dose tenecteplase plus enoxaparin; the investigators compared these strategies with standard tenecteplase with UFH in 6095 patients. This study demonstrated an impressive reduction in reinfarction in both tenecteplase combination-therapy groups, confirming both the potency of the half-dose thrombolytics–abciximab combination and the efficacy of enoxaparin in this setting. However, this benefit was tempered by an increased rate of bleeding complications that required blood transfusions in both of the combination-therapy groups compared with the tenecteplase-plus-heparin group. Also disconcerting was the relatively high rate of intracerebral hemorrhage in all three groups of the study (0.8% to 0.9%), particularly in older adults. The trial did provide encouraging data for the use of tenecteplase plus enoxaparin, rather than heparin, to reduce the short-term outcome of reinfarction, even though long-term follow-up at 1 year showed no difference among the treatment groups in terms of mortality.[65]

The Enoxaparin as Adjunctive Antithrombin Therapy for ST-Elevation Myocardial Infarction (ENTIRE)–TIMI 23 trial[66] evaluated ST-segment resolution at 180 minutes and early angiographic patency in 483 patients with AMI using (1) full-dose tenecteplase plus either UFH or enoxaparin or (2) half-dose tenecteplase with abciximab plus either UFH or enoxaparin. This study demonstrated a reduction in death and nonfatal MI at 30 days in the full-dose tenecteplase-plus-enoxaparin group compared with the full-dose tenecteplase plus UFH group (4.4% vs. 15.9%, $P = .005$) without any difference in TIMI major hemorrhage (1.9% vs. 2.4%). Furthermore, no difference was reported in death or nonfatal MI at 30 days in the group who received tenecteplase plus abciximab and enoxaparin compared with those who received tenecteplase plus abciximab and UFH, although bleeding in both combination-therapy groups was higher than in the full-dose tenecteplase groups.

Validating the benefit of enoxaparin in reducing reinfarction, the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (ExTRACT)–TIMI 25 trial[67] compared enoxaparin with UFH in 20,506 patients with STEMI undergoing fibrinolysis and demonstrated a 17% relative risk reduction in the primary end point of death or nonfatal reinfarction at 30 days (9.9% in the enoxaparin group vs. 12.0% in UFH group, $P < .001$). This observed benefit was driven primarily by a reduction in nonfatal reinfarction and was sustained at 1-year follow-up with no significant reduction in mortality.[68] However, this benefit occurred at the cost of a significant increase in major bleeding in those treated with enoxaparin (2.1% in the enoxaparin group vs. 1.4% in the UFH group, $P < .001$). The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation (CREATE)[69] of more than 15,000 patients with STEMI treated with thrombolytic therapy randomized to the adjunctive use of the LMWH reviparin or placebo demonstrated benefit in favor of reviparin in the primary composite end point of death, reinfarction, or stroke at 7 days (9.6% vs. 11%, $P = .005$),

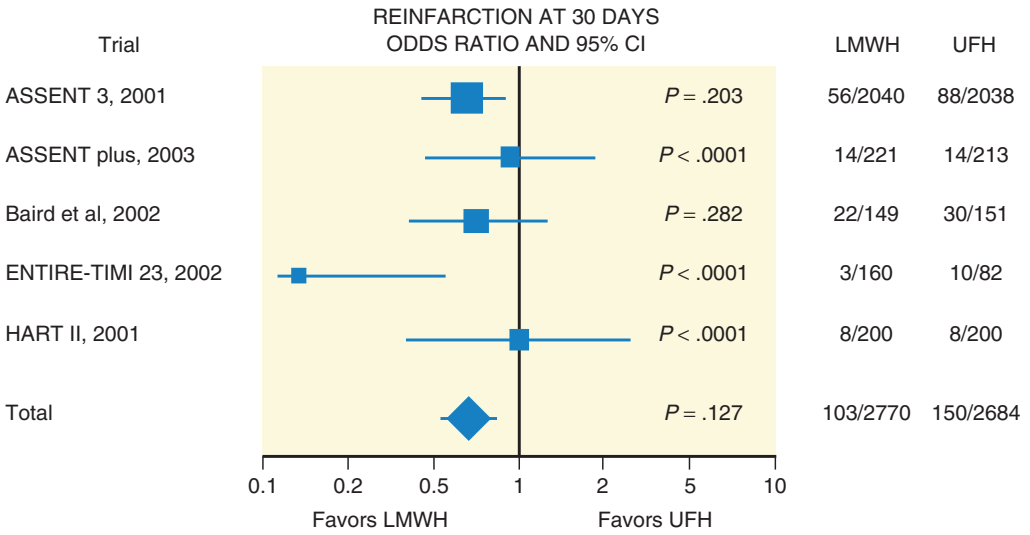


FIGURE 13-12 Rates of reinfarction in patients treated with unfractionated heparin (UFH) versus low-molecular-weight heparin (LMWH) as adjuncts to thrombolysis in ST-elevation myocardial infarction (STEMI). *CI,* Confidence interval. (Eikelboom JW, Quinlan DJ, Mehta SR, et al: Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. *Circulation* 112[25]:3855-3867, 2005.)

although this too was offset by a small but significant increase in severe bleeding.

In their meta-analysis of randomized trials of LMWH versus UFH with thrombolytic therapy in STEMI, Eikelboom and colleagues[70,71] suggested a benefit of LMWH in terms of preventing reinfarction at 30 days, although no benefit was appreciated with regard to death (Fig. 13-12). These findings were confirmed by a subsequent meta-analysis by De Luca and Marino[72] of eight randomized trials that showed a reduction in reinfarction at 30 days with LMWH compared with UFH (3.2% vs. 4.8%, OR 0.65; 95% CI, 0.58 to 0.64). However, as highlighted earlier, this must be weighed against the risk of bleeding with caution in approaching older patients (>75 years old) and those with significant renal dysfunction, both of whom are more likely to bleed. Eikelboom and colleagues[70] found no increase in major bleeding with LMWH compared with UFH (3.3% vs. 2.5%, OR 1.30; 95% CI, 0.98 to 1.72), although the increase in minor bleeding was significant (22.8% vs. 19.4%, OR 1.26; 95% CI, 1.12 to 1.43), and De Luca and Marino[72] found a higher risk of major bleeding complications (2.4% vs. 1.8%, OR 1.37; 95% CI, 1.16 to 1.61). Furthermore, increasing evidence underscores the importance of bleeding that adversely affects the prognosis of patients with ACS, as reflected by the directly proportional relationship observed between risk of death and severity of bleeding in these patients.[71] Therefore the decision to use LMWH instead of UFH should be individualized to the patient.

Direct Thrombin Inhibitors

The deficiencies of UFH and LMWH have led to studies of direct thrombin inhibitors such as hirudin and its synthetic peptide congener bivalirudin as adjuncts to thrombolytic therapy. The clot-bound thrombin is quarantined from the inhibition of heparin, where it amplifies its own generation through a positive feedback loop and activates platelets through thromboxane-independent mechanisms, making it an important effector of thrombus formation. Unlike heparin and LMWH, which potentiate the inhibitory effect of antithrombin III on soluble thrombin and can be highly variable from patient to patient (and even within the same patient), direct thrombin inhibitors directly bind and inactivate both soluble and bound thrombin.

A meta-analysis including five trials of thrombolytic therapy in STEMI ($N = 9947$) showed that bivalent direct thrombin inhibitors, including hirudin (lepirudin) and bivalirudin, reduced the rates of recurrent MI but not mortality, with no such benefit observed with univalent agents such as argatroban.[73] Hirudin was tested against UFH in two thrombolytic regimens, including streptokinase and alteplase, in the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) trial[74] with 4000 STEMI patients; hirudin demonstrated a favorable interaction with streptokinase (but not alteplase) in reducing 30-day death or reinfarction. This study illustrated the crucial role of thrombin generation after streptokinase administration and its relationship to outcomes. The largest dedicated trial using a direct thrombin inhibitor was the Hirulog and Early Reperfusion or Occlusion 2 (HERO-2) trial,[75] in which 17,073 patients with STEMI were treated with streptokinase plus either heparin or bivalirudin. This multicenter international trial demonstrated a relatively high overall mortality (10.9% in the streptokinase-plus-heparin group vs. 10.8% in the streptokinase-plus-bivalirudin group). The reasons for this remain unclear but may have been related to the use of streptokinase as the thrombolytic agent, the relatively late entry of patients from the time of symptom onset, and underutilization of reperfusion therapies for reinfarction across multiple study sites.[76] Whereas it did show a significant reduction in reinfarction (1.6% in the streptokinase-plus-bivalirudin group vs. 2.3% in the streptokinase-plus-heparin group, $P = 0.001$), a trend toward increased intracerebral hemorrhage and blood transfusions was noted in the streptokinase-plus-bivalirudin group. According to the 2013 update to the ACCF/AHA STEMI guidelines, bivalirudin is an acceptable alternative to UFH as adjunctive therapy to thrombolysis in patients with heparin-induced thrombocytopenia.[2] Although recent trials have established the safety and efficacy of bivalirudin as adjunctive therapy to PCI in the management of ACS, no studies have evaluated this agent in combination with newer-generation thrombolytic agents in the treatment of STEMI.[77,78]

Glycoprotein IIb/IIIa Inhibitors

The rationale for more potent adjunctive therapies for thrombolysis originated from angiographic studies of thrombolysis monotherapy that showed incomplete clot dissolution. This is thought to occur because of platelet activation in the setting of fibrinolysis, which results in residual platelet-rich thrombus that is resistant to pharmacologic thrombolysis. Hence maximal platelet inhibition remains an important target for adjunctive therapy to thrombolysis in the management of

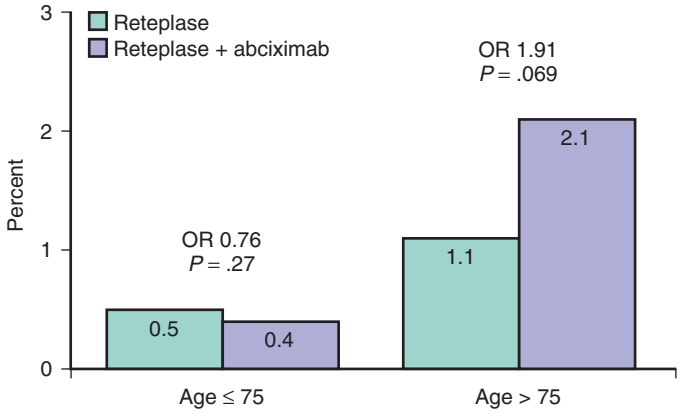


FIGURE 13-13 GUSTO V trial data. Intracranial hemorrhage and treatment by age interaction. OR, odds ratio. (From the GUSTO V Investigators: Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. *Lancet* 357 [9272]:1905-1914, 2001.)

STEMI. The combination of a thrombolytic agent at a half dose with a full-dose glycoprotein (GP) IIb/IIIa inhibitor was attractive in light of a number of studies that indicated better infarct vessel patency, more complete angiographic clot dissolution, and more ST-segment resolution.

Most of the available data for the use of the GP IIb/IIIa inhibitors as adjunctive therapy in STEMI involve abciximab and are demonstrated by the GUSTO V trial,[79] which evaluated the combination of half-dose reteplase plus abciximab compared with full-dose reteplase in 16,588 patients. The primary end point of 30-day mortality was slightly better with combination therapy (5.6% vs. 5.9%, $P = .45$), which fulfilled noninferiority criteria and represented the first combination reperfusion strategy validated as "at least as good as" full-dose thrombolytic therapy. However, an increase in bleeding complications required blood transfusions in 4% of the patients treated with full-dose reteplase and in 5.7% of the combination-treated patients, and most of this bleeding occurred in older patients who also had a significantly increased risk of intracerebral hemorrhage (Fig. 13-13). The main findings of the trial suggested that combination therapy may be useful in younger patients (<75 years old), particularly in those with anterior MI. Disappointingly, long-term data highlighted that there was no difference in 1-year mortality between the two strategies.[80] A meta-analysis by De Luca and colleagues[81] summarized the use of abciximab in this context and showed that as adjunctive therapy for thrombolysis for STEMI, it had no mortality benefit at 30 days or long term compared with primary angioplasty for STEMI. They also showed that although there were similar reductions in reinfarction at 30 days, the bleeding trade-offs with abciximab were significant.

Regarding the small-molecule GP IIb/IIIa inhibitor tirofiban, in the small, randomized dose-finding study Fibrinolytic and Aggrastat for ST-Elevation Resolution (FASTER)–TIMI 24,[82] the combination of tenecteplase plus tirofiban versus tenecteplase alone demonstrated more rapid and complete ST-segment resolution without an increase in major bleeding. The Safety and Efficacy of a Conjunctive Strategy for Reperfusion Enhancement (SASTRE)[83] investigators demonstrated higher rates of TIMI grade 3 flow and TIMI grade 3 myocardial perfusion, which translated to better clinical outcomes and no increased bleeding risk, when tirofiban was used as an adjunct to reperfusion therapy both with half-dose thrombolysis (alteplase) and with primary PCI in 144 patients. The Integrilin and Tenecteplase in Acute Myocardial Infarction (INTEGRITI)[84] trial evaluated tenecteplase with combinations of eptifibatide in STEMI and showed that double-bolus eptifibatide plus half-dose tenecteplase improved arterial patency and ST-segment resolution over tenecteplase monotherapy. However, this was at the expense of increased major bleeding and blood transfusions, which limits this as a useful strategy. Furthermore, the dose-confirmation arm of the Integrilin and Low-Dose Thrombolysis in Acute Myocardial Infarction (INTRO AMI) trial randomized 305 patients with STEMI to half-dose alteplase plus double-bolus eptifibatide with 30 minutes between boluses and low-dose infusion (group I) or half-dose alteplase plus double-bolus eptifibatide with 10 minutes between boluses (group II) and high-dose infusion versus full-dose alteplase (group III).[85] Group II had improved arterial flow with no differences in ST-segment resolution, death, reinfarction, need for revascularization, TIMI major bleeding, or intracranial hemorrhage.

Therefore large-scale trials showing a survival benefit with the adjunctive use of the small molecule GP IIb/IIIa inhibitors with thrombolysis as primary reperfusion therapy are still lacking. Limited data are available with regard to the role of the GP IIb/IIIa inhibitors in rescue PCI following failed full-dose thrombolytic therapy; the excessive bleeding (despite lower heparin doses) seen in the subjects in the GUSTO-III subgroup who underwent rescue angioplasty with abciximab is of particular concern.[86] A small series from the stenting era suggests that short-term clinical outcomes may be improved with this strategy with no significant trade-offs in terms of bleeding complications, although caution is certainly warranted.[87]

Factor Xa Inhibitors

The OASIS-6 trial[88] evaluated the adjunctive use of a selective factor Xa inhibitor, fondaparinux, versus UFH in 12,092 patients with STEMI and found no benefit in those undergoing primary PCI. However, this study did demonstrate a significant reduction in death and reinfarction at 30 days and at 3 to 6 months in those undergoing thrombolysis treated with fondaparinux and found no increase in severe bleeding after 9 days of therapy.[88,89] Unfortunately, an increased frequency of guide catheter thrombosis was observed with fondaparinux. Combined with the OASIS-5 trial in the non-STEMI population, in whom a mortality benefit was seen at 3 and 6 months with less major bleeding with fondaparinux compared with enoxaparin, there appears to be promise for fondaparinux across the spectrum of patients with ACS.[90] The available evidence has garnered a class I recommendation for the use of fondaparinux as adjunctive antithrombotic therapy in thrombolysis-treated patients as an alternative to UFH or LMWH.[2] However, fondaparinux should not be used as the sole anticoagulant for PCI given the increased incidence of guide catheter thrombosis, and it is contraindicated in patients with a creatinine clearance below 30 mL/minute.

FACILITATED PERCUTANEOUS CORONARY INTERVENTION

Considerable attention has been given to the concept of facilitated PCI, which refers to the use of upstream pharmacologic therapy to serve as a "bridge" to primary PCI, given that survival is improved if TIMI grade 3 flow is present before mechanical reperfusion.[91] The use of full-dose thrombolytic therapy before PCI for STEMI was unhelpful and even harmful in the early major trials that combined thrombolytic therapy with immediate angioplasty.[92] This was thought to be largely because of the prothrombotic effect of plasminogen activators and the showering of platelet-rich microthrombi into the microcirculation, leading to poorer outcomes. Notably, these early trials were conducted before the routine use of intensive antiplatelet therapy (including GP IIb/IIIa inhibitors and thienopyridines) and stents, which have improved outcomes with contemporary PCI for STEMI. One of the largest facilitated PCI trials to date, the Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction (ASSENT-4),[93] assessed the role of full-dose tenecteplase with primary PCI. This study was stopped prematurely because of higher in-hospital mortality in the facilitated PCI group compared with the primary PCI group (6% vs. 3%, $P = .01$), with the occurrence of significantly more frequent ischemic complications such as reinfarction and repeat

target-vessel revascularization in the facilitated group. The strategy of using half-dose thrombolytic therapy plus a full-dose GP IIb/IIIa inhibitor before PCI would seem especially attractive, given the benefit of the GP IIb/IIIa inhibitor in those undergoing primary PCI. The prematurely terminated (because of lack of enrollment) trial Addressing the Value of Facilitated Angioplasty After Combination Therapy or Eptifibatide Monotherapy in Acute Myocardial Infarction (ADVANCE MI)[94] tested this strategy by comparing eptifibatide plus half-dose tenecteplase to eptifibatide plus placebo before primary PCI for STEMI. This study suggested that eptifibatide plus half-dose tenecteplase was associated with adverse clinical outcomes and higher bleeding rates despite demonstrating improved pre-PCI coronary flow. The Bavarian Reperfusion Alternatives Evaluation (BRAVE) trial[95] addressed the use of upstream abciximab plus half-dose reteplase versus abciximab monotherapy in 253 patients undergoing PCI for STEMI. This trial found no reduction in infarct size by single-photon emission computed tomography (performed between 5 and 10 days after randomization), with nonsignificant trends toward more adverse cardiac events at 6 months and more major bleeding in the abciximab-plus-reteplase group. The more recent Leipzig Immediate Prehospital Facilitated Angioplasty in ST-Segment Myocardial Infarction (LIPSIA-STEMI)[96] trial failed to show a benefit of facilitated PCI with full-dose tenecteplase pre-treatment versus primary PCI alone with regard to the primary end point of infarct size by magnetic resonance imaging, infarct size by biomarker release, resolution of ST-segment elevation, or clinical end points among 162 patients with long transfer delays to PCI (median overall symptom onset to first balloon inflation times of 158 min in the facilitated PCI group and 131 min in the primary PCI group).

The Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events (FINESSE) trial[97] is the largest study to date to evaluate facilitated PCI using thrombolytic therapy. This double-blind international placebo-controlled trial randomized 2452 patients with STEMI undergoing PCI to half-dose reteplase plus abciximab pretreatment (combination-facilitated PCI), abciximab pretreatment (abciximab-facilitated PCI), or abciximab started at the time of PCI (primary PCI). The combination-facilitated PCI group demonstrated more rapid ST-segment resolution compared with the abciximab-facilitated PCI and primary PCI groups (43.9% vs. 33.1% and 31.0%, $P = .01$ and $P = .003$, respectively). However, at 90 days of follow-up, no differences were observed between the three groups with regard to the primary composite end point of all-cause death, ventricular fibrillation within 48 hours, and new-onset congestive heart failure (9.8%, 10.5%, and 10.7%, respectively, $P = .55$) or mortality (5.2%, 5.5%, and 4.5%, respectively, $P = .49$). Significantly higher rates of all bleeding, intracerebral hemorrhage, and transfusions were observed in the facilitated PCI groups. Specifically, TIMI major or minor bleeding occurred in 14.5% of the combination-facilitated group compared with 10.1% in the abciximab-facilitated group and 6.9% in the primary PCI groups ($P < .001$ for combination-facilitated PCI vs. primary PCI). A 1-year follow-up analysis of the FINESSE trial recapitulated the outcomes observed at 90 days.[98] Notably, a retrospective post hoc analysis of this study suggested a mortality benefit of the combination-facilitated PCI in high-risk patients as defined by a TIMI risk score of 3 or higher who presented to non-PCI hospitals within 4 hours of symptom onset.[99] This suggested a possible role for facilitated PCI in carefully selected patients.

A meta-analysis of 17 trials of 4504 patients with STEMI by Keeley and coworkers[100] and a more recent meta-analysis of six trials that included 2684 patients by De Luca and Marino[101] (including the FINESSE trial) summarized the lack of benefit of the facilitated PCI strategy and demonstrated that despite achieving initial improvements in early metrics of reperfusion, short-term outcomes are not improved, and rates of target-vessel revascularization, reinfarction, stroke, bleeding, and death may be increased with the facilitated approach (Figs. 13-14 and 13-15). In light of these observations, the 2013 ACCF/AHA STEMI guidelines recommend that, because of an increased bleeding risk, very early catheterization (within 2 to 3 hr) with intent to perform revascularization after thrombolytic administration should be limited to rescue PCI; that is, it should be attempted in those patients who fail thrombolysis and have significant myocardial territory in jeopardy.[2] Facilitated PCI is reviewed in more depth in Chapter 20.

PHARMACOINVASIVE STRATEGY

A growing body of evidence supports the role of routine systematic coronary angiography with PCI following primary thrombolytic therapy for STEMI in selected patients. This pharmacoinvasive strategy is distinct from facilitated PCI in that thrombolytics are not administered as adjunctive or facilitative therapy at reduced doses in combination with other adjunctive pharmacologic agents when primary PCI is planned and available in a timely fashion. Instead, thrombolytics are administered as the primary reperfusion strategy when timely primary PCI is not available, and routine early (more than 2 to 3 hr after thrombolytic administration) coronary angiography with provisional PCI is implemented to avoid recurrent ischemia related to incomplete recanalization and propagation of platelet-rich thrombus following fibrinolysis. This strategy is attractive given that many patients with STEMI do not have access to primary PCI within 120 minutes of their first contact with medical care, and it may be important in the management of STEMI patients who may live some distance from PCI-capable centers.

The Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI) trial[44] compared routine coronary angiography and immediate PCI with ischemia-guided coronary angiography following treatment with half-dose reteplase and adjunctive abciximab, UFH, and aspirin in 600 patients with STEMI who presented to non–PCI-capable hospitals with at least one high-risk feature, defined as extensive ST-segment elevation, new-onset left bundle branch block, previous MI, a Killip class greater than 2, or a left ventricular ejection fraction (LVEF) of 35% or less. The mean time from symptom onset to thrombolysis was 165 minutes for both groups. PCI was performed in 85.6% of patients in the immediate PCI group compared with 30.3% in the standard care or rescue PCI group, with median times from thrombolysis to angiography of 125 and 200 minutes, respectively ($P < .0001$). The primary end point of all-cause death, reinfarction, or refractory ischemia at 30 days occurred in 4.4% of the immediate PCI group versus 10.7% of the standard care group, with no difference in bleeding (3.4% vs. 2.3%, $P = .47$) or stroke (0.7% vs. 1.3%, $P = .50$) between the two groups. This observed benefit was driven primarily by reductions in reinfarction and recurrent ischemia, with a trend toward reduced mortality in the immediate PCI group (Fig. 13-16).

The Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) study[102] randomized 1059 patients with STEMI with at least one high-risk feature, who presented to non–PCI-capable hospitals to undergo immediate transfer and PCI within 6 hours of thrombolytic therapy (routine PCI group) or standard treatment with rescue PCI (standard group) following primary reperfusion therapy with full-dose tenecteplase and adjunctive aspirin and UFH or enoxaparin; clopidogrel loading therapy was also encouraged.[43] High-risk features for enrollment into this trial were defined as 2 mm or more of ST-segment elevation or depression in two anterior leads, systolic blood pressure below 100 mm Hg, heart rate greater than 100 beats/min, Killip class 2 to 3, or 1 mm or more ST-segment elevation in right-sided lead V_4 indicative of right ventricular involvement for inferior MIs. The median time from onset of symptoms to thrombolysis was approximately 2 hours in both groups, whereas the median time from tenecteplase administration to angiography was 2.8 hours in the routine PCI group and 32.5 hours in the standard treatment group ($P < .001$). PCI was performed in 84.9% of the routine PCI group versus 67.4% of the standard treatment group, and more patients in the routine PCI group received clopidogrel (90.3% vs. 81.4%, respectively; $P < .001$) and β-blockers (90.1% vs. 85.4%, respectively; $P = .02$). The primary end point—a composite of death, reinfarction, recurrent ischemia, new or worsening heart failure, or cardiogenic shock at 30 days—occurred in 11.0% of the routine early PCI group and in 17.2% of the standard

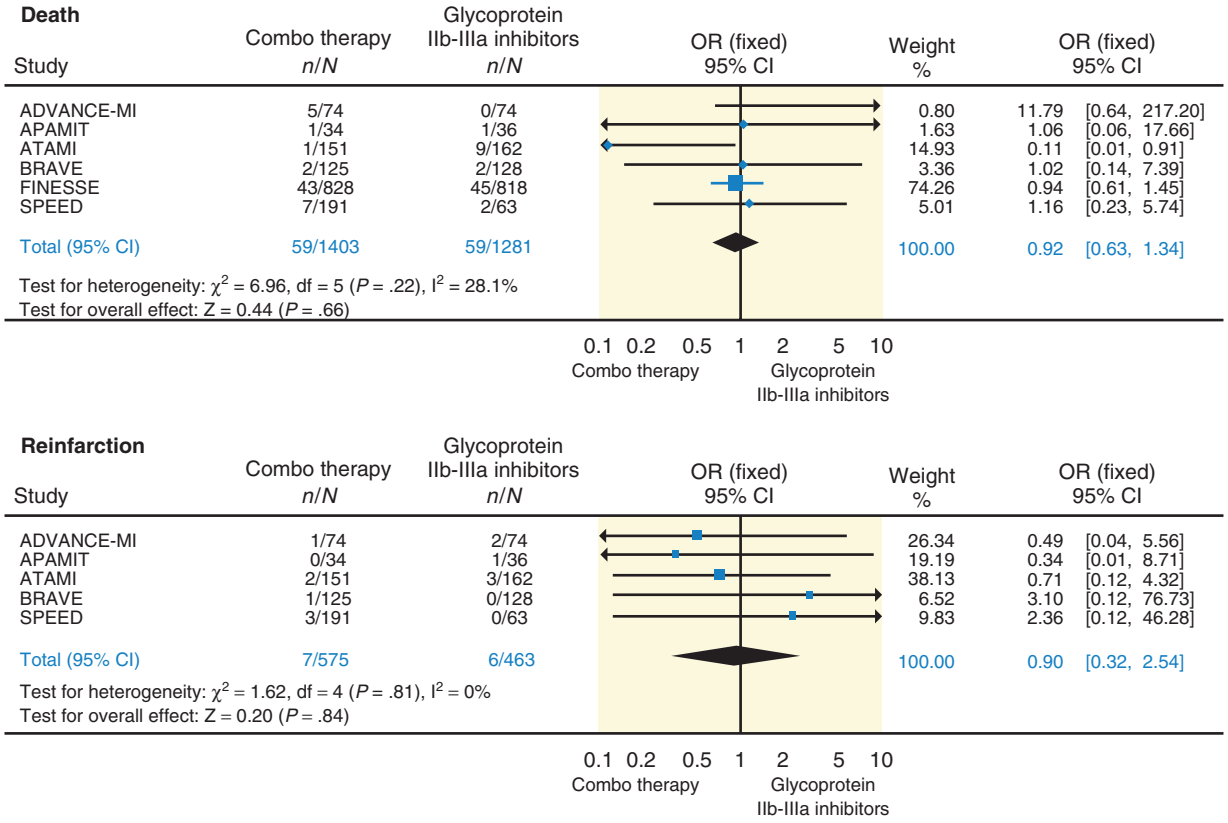


FIGURE 13-14 Combination facilitated percutaneous coronary intervention (PCI) and benefits in mortality (*upper graph*) and reinfarction (*lower graph*) at 30-day follow-up compared with early glycoprotein IIb/IIIa inhibitor administration from a meta-analysis of trials of facilitated PCI with odds ratios (ORs) and 95% confidence intervals (CIs). The size of the data markers (*squares*) is approximately proportional to the statistical weight of each trial. (Adapted from De Luca G, Marino P: Facilitated angioplasty with combo therapy among patients with ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *Am J Emerg Med* 27[6]:683-690, 2009.)

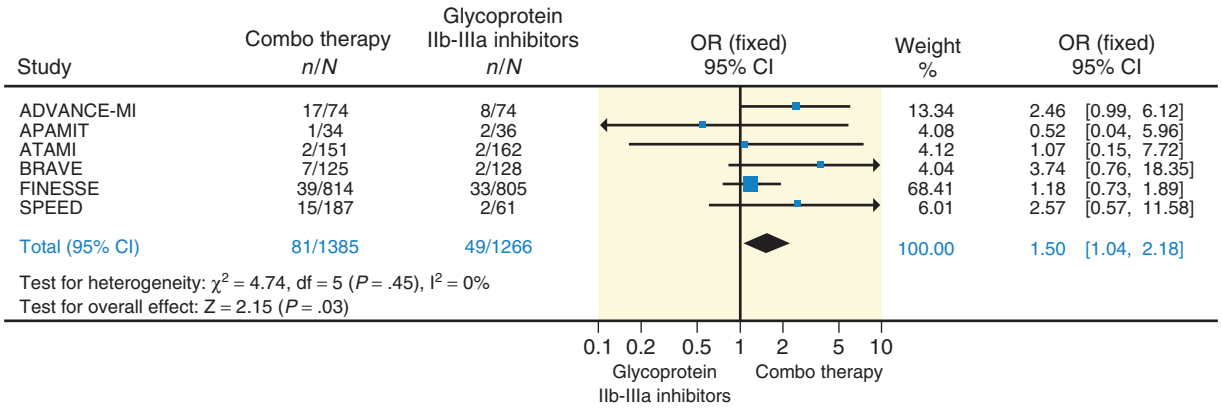


FIGURE 13-15 Combination facilitated percutaneous coronary intervention (PCI) and risk of major bleeding complications compared with early glycoprotein IIb/IIIa inhibitor administration from a meta-analysis of trials of facilitated PCI with odds ratios (ORs) and 95% confidence intervals (CIs). The size of the data markers (*squares*) is approximately proportional to the statistical weight of each trial. (Adapted from De Luca G, Marino P: Facilitated angioplasty with combo therapy among patients with ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *Am J Emerg Med* 27[6]:683-690, 2009.)

treatment group ($P = .004$), with no significant difference in significant bleeding between the two groups. Reduction in reinfarction was also observed in the routine PCI group at 6 months of follow-up. No difference was reported in the rates of death or reinfarction (10.3% vs. 11.6%, $P = .50$), hospital readmission (15.4% vs. 16.5%, $P = .64$), or subsequent revascularization with either PCI or coronary artery bypass grafting (CABG) after index hospitalization (6.9% vs. 8.7%, $P = .30$) between the two groups at 1 year with excellent (98%) follow-up. An economic analysis also showed no difference in costs between the two treatment strategies.[102]

The Norwegian Study on District Treatment of ST-Elevation Myocardial Infarction (NORDISTEMI)[103] compared a strategy of

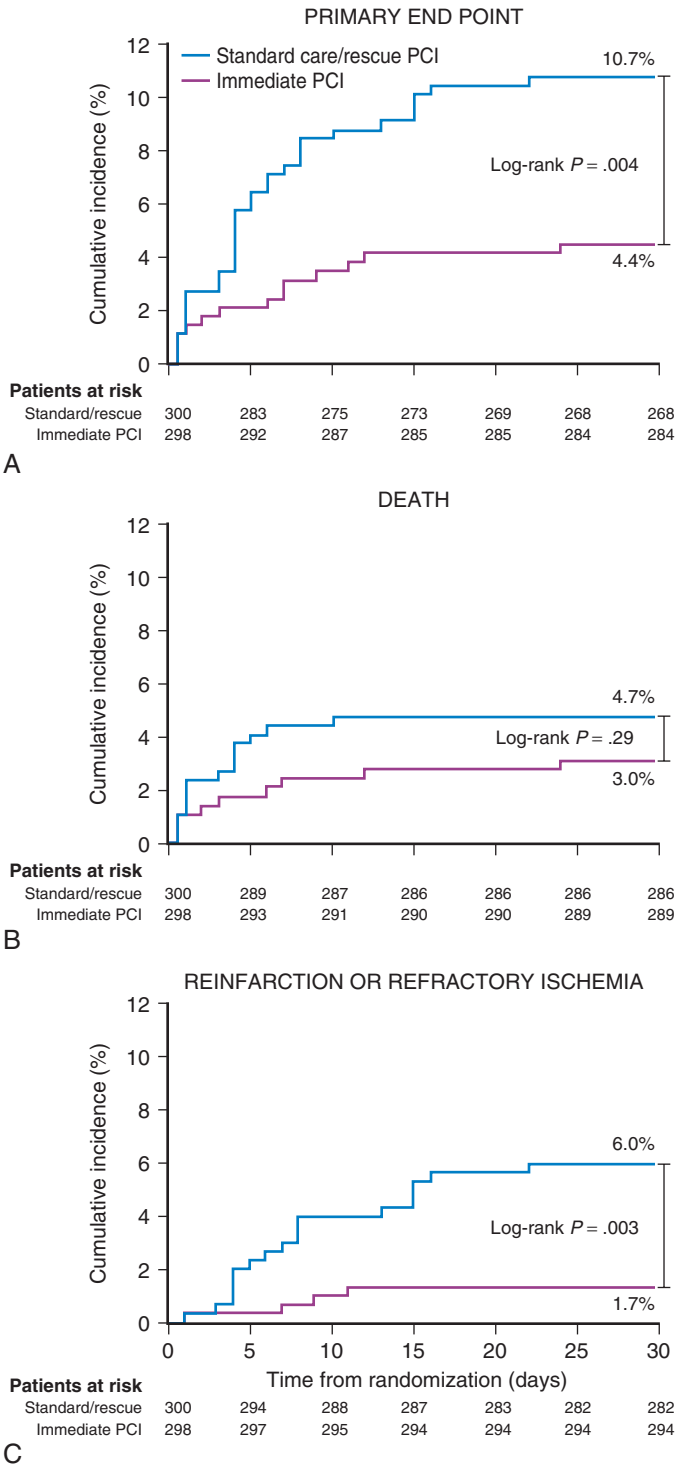


FIGURE 13-16 Kaplan-Meier curves for the primary composite end point (**A**), death (**B**), reinfarction (**C**), and refractory ischemia in the CARESS-in-AMI trial. *PCI,* Percutaneous coronary intervention. (Di Mario C, Dudek D, Piscione F, et al: Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised, multicentre trial. *Lancet* 371[9612]:559-568, 2008.)

immediate transfer for PCI with an ischemia-guided approach after thrombolysis with full-dose tenecteplase in 276 patients with long transfer distances to PCI (expected delay from first medical contact to PCI of >90 min). This study showed a reduction in the primary combined end point of death, reinfarction, stroke, or new myocardial ischemia in the immediate PCI group at 30 days (relative risk [RR] 0.49; 95% CI, 0.27 to 0.89; $P = .03$) with a nonsignificant trend toward benefit with this approach at 12 months (HR 0.72; 95% CI, 0.44 to 1.18; $P = .19$). No difference in bleeding was found between the two treatment groups. Notably, this study demonstrated a benefit for immediate PCI following thrombolysis despite allowing for more liberal use of coronary angiography and PCI in the ischemia-guided group, with 95% of subjects in this group undergoing angiography (mean of 5.5 days after receiving tenecteplase) compared with 99% in the immediate-PCI group (mean of 130 min after receiving tenecteplase). Additionally, use of clopidogrel loading and enoxaparin was universal, with no difference in the use of other evidence-based therapies between the two treatment groups.

The pharmacoinvasive approach was also recently compared with delayed primary PCI in the Strategic Reperfusion Early After Myocardial Infarction (STREAM) study,[46] which randomized 1892 patients who presented with STEMI within 3 hours of symptom onset and were unable to undergo PCI within 60 minutes of symptom onset to prehospital thrombolysis with full-dose tenecteplase followed by routine coronary angiography within 6 to 24 hours or to primary PCI. The median delay from symptom onset to arrival in the cardiac catheterization laboratory was 600 minutes in the thrombolysis group and 170 minutes in the primary PCI group; the median time from symptom onset to tenecteplase infusion in the thrombolysis group was 100 minutes. The composite primary end point of death from any cause, shock, congestive heart failure, or reinfarction at 30 days occurred in 12.4% of patients in the thrombolysis group and in 14.3% of patients in the primary PCI group (RR 0.86; 95% CI, 0.68 to 1.09; $P = .21$). More strokes occurred in the thrombolysis group (1.6% vs. 0.5%; $P = .03$), driven primarily by an excess in intracranial hemorrhage among older adult subjects at the start of the trial (1.0% vs. 0.2%; $P = .04$). This resulted in a protocol amendment mandating a 50% tenecteplase dose reduction in patients over the age of 75. Thereafter, no difference was observed in the occurrence of intracranial hemorrhage between the two study groups (0.5% vs. 0.3%; $P = .45$). No differences in extracranial bleeding were noted between the groups. Of interest, whereas the vast majority of patients in both groups were treated with PCI, more patients in the thrombolysis group were ultimately treated with surgical revascularization (4.7% vs. 2.1%; $P = .002$). This study suggests that the pharmacoinvasive strategy of early full-dose thrombolysis followed by routine coronary angiography is an effective reperfusion strategy, with a statistically nonsignificant trend toward benefit versus delayed primary PCI, but it is associated with an increased risk of intracranial bleeding.

Two contemporary systematic reviews and meta-analyses of randomized trials to compare thrombolysis coupled with a routine invasive strategy with ischemia-guided provisional coronary angiography following thrombolysis have demonstrated a consistent benefit for the pharmacoinvasive approach in reducing both reinfarction and death at 6 months and 1 year.[104-105] One study of 197 patients with a mean follow-up time of 7.9 years (±3.4 yr; maximum, 11.2 yr) showed a persistent and significant reduction in the composite of death, reinfarction, target-lesion revascularization, and ischemic events with the pharmacoinvasive approach (HR 0.61; 95% CI, 0.42 to 0.88; $P = .008$).[106] In aggregate, these data support the use of a pharmacoinvasive strategy with primary thrombolysis followed by routine early angiography and PCI in high-risk STEMI patients who present to non–PCI-capable hospitals. This strategy may also enable more rapid reperfusion with initiation of prehospital therapy in cases that may require prolonged transport times to PCI-capable centers.[107] The pharmacoinvasive strategy was given a class IIa recommendation in the 2013 update to the ACCF/AHA STEMI guidelines.[2]

INTERNATIONAL PERSPECTIVE

Cardiovascular disease (CVD) remains a major cause of mortality and morbidity globally, and the burden of CVD is only expected to increase in the future. The World Health Organization estimates that by 2030, 23.3 million people will die from CVD. Low-income and middle-income countries are disproportionately affected by the global CVD epidemic, with more than 80% of all CVD deaths around the world occurring in these nations. Many individuals will die younger, often in their productive years, which will result in a significant economic impact, both at the individual family level and at the national level, hampering ongoing economic development.[108] Given that STEMI will continue to account for a significant proportion of the growing international CVD burden, and most patients in low-income and middle-income countries—as well as significant numbers in the high-income nations—will not have timely access to primary PCI, thrombolysis will serve as the primary reperfusion strategy for the majority of patients with STEMI worldwide. Developing systems for the early recognition and triage of these patients with prompt administration of thrombolytic therapy (unless timely primary PCI is available) and appropriate postthrombolytic care will be critical in reducing the tremendous global burden of CVD.

SUMMARY

Despite a deeper understanding of the pathophysiology of AMI, as well as the vast improvements in both the pharmacologic and mechanical reperfusion tools available, outcomes with STEMI remain suboptimal. Thrombolytic therapy revolutionized the management of STEMI and ushered in the modern era of reperfusion therapy as the primary treatment modality in AMI. Whereas thrombolytics were once the mainstay of reperfusion therapy in STEMI, timely primary PCI has evolved to become the favored and recommended reperfusion strategy. However, many patients with STEMI do not have access to primary PCI within the critical time interval in which outcomes are maximally preserved with mechanical reperfusion, which underscores the continued importance of thrombolytic therapy in the management of STEMI. Outcomes with thrombolytics will only improve as new thrombolytic agents are engineered with greater specificity for the actively forming thrombus, potentially reducing the risk of bleeding; more potent adjunctive antiplatelet and antithrombotic therapies will possibly reduce thrombolytic-mediated platelet aggregation and distal embolization of thrombus. Furthermore, a pharmacoinvasive approach using thrombolytic therapy as the primary reperfusion strategy with routine subsequent coronary angiography has the potential to improve outcomes in patients with STEMI who do not have access to timely primary PCI. Such a strategy is particularly attractive in light of the fact that the global burden of CVD will continue to grow and will disproportionately affect developing nations, where timely primary PCI may not be readily available. Along with innovations in pharmacology and postthrombolytic management, systems of care will continue to evolve to facilitate rapid and appropriate risk stratification and initiation of reperfusion therapy. Whatever strategy is used, prompt restoration of both epicardial and microcirculatory flow to limit myonecrosis, preserve left ventricular function, and improve survival is crucial. Thrombolytic agents will continue to play an important role in the management of STEMI, particularly as CVD affects a growing population throughout the world and access to primary PCI remains limited.

REFERENCES

1. Kiernan TJ, Gersh BJ: Thrombolysis in acute myocardial infarction: current status. *Med Clin North Am* 91(4):617–637, 2007.
2. O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 61(4):e78–e140, 2013.
3. Andersen HR, Nielsen TT, Rasmussen K, et al: A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* 349(8):733–742, 2003.
4. Aversano T, Aversano LT, Passamani E, et al: Thrombolytic therapy vs primary percutaneous coronary intervention for myocardial infarction in patients presenting to hospitals without on-site cardiac surgery: a randomized controlled trial. *JAMA* 287(15):1943–1951, 2002.
5. The Primary Coronary Angioplasty vs. Thrombolysis (PCAT)-2 Trialists' Collaborative Group: Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J* 27(7):779–788, 2006.
6. Keeley EC, Boura JA, Grines CL: Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 361(9351):13–20, 2003.
7. Concannon TW, Nelson J, Goetz J, Griffith JL: A percutaneous coronary intervention lab in every hospital? *Circ Cardiovasc Qual Outcomes* 5(1):14–20, 2012.
8. Nallamothu BK, Bates ER, Herrin J, et al: Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NRMI)-3/4 analysis. *Circulation* 111(6):761–767, 2005.
9. Magid DJ, Wang Y, Herrin J, et al: Relationship between time of day, day of week, timeliness of reperfusion, and in-hospital mortality for patients with acute ST-segment elevation myocardial infarction. *JAMA* 294(7):803–812, 2005.
10. De Luca G, Suryapranata H, Ottervanger JP, Antman EM: Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation* 109(10):1223–1225, 2004.
11. Tillett WS, Garner RL: The fibrinolytic activity of hemolytic streptococci. *J Exp Med* 58(4):485–502, 1933.
12. Tillett WS, Sherry S: The effect in patients of streptococcal fibrinolysin (streptokinase) and streptococcal desoxyribonuclease on fibrinous, purulent, and sanguinous pleural exudations. *J Clin Invest* 28(1):173–190, 1949.
13. European Working Party: Streptokinase in recent myocardial infarction: a controlled multicentre trial. *BMJ* 770:325–331, 1971.
14. Rentrop P, Blanke H, Karsch KR, et al: Selective intracoronary thrombolysis in acute myocardial infarction and unstable angina pectoris. *Circulation* 63(2):307–317, 1981.
15. Markis JE, Malagold M, Parker JA, et al: Myocardial salvage after intracoronary thrombolysis with streptokinase in acute myocardial infarction. *N Engl J Med* 305(14):777–782, 1981.
16. Rijken DC, Collen D: Purification and characterization of the plasminogen activator secreted by human melanoma cells in culture. *J Biol Chem* 256(13):7035–7041, 1981.
17. Van de Werf F, Ludbrook PA, Bergmann SR, et al: Coronary thrombolysis with tissue-type plasminogen activator in patients with evolving myocardial infarction. *N Engl J Med* 310(10):609–613, 1984.
18. Hilleman DE, Tsikouris JP, Seals AA, Marmur JD: Fibrinolytic agents for the management of ST-segment elevation myocardial infarction. *Pharmacotherapy* 27(11):1558–1570, 2007.
19. The International Study Group: In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. *Lancet* 336(8707):71–75, 1990.
20. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group: ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 339(8796):753–770, 1992.
21. The GUSTO Investigators: An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 329(10):673–682, 1993.
22. The GUSTO Angiographic Investigators: The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 329(22):1615–1622, 1993.
23. Smalling RW, Bode C, Kalbfleisch J, et al: More rapid, complete, and stable coronary thrombolysis with bolus administration of reteplase compared with alteplase infusion in acute myocardial infarction. *Circulation* 91(11):2725–2732, 1995.
24. Bode C, Smalling RW, Berg G, et al: Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. *Circulation* 94(5):891–898, 1996.
25. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators: A comparison of reteplase with alteplase for acute myocardial infarction. *N Engl J Med* 337(16):1118–1123, 1997.
26. Van de Werf F, Adgey J, Ardissino D, et al: Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 354(9180):716–722, 1999.
27. Nielsen PH, Terkelsen CJ, Nielsen TT, et al: System delay and timing of intervention in acute myocardial infarction (from the Danish Acute Myocardial Infarction-2 [DANAMI-2] trial). *Am J Cardiol* 108(6):776–781, 2011.
28. Stone GW, Gersh BJ: Facilitated angioplasty: paradise lost. *Lancet* 367(9510):543–546, 2006.
29. Morrison LJ, Verbeek PR, McDonald AC, et al: Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis. *JAMA* 283(20):2686–2692, 2000.
30. Bjorklund E, Stenestrand U, Lindback J, et al: Pre-hospital thrombolysis delivered by paramedics is associated with reduced time delay and mortality in ambulance-transported real-life patients with ST-elevation myocardial infarction. *Eur Heart J* 27(10):1146–1152, 2006.
31. Morrow DA, Antman EM, Sayah A, et al: Evaluation of the time saved by prehospital initiation of reteplase for ST-elevation myocardial infarction: results of The Early Retavase-Thrombolysis in Myocardial Infarction (ER-TIMI) 19 trial. *J Am Coll Cardiol* 40(1):71–77, 2002.
32. Wallentin L, Goldstein P, Armstrong PW, et al: Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. *Circulation* 108(2):135–142, 2003.
33. Sayah AJ, Roe MT: The role of fibrinolytics in the prehospital treatment of ST-elevation myocardial infarction (STEMI). *J Emerg Med* 34(4):405–416, 2008.
34. Schull MJ, Vaillancourt S, Donovan L, et al: Underuse of prehospital strategies to reduce time to reperfusion for ST-elevation myocardial infarction patients in 5 Canadian provinces. *CJEM* 11(5):473–480, 2009.
35. Stenestrand U, Lindback J, Wallentin L: Long-term outcome of primary percutaneous coronary intervention vs prehospital and in-hospital thrombolysis for patients with ST-elevation myocardial infarction. *JAMA* 296(14):1749–1756, 2006.
36. Schömig A, Ndrepepa G, Mehilli J, et al: Therapy-dependent influence of time-to-treatment interval on myocardial salvage in patients with acute myocardial infarction treated with coronary artery stenting or thrombolysis. *Circulation* 108(9):1084–1088, 2003.
37. Aasa M, Dellborg M, Herlitz J, et al: Risk reduction for cardiac events after primary coronary intervention compared with thrombolysis for acute ST-elevation myocardial infarction (five-year results of the Swedish early decision reperfusion strategy [SWEDES] trial). *Am J Cardiol* 106(12):1685–1691, 2010.

38. Widimsky P, Budesinsky T, Vorac D, et al: Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial–PRAGUE-2. *Eur Heart J* 24(1):94–104, 2003.
39. Nielsen PH, Maeng M, Busk M, et al: Primary angioplasty versus fibrinolysis in acute myocardial infarction: long-term follow-up in the Danish Acute Myocardial Infarction 2 Trial. *Circulation* 121(13):1484–1491, 2010.
40. Gershlick AH, Stephens-Lloyd A, Hughes S, et al: Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 353(26):2758–2768, 2005.
41. Collet JP, Montalescot G, Le May M, et al: Percutaneous coronary intervention after fibrinolysis: a multiple meta-analyses approach according to the type of strategy. *J Am Coll Cardiol* 48(7):1326–1335, 2006.
42. Patel TN, Bavry AA, Kumbhani DJ, Ellis SG: A meta-analysis of randomized trials of rescue percutaneous coronary intervention after failed fibrinolysis. *Am J Cardiol* 97(12):1685–1690, 2006.
43. Cantor WJ, Fitchett D, Borgundvaag B, et al: Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Engl J Med* 360(26):2705–2718, 2009.
44. Di Mario C, Dudek D, Piscione F, et al: Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised, multicentre trial. *Lancet* 371(9612):559–568, 2008.
45. Fernandez-Avilés F, Alonso JJ, Castro-Beiras A, et al: Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. *Lancet* 364(9439):1045–1053, 2004.
46. Armstrong PW, Gershlick AH, Goldstein P, et al: Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 368(15):1379–1387, 2013.
47. Estudio Multicentrico Estreptoquinasa Republicas de America del Sur (EMERAS) Collaborative Group: Randomised trial of late thrombolysis in patients with suspected acute myocardial infarction. *Lancet* 342(8874):767–772, 1993.
48. LATE Study Group: Late Assessment of Thrombolytic Efficacy (LATE) study with alteplase 6-24 hours after onset of acute myocardial infarction. *Lancet* 342(8874):759–766, 1993.
49. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group: Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 343(8893):311–322, 1994.
50. Antithrombotic Trialists' Collaboration: Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 324(7329):71–86, 2002.
51. Berger JS, Stebbins A, Granger CB, et al: Initial aspirin dose and outcome among ST-elevation myocardial infarction patients treated with fibrinolytic therapy. *Circulation* 117(2):192–199, 2008.
52. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group: Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 2(8607):349–360, 1988.
53. Baigent C, Collins R, Appleby P, et al: ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. *BMJ* 316(7141):1337–1343, 1998.
54. Mehta SR, Tanguay JF, Eikelboom JW, et al: Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet* 376(9748):1233–1243, 2010.
55. Chen ZM, Jiang LX, Chen YP, et al: Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 366(9497):1607–1621, 2005.
56. Sabatine MS, Cannon CP, Gibson CM, et al: Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 352(12):1179–1189, 2005.
57. Sabatine MS, Cannon CP, Gibson CM, et al: Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA* 294(10):1224–1232, 2005.
58. Dangas G, Mehran R, Guagliumi G, et al: Role of clopidogrel loading dose in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty: results from the HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial. *J Am Coll Cardiol* 54(15):1438–1446, 2009.
59. Wiviott SD, Braunwald E, McCabe CH, et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 357(20):2001–2015, 2007.
60. Storey RF, Husted S, Harrington RA, et al: Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol* 50(19):1852–1856, 2007.
61. Wallentin L, Becker RC, Budaj A, et al: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 361(11):1045–1057, 2009.
62. Greenbaum AB, Ohman EM, Gibson CM, et al: Preliminary experience with intravenous P2Y12 platelet receptor inhibition as an adjunct to reduced-dose alteplase during acute myocardial infarction: results of the Safety, Tolerability and Effect on Patency in Acute Myocardial Infarction (STEP-AMI) angiographic trial. *Am Heart J* 154(4):702–709, 2007.
63. Scrutinio D, Cimminiello C, Marubini E, et al: Ticlopidine versus aspirin after myocardial infarction (STAMI) trial. *J Am Coll Cardiol* 37(5):1259–1265, 2001.
64. The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators: Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 358(9282):605–613, 2001.
65. Sinnaeve PR, Alexander JH, Bogaerts K, et al: Efficacy of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: one-year follow-up results of the Assessment of the Safety of a New Thrombolytic-3 (ASSENT-3) randomized trial in acute myocardial infarction. *Am Heart J* 147(6):993–998, 2004.
66. Antman EM, Louwerenburg HW, Baars HF, et al: Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 Trial. *Circulation* 105(14):1642–1649, 2002.
67. Antman EM, Morrow DA, McCabe CH, et al: Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 354(14):1477–1488, 2006.
68. Morrow DA, Antman EM, Fox KA, et al: One-year outcomes after a strategy using enoxaparin vs. unfractionated heparin in patients undergoing fibrinolysis for ST-segment elevation myocardial infarction: 1-year results of the ExTRACT-TIMI 25 trial. *Eur Heart J* 31(17):2097–2102, 2010.
69. Yusuf S, Mehta SR, Xie C, et al: Effects of reviparin, a low-molecular-weight heparin, on mortality, reinfarction, and strokes in patients with acute myocardial infarction presenting with ST-segment elevation. *JAMA* 293(4):427–435, 2005.
70. Eikelboom JW, Quinlan DJ, Mehta SR, et al: Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. *Circulation* 112(25):3855–3867, 2005.
71. Eikelboom JW, Mehta SR, Anand SS, et al: Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* 114(8):774–782, 2006.
72. De Luca G, Marino P: Adjunctive benefits from low-molecular-weight heparins as compared to unfractionated heparin among patients with ST-segment elevation myocardial infarction treated with thrombolysis. A meta-analysis of the randomized trials. *Am Heart J* 154(6):1085, e1081–e1086, 2007.
73. Direct Thrombin Inhibitor Trialists' Collaborative Group: Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patients' data. *Lancet* 359(9303):294–302, 2002.
74. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators: A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 335(11):775–782, 1996.
75. Hirulog and Early Reperfusion or Occlusion (HERO)-2 Trial Investigators: Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. *Lancet* 358(9296):1855–1863, 2001.
76. Edmond JJ, French JK, Aylward PE, et al: Variations in the use of emergency PCI for the treatment of re-infarction following intravenous fibrinolytic therapy: impact on outcomes in HERO-2. *Eur Heart J* 28(12):1418–1424, 2007.
77. Stone GW, White HD, Ohman EM, et al: Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial. *Lancet* 369(9565):907–919, 2007.
78. Mehran R, Lansky AJ, Witzenbichler B, et al: Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. *Lancet* 374(9696):1149–1159, 2009.
79. GUSTO V Investigators: Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. *Lancet* 357(9272):1905–1914, 2001.
80. Lincoff AM, Califf RM, Van de Werf F, et al: Mortality at 1 year with combination platelet glycoprotein IIb/IIIa inhibition and reduced-dose fibrinolytic therapy vs conventional fibrinolytic therapy for acute myocardial infarction: GUSTO V randomized trial. *JAMA* 288(17):2130–2135, 2002.
81. De Luca G, Suryapranata H, Stone GW, et al: Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *JAMA* 293(14):1759–1765, 2005.
82. Ohman EM, Van de Werf F, Antman EM, et al: Tenecteplase and tirofiban in ST-segment elevation acute myocardial infarction: results of a randomized trial. *Am Heart J* 150(1):79–88, 2005.
83. Martinez-Rios MA, Rosas M, Gonzalez H, et al: Comparison of reperfusion regimens with or without tirofiban in ST-elevation acute myocardial infarction. *Am J Cardiol* 93(3):280–287, 2004.
84. Giugliano RP, Roe MT, Harrington RA, et al: Combination reperfusion therapy with eptifibatide and reduced-dose tenecteplase for ST-elevation myocardial infarction: results of the Integrilin and Tenecteplase in Acute Myocardial Infarction (INTEGRITI) Phase II Angiographic Trial. *J Am Coll Cardiol* 41(8):1251–1260, 2003.
85. Brener SJ, Zeymer U, Adgey AA, et al: Eptifibatide and low-dose tissue plasminogen activator in acute myocardial infarction: the Integrilin and Low-Dose Thrombolysis in Acute Myocardial Infarction (INTRO AMI) trial. *J Am Coll Cardiol* 39(3):377–386, 2002.
86. Miller JM, Smalling R, Ohman EM, et al: Effectiveness of early coronary angioplasty and abciximab for failed thrombolysis (reteplase or alteplase) during acute myocardial infarction (results from the GUSTO-III trial). *Am J Cardiol* 84(7):779–784, 1999.
87. Gruberg L, Suleiman M, Kapeliovich M, et al: Glycoprotein IIb/IIIa inhibitors during rescue percutaneous coronary intervention in acute myocardial infarction. *J Invasive Cardiol* 18(2):59–62, 2006.
88. Yusuf S, Mehta SR, Chrolavicius S, et al: Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 295(13):1519–1530, 2006.
89. Peters RJ, Joyner C, Bassand JP, et al: The role of fondaparinux as an adjunct to thrombolytic therapy in acute myocardial infarction: a subgroup analysis of the OASIS-6 trial. *Eur Heart J* 29(3):324–331, 2008.
90. Yusuf S, Mehta SR, Chrolavicius S, et al: Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 354(14):1464–1476, 2006.
91. Stone GW, Cox D, Garcia E, et al: Normal flow (TIMI-3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction: analysis from the primary angioplasty in myocardial infarction trials. *Circulation* 104(6):636–641, 2001.
92. Topol EJ, Califf RM, George BS, et al: A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. *N Engl J Med* 317(10):581–588, 1987.
93. ASSENT-4 PCI Investigators: Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 367(9510):569–578, 2006.
94. ADVANCE MI Investigators: Facilitated percutaneous coronary intervention for acute ST-segment elevation myocardial infarction: results from the prematurely terminated ADdressing the Value of facilitated ANgioplasty after Combination therapy or Eptifibatide monotherapy in acute Myocardial Infarction (ADVANCE MI) trial. *Am Heart J* 150(1):116–122, 2005.
95. Kastrati A, Mehilli J, Schlotterbeck K, et al: Early administration of reteplase plus abciximab vs abciximab alone in patients with acute myocardial infarction referred for percutaneous coronary intervention: a randomized controlled trial. *JAMA* 291(8):947–954, 2004.
96. Thiele H, Eitel I, Meinberg C, et al: Randomized comparison of pre-hospital-initiated facilitated percutaneous coronary intervention versus primary percutaneous coronary intervention in acute myocardial infarction very early after symptom onset: the LIPSIA-STEMI Trial (Leipzig Immediate Prehospital Facilitated Angioplasty in ST-segment Myocardial Infarction). *JACC Cardiovasc Interv* 4(6):605–614, 2011.
97. Ellis SG, Tendera M, de Belder MA, et al: Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med* 358(21):2205–2217, 2008.
98. Ellis SG, Tendera M, de Belder MA, et al: 1-year survival in a randomized trial of facilitated reperfusion: results from the FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial. *JACC Cardiovasc Interv* 2(10):909–916, 2009.
99. Herrmann HC, Lu J, Brodie BR, et al: Benefit of facilitated percutaneous coronary intervention in high-risk ST-segment elevation myocardial infarction patients presenting to nonpercutaneous coronary intervention hospitals. *JACC Cardiovasc Interv* 2(10):917–924, 2009.
100. Keeley EC, Boura JA, Grines CL: Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. *Lancet* 367(9510):579–588, 2006.
101. De Luca G, Marino P: Facilitated angioplasty with combo therapy among patients with ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *Am J Emerg Med* 27(6):683–690, 2009.
102. Bagai A, Cantor WJ, Tan M, et al: Clinical outcomes and cost implications of routine early PCI after fibrinolysis: one-year follow-up of the Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) study. *Am Heart J* 165(4):630–637.e632, 2013.
103. Bohmer E, Hoffmann P, Abdelnoor M, et al: Efficacy and safety of immediate angioplasty versus ischemia-guided management

after thrombolysis in acute myocardial infarction in areas with very long transfer distances results of the NORDISTEMI (NORwegian study on DIstrict treatment of ST-elevation myocardial infarction). *J Am Coll Cardiol* 55(2):102–110, 2010.

104. Borgia F, Goodman SG, Halvorsen S, et al: Early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST-segment elevation myocardial infarction: a meta-analysis. *Eur Heart J* 31(17):2156–2169, 2010.
105. D'Souza SP, Mamas MA, Fraser DG, Fath-Ordoubadi F: Routine early coronary angioplasty versus ischaemia-guided angioplasty after thrombolysis in acute ST-elevation myocardial infarction: a meta-analysis. *Eur Heart J* 32(8):972–982, 2011.
106. Clever YP, Cremers B, Link A, et al: Long-term follow-up of early versus delayed invasive approach after fibrinolysis in acute myocardial infarction. *Circ Cardiovasc Interv* 4(4):342–348, 2011.
107. Thiele H, Scholz M, Engelmann L, et al: ST-segment recovery and prognosis in patients with ST-elevation myocardial infarction reperfused by prehospital combination fibrinolysis, prehospital initiated facilitated percutaneous coronary intervention, or primary percutaneous coronary intervention. *Am J Cardiol* 98(9):1132–1139, 2006.
108. World Health Organization: Cardiovascular Diseases Fact Sheet 2013, accessed online 2014 June 25 at http://www.who.int/mediacentre/factsheets/fs317/en/.

14 Other Adjunctive Drugs for Coronary Intervention: Beta-Blockers, Calcium-Channel Blockers, and Angiotensin-Converting Enzyme Inhibitors

VIVEK RAJAGOPAL

KEY POINTS

- Beta-blockers provide long-term mortality reduction after myocardial infarction (MI).
- Although beta-blockers are beneficial, they should be used carefully immediately after MI to avoid cardiogenic shock in susceptible patients.
- Calcium-channel blockers are reasonable alternatives to beta-blockers after MI in the few patients with strong contraindications to beta-blockers.
- Angiotensin-converting enzyme (ACE) inhibitors provide mortality reduction in patients after MI, especially in those with left ventricular (LV) dysfunction.
- Genomic studies have demonstrated differential response of some populations to these agents, and further studies might help us target individuals with specific agents in the future.

For several decades, beta-blockers, calcium-channel blockers, and ACE inhibitors have been beneficial in a wide spectrum of coronary artery disease (CAD)—stable and unstable angina, ST-elevation myocardial infarction (STEMI), and non–ST-elevation myocardial infarction (NSTEMI). Multiple clinical trials since the 1980s have demonstrated benefits of these agents, which work either by reducing myocardial oxygen demand or by promoting favorable myocardial remodeling.

This chapter will discuss the basic pharmacology of these agents, followed by an in-depth discussion of randomized trials that have used them. Finally, we will discuss ongoing research and will also provide treatment recommendations.

BETA-ADRENERGIC RECEPTORS

Beta-receptors belong to a well-characterized family of receptors known as *G protein–coupled receptors*.[1] The pathway involves binding of an agonist, such as catecholamines for beta-receptors, to an extracellular receptor. Receptor activation causes a coupled G protein to stimulate adenylyl cyclase, which increases intracellular concentrations of cyclic adenosine monophosphate (cAMP). In turn, cAMP activates several AMP-dependent protein kinases, which phosphorylate other proteins and result in a cellular response.

The cellular response for beta-receptors differs according to three major subtypes: β_1, β_2, and β_3. Whereas stimulation of β_2-receptors causes bronchodilation and peripheral vasodilation, stimulation of β_1-receptors predominantly affects the heart, increasing contractility, heart rate, and lipolysis. The β_3-receptor increases heat production in brown adipose tissue and increases lipolysis in both brown and white adipose tissue.[2,3] Notably, the β_3-receptor likely plays a role in obesity and insulin resistance and may promote endothelial nitric oxide synthase and nitric oxide bioavailability.[3-15]

Beta-Adrenergic Receptor Blockers

Beta-blockers act by directly competing with binding of catecholamines to β-adrenergic receptors. These agents differ in their selectivity, lipid solubility, metabolism, and partial-agonist ability (intrinsic sympathomimetic ability [ISA]; Table 14-1). Although some data suggest that these differences might impact efficacy in certain conditions, such as chronic congestive heart failure (CHF), these differences mainly affect side effects, contraindications, and frequency of dosing. For example, nonselective agents may increase bronchospasm in asthmatic patients, whereas lipophilic agents may have more central nervous system (CNS) effects such as sedation and depression. Type of metabolism will affect plasma half-life in patients with renal or hepatic insufficiency. Beta-blockers with ISA slow heart rate less than beta-blockers without ISA; also, beta-blockers with ISA are less likely to decrease high-density lipoprotein cholesterol (HDL-C) or to increase triglycerides.

Despite these pharmacokinetic differences, efficacy in CAD arises primarily from β_1-receptor antagonism. In acute MI, for example, the catecholamine storm decreases the fibrillation threshold, increases myocardial oxygen consumption, and promotes myocardial necrosis. By decreasing heart rate and contractility, blockade of the β_1-receptor lowers myocardial stress, which decreases necrosis. Beta-blockade also raises the fibrillation threshold. By antagonizing lipolysis, beta-blockers reduce concentrations of free fatty acids and cause greater use of glucose and less use of oxygen. Although controversial, beta-blockers—in particular carvedilol—may also inhibit platelet aggregation, but the mechanism could be membrane interaction instead of β-receptor antagonism.[16]

Given these beneficial effects, it is not surprising that numerous clinical trials have demonstrated the benefits of beta-blockers in acute coronary syndromes (ACSs). Nonetheless, prudence is still required because beta-blockers decrease inotropy and slow atrioventricular conduction, which can harm certain subgroups of patients.

Unstable Angina Pectoris

Because beta-blockers potently reduce myocardial oxygen demand and possibly reduce inflammation in ACSs,[17] treating unstable angina with beta-blockers has much intuitive appeal. A few small randomized trials have supported this. Gottlieb and colleagues[18] randomized patients with unstable angina to 4 weeks of propranolol or placebo. All patients received calcium-channel blockers and/or nitrates. Although incidence of death, MI, or need for urgent coronary artery bypass grafting (CABG) did not differ between the groups, propranolol significantly reduced frequency and severity of recurrent ischemia. In the Holland Interuniversity Nifedipine and Metoprolol Trial (HINT),[19] 338 patients with unstable angina not pretreated with a beta-blocker randomly received nifedipine alone, metoprolol alone, or nifedipine and metoprolol. The odds ratios (ORs) for recurrent ischemia or MI by 48 hours were 1.15 for nifedipine (95% confidence interval [CI], 0.83 to 1.64), 0.76 for metoprolol (95% CI, 0.49 to 1.16), and 0.80 for both (95% CI, 0.53 to 1.19). Not surprisingly, small numbers limited the power of this

TABLE 14-1 Beta-Blockers

Type	Dose (mg)	Frequency (Q)	Excretion	Lipid Solubility	ISA
Selective β_1					
Acebutolol	200-600	12 hr	Kidney	Moderate	Low
Atenolol	25-200	24 hr	Kidney	None	None
Betaxolol	20-40	24 hr	Kidney	Moderate	Low
Metoprolol	50-400	12 hr	Liver	Moderate	None
Long-acting metoprolol		24 hr			
Nonselective β					
Labetolol (α, β_1, β_2)	600-2400	6-8 hr	Liver	None	None
Nadolol	80-240	24 hr	Kidney	Low	None
Pindolol	15-45	8-12 hr	Kidney	Moderate	Moderate
Propranolol	80-320	4-6 hr	Liver	High	None
Long-acting propranolol		12 hr			
Timolol	15-45	12 hr	Liver	Moderate	None

Adapted from Griffin B, Topol E, Nair D, Ashley K: Manual of cardiovascular medicine, ed 3, Philadelphia, 2008; Lippincott, Williams, & Wilkins.
ISA, Intrinsic sympathomimetic ability.

study, and these differences were not statistically significant. Hohnloser and associates[20] examined effects of esmolol, a short-acting (half-life 9 min) intravenous (IV) beta-blocker in a randomized, placebo-controlled trial of 113 patients. Investigators increased esmolol until they reduced the double-product by about 25%; thereafter, the esmolol infusion continued for up to 72 hours. Acute MI or urgent revascularization occurred in 9 patients treated with placebo compared with 3 patients treated with esmolol ($P = .06$). In a more recent randomized trial, Brunner and colleagues[21] randomized 116 patients with unstable angina to placebo or carvedilol at 25 mg twice a day. Patients received 48-hour Holter monitoring to document ischemia. Carvedilol reduced ischemic time by 76% (204 vs. 49 min, $P < .05$) with a 66% reduction in number of ischemic episodes (24 vs. 8, $P < .05$).

Some retrospective data from recent studies also demonstrate benefit of beta-blockers in unstable angina. Ellis and associates[22] pooled data from five randomized trials of abciximab during percutaneous coronary intervention: Evaluation of the 7E3 for the Prevention of Ischaemic Complications (EPIC) trial, Evaluation in PTCA to Improve Long-Term Outcome With Abciximab GP IIb/IIIa Blockade (EPILOG), Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT), c7E3 FAB Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE), and ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT). Except for RAPPORT, which had STEMI patients, the other four trials included patients with unstable angina or NSTEMI. All-cause mortality by 30 days occurred in 0.6% of patients receiving beta-blockers compared with 2.0% for patients who did not receive beta-blockers. After adjusting for baseline characteristics and propensity score to receive beta-blockers, beta-blockers remained predictive of lower mortality (hazard ratio [HR], 0.25; 95% CI, 0.11 to 0.57; $P = .001$). This mortality difference persisted at 6 months (1.7% vs. 3.7%; adjusted HR, 0.53; 95% CI, 0.29 to 0.94; $P = .03$). Among patients with unstable angina, beta-blockers reduced mortality at 3 months (1.6% to 0.6%, $P = .029$) and at 6 months (3.1% to 1.4%, $P = .009$).

Similarly, investigators found a mortality benefit of beta-blockers in patients enrolled in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) initiative.[23] In 72,054 patients with NSTEMI at 509 U.S. hospitals from 2001 through 2004, acute beta-blocker use was associated with a lower hospital mortality (adjusted OR, 0.66; 95% CI, 0.60 to 0.72; $P < .01$). Notably, nearly all patient subgroups benefited, including patients aged 80 years and older.

Percutaneous Coronary Intervention

Although trials have evaluated adjunctive beta-blockade in patients with unstable angina or MI undergoing percutaneous coronary intervention (PCI), fewer data exist for effect of beta-blockade as a specific adjunct to PCI. In fact, most data for adjunctive benefit arise from nonrandomized registries.

Sharma and colleagues[24] evaluated 1675 consecutive patients undergoing PCI, none of whom had a previous MI; the authors did not specify how many patients presented with unstable angina. Creatine kinase myocardial band (CK-MB) elevation occurred in 13.2% of patients on beta-blockers before the procedure compared with 22.1% of patients not on beta-blockers ($P < .001$). On multivariate analysis, beta-blockers remained an independent predictor of lower CK-MB release. Over a mean 15 months of follow-up, patients on preprocedural beta-blockers had a mortality of 0.8% compared with 2.0% for patients not on preprocedural beta-blockers ($P = .04$). Chan and colleagues[25] evaluated 4553 consecutive patients without acute or recent MI who underwent PCI according to whether they had been treated with beta-blockers at the time of the PCI. Of these patients, 2056 (45%) were on beta-blockers at the time of the intervention. Mortality was lower at 30 days for patients who received beta-blockers (1.3% vs. 0.8%, $P = .13$) and at 1 year (6.0% vs. 3.9%, $P = .0014$). After adjusting for differences in the baseline characteristics by propensity analysis, beta-blocker therapy remained independently predictive of 1 year survival (HR, 0.63; 95% CI, 0.46 to 0.87; $P = .0054$).

Along with these mortality data, other data suggest a benefit of beta-blockers on restenosis. Jackson and colleagues[26] followed 4840 people who underwent PCI according to whether they received beta-blockers on discharge. Patients treated with beta-blockers had a 5-year clinical restenosis rate of 12% versus 14% (adjusted OR, 0.83; $P = .046$). These data are controversial, however, because a small randomized trial of adjunctive carvedilol failed to reduce restenosis in patients undergoing atherectomy.[27]

In another small randomized trial, Wang and colleagues[28] examined the effect of intracoronary (IC) propranolol during PCI. In this trial, investigators randomized 150 patients undergoing PCI to placebo or propranolol (15 μg/kg) injected into the distal coronary artery via the balloon catheter positioned across the stenosis. CK-MB elevation occurred in 17% of propranolol patients compared with 36% of placebo patients ($P = .01$). The incidence of death, MI, or urgent revascularization by 30 days occurred in 18% of propranolol patients compared with 40% of placebo patients ($P = .004$). The relative risk (RR) of MI did not differ between patients on prior beta-blocker therapy and those not on prior therapy.

Uretsky and colleagues[29] also examined the effect of IC beta-blockers during PCI by randomizing 400 patients to IC propranolol or placebo combined with systemic eptifibatide. At 1 year, the composite end point of death, postprocedural MI, urgent target-lesion revascularization (TLR), or MI after hospitalization occurred in 21.5% of propranolol patients and in 32.5% of placebo patients ($P < .01$),

driven primarily by lower periprocedural MI (12.5% propranolol vs. 21.5% placebo; RR reduction 0.43; 95% CI, 0.08 to 0.65; $P = .018$).

In a unique study design, Park and colleagues[30] randomly assigned 70 patients undergoing elective PCI to either placebo or the short-acting beta-blocker landiolol as a 1-minute IC infusion before and after first balloon inflation, followed by a 6-hour IV infusion. The troponin I (TnI) level at 24 hours trended lower in the landiolol group compared with placebo (0.5 ± 1.14 vs. 1.27 ± 2.48, $P = .07$), although it is unclear whether this difference, if verified in a larger cohort, would be clinically meaningful.

Acute Myocardial Infarction

Early Trials: The MIAMI and ISIS-1 Trials

The data for beta-blockade in acute MI come from 26 small trials and two large trials: the First International Study of Infarct Survival (ISIS-1) trial[31] and the Metoprolol in Acute Myocardial Infarction (MIAMI) trial.[32]

The MIAMI Trial

Patients with acute MI within 24 hours of symptom onset ($n = 5778$) were randomized to receive IV metoprolol (15 mg) or placebo followed by oral metoprolol (200 mg daily) or placebo for 15 days. Beta-blockade reduced Q-wave infarction significantly, from 53.9% to 50.9% ($P = .024$), with a nonsignificant reduction in mortality (4.9% to 4.3%, $P = .29$). However, the MIAMI trial was significantly limited in its applicability to the modern era; patients enrolled in MIAMI were low risk (e.g., all Killip class I), and the trial occurred in the prereperfusion era before routine ACE inhibition and statin treatment.

The ISIS-1 Trial

Although ISIS-1 was similarly limited by lack of reperfusion, its larger size and power are important. ISIS-1 randomized 16,207 patients with suspected acute MI (mean 5-hour symptom onset) to control or to IV atenolol (5 to 10 mg) followed by 100 mg oral atenolol daily for 7 days. Treatment with atenolol significantly reduced vascular mortality from 4.57% to 3.89% ($P < .04$) from day 0 to day 7. Atenolol-treated patients also had a significantly lower vascular mortality by 1 year (10.7% vs. 12.0%, $P < .01$), although much of this late difference might have arisen because patients randomized to atenolol were more likely to be discharged on beta-blockers compared with controls.

Recent Data: COMMIT and Other Trials

Given that most data for beta-blockade in acute MI are several decades old, benefit for beta-blockade in the current era—with aggressive use of antiplatelet therapy, thrombolysis, or primary angioplasty, statin therapy, and antialdosterone therapy—has remained uncertain, and physicians have hoped for trials with modern background therapy to assess the true value of beta-blockade. This uncertainty has remained relevant because of persistent fears that beta-blockers may exacerbate the condition of some acute MI patients, particularly those with signs and symptoms of CHF.

Recently, Ibanez and colleagues[33] randomized 270 patients of Killip class II or less with anterior STEMI to receive an IV beta-blocker or a placebo before primary PCI. In this small group of selected patients, infarct size estimated by creatine kinase curves was smaller in the IV beta-blocker group.

More definitive data come from the large-scale randomized trial Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT).[34] In fact, COMMIT was the largest trial ever to investigate beta-blockers in acute MI. As such, it is exceptionally important to understand the trial in depth and its implications for patient management.

The COMMIT trial, also known as the *Second Chinese Cardiac Study* (CCS-2), was a placebo-controlled randomized trial with a two-by-two factorial design that randomized acute MI patients to metoprolol or placebo, as well as to clopidogrel or placebo, with a background therapy of aspirin, anticoagulant therapy (mostly unfractionated heparin [UFH]), and thrombolysis.

Patient Selection

The scale of the trial was impressive. Between August of 1999 and February of 2005, COMMIT enrolled 45,852 patients in 1250 Chinese hospitals. Inclusion criteria comprised left bundle branch block (LBBB, presumably new), ST-segment elevation, or ST depression within 24 hours of ischemic symptoms. Exclusion criteria comprised patients scheduled for primary PCI (because of combined aspirin and clopidogrel use that would have interfered with the other study arm) or those with conditions considered high risk for beta-blocker therapy: systolic blood pressure less than 100 mm Hg or heart rate below 50 beats/minute, heart block, or cardiogenic shock. Notably, moderate heart failure (Killip class II or III) was not a contraindication, unlike trials such as MIAMI.[32]

Study Protocol

Patients randomized to metoprolol received a 5 mg IV dose followed by second and third dose as long as systolic blood pressure was above 90 mm Hg and heart rate was above 50 beats/minute after each dose. Patients then received 50 mg metoprolol 15 minutes after the last IV dose, repeated every 6 hours for 24 hours, followed by 200 mg controlled-release metoprolol once daily for up to 4 weeks.

End Points

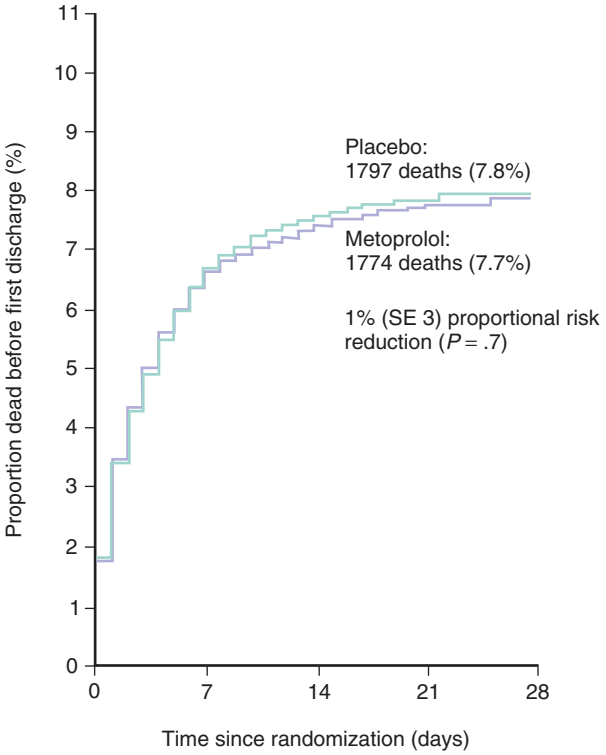
The COMMIT trial had two primary end points: all-cause mortality until discharge or until day 28 and the composite of death, reinfarction, or cardiac arrest. Secondary end points included cardiogenic shock, cardiac arrest, and reinfarction. Prespecified subgroup analyses included effects of metoprolol on primary outcomes according to hospital days and the following subgroups: age, sex, time from symptom onset, fibrinolysis, Killip class, heart rate, systolic blood pressure, and shock risk index (absolute risk of shock calculated from a Cox regression model using baseline prognostic characteristics).

Results

Not surprisingly, the large sample size of COMMIT ensured that baseline characteristics between groups were similar (Fig. 14-1). The mean age was 61 years; 26% were older than 70, and 72% were male. ST-segment elevation occurred in 87%, LBBB in 6%, and ST depression in 7%. Time from symptom onset to treatment was evenly distributed over 24 hours, and approximately one third of patients were treated within 6 hours, one third within 6 to 13 hours, and one third within 13 to 24 hours. Although most patients had no signs or symptoms of CHF, a sizable percentage (24%) were Killip class II or III on presentation. Again, this contrasts with early beta-blocker trials that enrolled lower-risk patients with no evidence of CHF. In COMMIT, 54% of patients received thrombolysis, and most of these patients received urokinase. Of those who presented within 12 hours, 68% received thrombolysis; it is unknown how many of the remaining patients did not receive thrombolytics because of clear contraindications. Notably, slightly fewer metoprolol-treated patients received ACE inhibitors (67.2% vs. 69.3%, $P < .0001$).

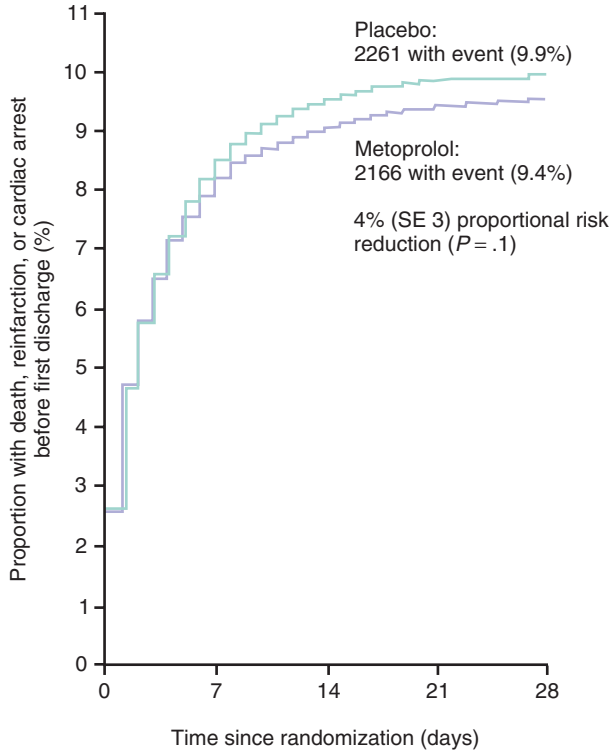
The primary composite outcome of death, reinfarction, or cardiac arrest did not differ between metoprolol-treated patients (9.4%) and placebo-treated patients (9.9%; OR, 0.96%; 95% CI, 0.90 to 1.01; $P = .10$; Fig. 14-2). Similarly, the co–primary outcome of death did not differ between metoprolol (7.7%) and placebo (7.8%) patients (see Fig. 14-1). Given the prior clinical data that support early beta-blockade in acute MI, reasons for these counterintuitive results require a careful dissection; in particular, did beta-blockade reduce any particular clinical events, and did beta-blockade benefit some patients much more than others?

Beta-blockade significantly reduced any reinfarction (2.0% for metoprolol vs. 2.5% for placebo, $P = .001$) and risk of ventricular fibrillation (2.5% vs. 3.0%, $P = .001$). Treatment, however, increased risk of cardiogenic shock by 30% (5.0% vs. 3.9%, $P < .0001$). Therefore,



Days	0-6	7-13	14-20	21-28
No. of events				
Metoprolol	1441	220	83	30
Placebo	1449	249	75	24

FIGURE 14-1 Death, reinfarction, or cardiac arrest in COMMIT. *SE,* Standard error.



Days	0-6	7-13	14-20	21-28
No. of events				
Metoprolol	1796	244	93	33
Placebo	1862	291	83	25

FIGURE 14-2 Death in COMMIT. *SE,* Standard error.

although beta-blockade significantly reduced arrhythmic death by 22% (1.7% for metoprolol vs. 2.2% for placebo, $P = .0002$), beta-blockade significantly increased death secondary to cardiogenic shock by 29% (2.2% vs. 1.7%, $P = .0002$). Therefore benefit in reducing arrhythmic death was counteracted by harm in increasing cardiogenic shock. In absolute terms, metoprolol prevented 5 episodes of ventricular fibrillation and 5 episodes of reinfarction per 1000 treated, but it caused 11 episodes of cardiogenic shock per 1000 treated. Of interest, these effects had differential time courses. In particular, a 10 per 1000 excess risk for cardiogenic shock was noted within the first 24 hours. By contrast, reductions in risk of reinfarction and ventricular fibrillation began approximately 48 hours after treatment initiation.

Propensity of metoprolol to cause cardiogenic shock differed according to baseline characteristics. Metoprolol caused a much higher excess of cardiogenic shock in the various subgroups: 56.9 per 1000 for patients in Killip class III; 34.6 per 1000 for patients who presented with a heart rate greater than 110 beats/minute; 23.3 per 1000 for patients presenting with systolic blood pressure below 120 mm Hg; and 23.1 per 1000 for patients aged 70 years or older. Not surprisingly, these differences translated into a much higher risk of cardiogenic shock with metoprolol according to baseline risk of shock: 3.7 per 1000 (low risk) versus 16.2 per 1000 (medium risk) versus 56.9 per 1000 (high risk; $P < .0001$).

This differential effect on cardiogenic shock translated into a differential effect on mortality according to patients' baseline risk of shock. For patients at high risk of cardiogenic shock, metoprolol caused an absolute increase of 24.8 deaths per 1000 treated. Conversely, treatment caused an absolute *decrease* of 4.2 and 4.3 deaths per 1000 for medium-risk and low-risk patients, respectively.

Meta-Analysis Using COMMIT Patients

As the COMMIT investigators mentioned, patients in COMMIT had a significantly higher risk of shock and mortality compared with patients enrolled in prior trials. Therefore, the investigators examined the effect of beta-blockade on patients in COMMIT similar to the low-risk patients enrolled in MIAMI (i.e., heart rate > 65 beats/min, Killip class I, systolic blood pressure > 105 mm Hg). They also pooled these patients with patients from MIAMI, ISIS-1, and 26 small trials (Fig. 14-3). The magnitude of benefit in low-risk COMMIT patients (6.4% to 5.7%) was similar to that of MIAMI patients (4.9% to 4.3%). In the analysis of pooled patients (~52,000), beta-blockade significantly reduced cardiac arrest (3.1% vs. 3.6%, $P = .002$), reinfarction (2.3% vs. 2.8%, $P = .0002$), and mortality (4.8% vs. 5.5%, $P = .0006$).

Recommendations for Beta-Blockade During Acute Myocardial Infarction

Given COMMIT's applicability to the modern era and its enormous size—almost twice as many patients as all others combined—the COMMIT data must form the core basis for any recommendations. Accordingly, early IV beta-blocker therapy for acute MI cannot be recommended for all patients. Nevertheless, the neutrality of the primary end points was driven by excess of cardiogenic shock in patients at increased baseline risk of developing shock. Therefore it is rational to consider early beta-blockade in patients at low risk for shock: age younger than 70 years, heart rate below 110 beats/minute, systolic blood pressure above 120 mm Hg, and Killip class I. This is, of course, not supported on a strict scientific basis because such a group was not prespecified, although a recent analysis from the Global Registry of Acute Coronary Events (GRACE) also confirms some hazard

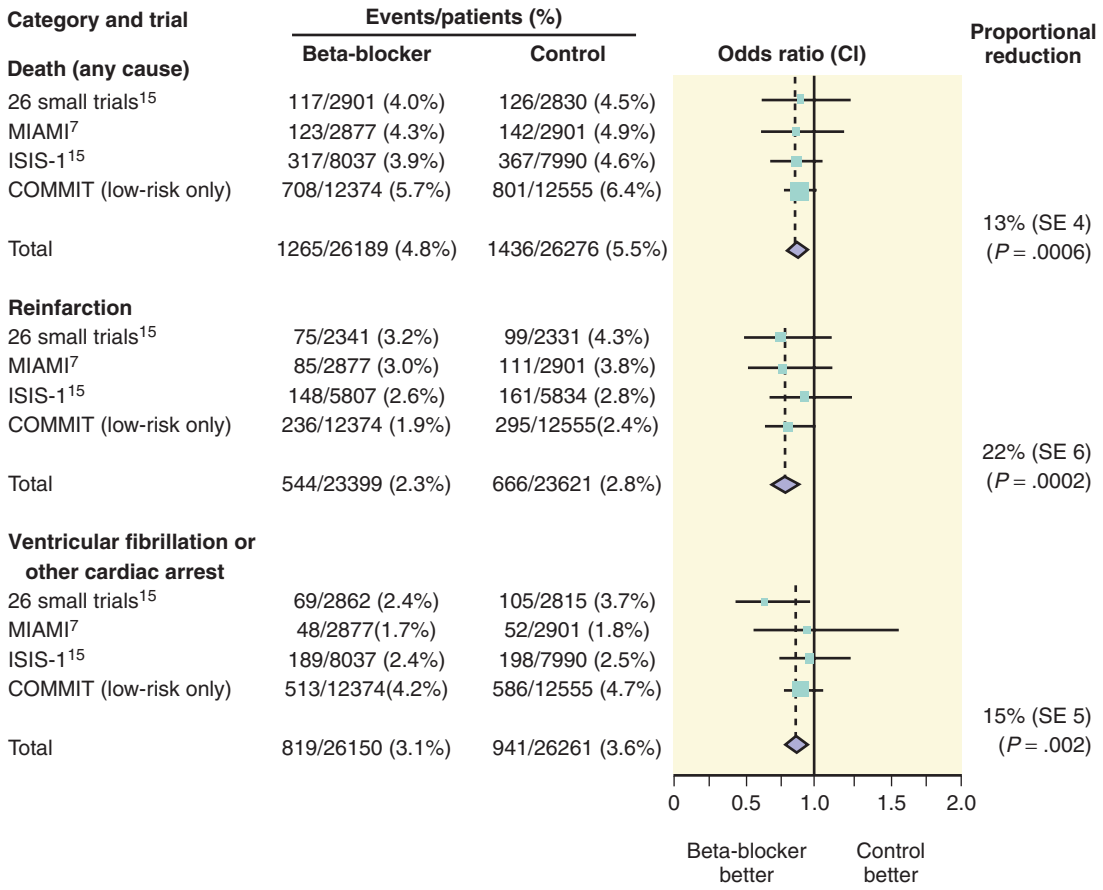


FIGURE 14-3 Meta-analysis using COMMIT data. *CI,* Confidence interval; *SE,* standard error.

of indiscriminate early IV beta-blockers.[35] A stronger recommendation can be made for waiting at least 24 hours to determine clinical stability before beginning beta-blockade. Because the cardiogenic shock hazard arises within 24 hours, it is possible that waiting could circumvent this hazard because it would allow those who are fittest for beta-blockade to emerge, thus giving these patients the reinfarction and cardiac arrest benefits, which emerge more slowly over the hospital course.

Chronic Therapy After Myocardial Infarction

ISIS-1 demonstrated a sustained benefit of beta-blockade for patients with acute MI; 1-year mortality for atenolol-treated patients was 10.7% versus 12.0% for placebo patients ($P < .01$). Given that patients randomized to atenolol in this trial were more likely to be discharged on atenolol, the further separation in survival curves at 1 year suggests a beneficial effect of beta-blockade given regularly after MI. Pooled data from all long-term trials of beta-blockade after MI also show a significant protective effect.[36] Long-term beta-blockade reduced sudden death from 5.2% to 3.6% ($P < .0001$), reinfarction from 7.3% to 5.5% ($P < .0001$), and mortality from 9.5% to 7.5% ($P < .0001$) over a follow-up period of 1 to 3 years.

The Effect of Carvedilol on Outcome After Myocardial Infarction in Patients With Left-Ventricular Dysfunction (CAPRICORN) trial supported this benefit for patients with recent MI and systolic dysfunction.[37] CAPRICORN randomized 1959 patients with acute MI and left ventricular ejection fraction (LVEF) of 40 or less to carvedilol 6.25 mg twice daily (starting during hospitalization) or placebo. Carvedilol was titrated up to 25 mg twice daily over 4 to 6 weeks. After a mean follow-up of 15 months, carvedilol treatment reduced all-cause mortality from 15% to 12% (HR, 0.77; 95% CI, 0.60 to 0.98; $P = .03$). Importantly, the CAPRICORN trial represented modern therapy with aggressive reperfusion, antiplatelet therapy, and anticoagulation; furthermore, all patients received ACE inhibitors for 48 hours prior to randomization. Similarly, an analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT)—which randomized 14,703 MI patients with heart failure to valsartan, captopril, or both—demonstrated a long-term survival advantage to patients on beta-blockers.[38]

Patient Selection: Role of Genomics

Because beta-blockade does not uniformly benefit patients after MI, as the COMMIT trial demonstrated, beta-blockers may harm certain subgroups while benefiting others. Therefore clinical trials remain blunt and crude instruments at best. Suppose, for example, a condition has 100% mortality, and a treatment demonstrates a large absolute reduction in mortality; for example, 40%. Thus, 4 of 10 patients given the treatment survive compared with 0 of 10 patients given placebo. That means that 6 treated patients did not receive benefit. This conundrum presented by clinical trials argues for a finer instrument to determine which patients will benefit.

Given recent advances in pharmacogenomics, characterization of patients' genetic polymorphisms may be a useful instrument to select the best candidates for beta-blocker therapy. Lanfear and colleagues[39] studied polymorphisms in the β_1- and β_2-receptors among patients ($N = 597$) on beta-blocker therapy after an ACS. No relationship existed between β_1-receptor polymorphisms and mortality in patients treated and not treated with beta-blockers. Polymorphisms in β_2-receptors, however, correlated significantly to mortality in patients discharged on beta-blockers. In particular, Kaplan-Meier 3-year mortality rates were 6%, 11%, and 16% for three different polymorphisms (GG, CG, and CC genotypes, respectively, for polymorphism Gln-27Glu with HR 0.24 [95% CI, 0.09 to 0.68] for GG vs. CC, $P = .004$). Similarly, Cresci and colleagues[40] recently described differential effects of polymorphisms in the *ADRB1, ADRB2, ADRA2C,* and the *GRK5*

genes in ACS patients in a race-specific manner. A β_2-receptor polymorphism, Gly16Arg, displayed a relationship between genotypes and mortality: 3-year Kaplan-Meier mortality rates of 10% for the GG and GA genotypes compared with 20% for the AA genotype (HR 0.44 [95% CI, 0.22 to 0.85] for GG vs. AA and 0.48 [95% CI, 0.27 to 0.86] for GA vs. AA, $P = .005$ for overall comparison). Significantly, these polymorphisms did not correlate with mortality in patients not treated with beta-blockers, indicating a specific interaction of the polymorphisms with beta-blocker treatment. Although the mechanism of this interaction is unknown, it is possible that these polymorphisms alter LV remodeling in response to beta-blockade, as has been described for β_1-receptor polymorphisms.[41,42] Similarly, polymorphisms in the peroxisome proliferator-activated receptor-α (PPARα) gene, which can alter LV remodeling, can interact with beta-blocker therapy, affecting rehospitalization rates after an ACS.[43]

Polymorphisms can also interact differentially with beta-blockers in the presence of diabetes. Beitelshees and colleagues[44] followed ACS patients ($N = 468$) with the −866G>A polymorphism in the mitochondrial uncoupling protein 2 (UCP-2) gene. Among diabetic patients with the GG genotype, beta-blocker use reduced cardiac rehospitalization by 80%, whereas beta-blocker use *increased* cardiac rehospitalization elevenfold among A-carrier patients with diabetes.

Although small, these studies suggest that genomic profiling might help tailor beta-blocker therapy in patients with ACSs, thereby maximizing benefit and reducing risk. Furthermore, advances in high-throughput genotyping suggest that widespread application is feasible.

CALCIUM CHANNELS

Intracellular calcium concentrations are tightly regulated by calcium exchangers, ion pumps, and channels. At baseline, cytoplasmic calcium ion concentrations exist at very low levels (<100 nM) compared with extracellular concentrations (>1 mM). When calcium channels open at the plasma membrane or endoplasmic reticular level, intracellular concentrations of calcium rapidly rise; adenosine triphosphate (ATP)–dependent ion pumps and sodium/calcium exchangers restore equilibrium.

Calcium channels exist as three major subgroups: voltage dependent, stretch operated, and receptor operated. The *voltage-dependent* receptors exist as three subtypes: N type, L type, and T type. The *L-type* and *T-type* channels are important to cardiovascular medicine and are inhibited by calcium-channel blockers. L-type channels exist throughout the cardiovascular system in cardiac and smooth muscles; they mediate the slow inward current (plateau phase) of the action potential and might play a role in activation of pathologic hypertrophy.[45] T-type channels are found mainly in sinus nodal tissue, and few are found in ventricular myocardium.

Calcium-Channel Blockers

The three main classes of calcium-channel blockers include dihydropyridines, phenylalkylamines, and benzothiazepines (Table 14-2). These classes differ in their vasodilatory and chronotropic effects. In particular, phenylalkylamines (e.g., verapamil) and benzothiazepines (e.g., diltiazem) decrease atrioventricular and sinoatrial conduction, whereas dihydropyridines (e.g., amlodipine) do not. On the other hand, dihydropyridines are more potent vasodilators. Nifedipine, in particular, can cause profound peripheral vasodilation, resulting in reflex tachycardia. Despite these differences, all classes of calcium-channel blockers have been shown to reduce infarct size in animal models. Some have speculated that calcium-channel blockers protect myocardium via coronary vasodilation and decreased ischemic calcium overload.

Acute Myocardial Infarction

Obviously, most data for calcium-channel blockade after acute MI are more than a decade old. The pivotal trials for early treatment of MI include the Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT-II), the First Danish Study Group on Verapamil in Myocardial Infarction Trial (DAVIT), and three small diltiazem trials.[46] None of these trials showed any significant difference in reinfarction or mortality with calcium-channel blockade; in fact, SPRINT-II was stopped prematurely because of increased mortality in the nifedipine group.

Data are limited and are only usable to generate hypothesis. In a Japanese trial, investigators randomized 1090 patients after acute MI to beta-blocker or calcium-channel blocker therapy.[47] At a mean follow-up of 455 days, patients treated with calcium-channel blockers did not have a different incidence of cardiovascular death (1.1% vs. 1.7%), reinfarction (1.3% vs. 0.9%), or nonfatal stroke (0.2% vs. 0.7%). Interestingly, the calcium-channel group had a significantly lower incidence of CHF (1.1% vs. 4.2%, $P = .001$) and coronary spasm (0.2% vs. 1.2%, $P = .027$). Obviously, more data in other populations are required to verify these differences.

TABLE 14-2 Calcium Channel Blockers

Type	Vasodilatory Effects	Conduction Effects	Negative Inotropy
Phenylalkylamine			
Verapamil	+++	++++	+++
Benzothiazepine			
Diltiazem	++	+++	++
Dihydropyridine			
Amlodipine	+++	+	+
Felodipine	++++	+	0
Isradipine	+++	++	0
Nicardipine	++++	+	0
Nifedipine	++++	+	+
Nisoldipine	+++	+	+

0, No activity; ++++, most potent.

Recommendations for Acute Coronary Syndromes

Given the lack of large trials that demonstrate benefit in acute MI, calcium-channel blockers should not be administered routinely, particularly for patients presenting with STEMI. A prominent exception is the patient who presents with ST-segment elevation following cocaine intoxication. Given the prominent role of coronary vasospasm after cocaine use and the possible exacerbation with beta-blockade, it is reasonable to administer calcium-channel blockers for these patients.

For patients with unstable angina or NSTEMI, the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines[48] endorse a class I recommendation for some with ACS: "patients with continuing or frequently recurring ischemia when beta-blockers are contraindicated, a nondihydropyridine calcium antagonist (e.g., verapamil or diltiazem), followed by oral therapy, as initial therapy in the absence of severe LV dysfunction or other contraindications (Level of Evidence: B)." Furthermore, these guidelines endorse a class IIa recommendation for other ACS patients with recurrent ischemia already on beta-blockers and nitrates: "oral long-acting calcium antagonists for recurrent ischemia in the absence of contraindications and when beta-blockers and nitrates are fully used (Level of Evidence: C)." The guidelines also clearly indicate that short-acting dihydropyridines (e.g., nifedipine) are contraindicated because of their propensity to decrease blood pressure abruptly and worsen ischemia/infarction.

Chronic Therapy After Myocardial Infarction

Early Trials

Like the data for acute treatment, many studies that have investigated chronic treatment are limited by being more than a decade old. These

trials started calcium-channel blockade weeks to months after MI and continued these agents long term. Data for nifedipine suggest harm, and trials evaluating verapamil and diltiazem show a nonsignificant reduction in noninfarction, although one large diltiazem trial showed this trend only in patients without CHF.[49] Taken together, the nifedipine trials demonstrate excess mortality with treatment; it is important to note that these trials had small numbers of events and used short-acting nifedipine, not controlled-release nifedipine. When the verapamil and diltiazem data are combined, treatment reduced reinfarction by 22% (95% CI, 33 to 0.8; $P < .01$).[50]

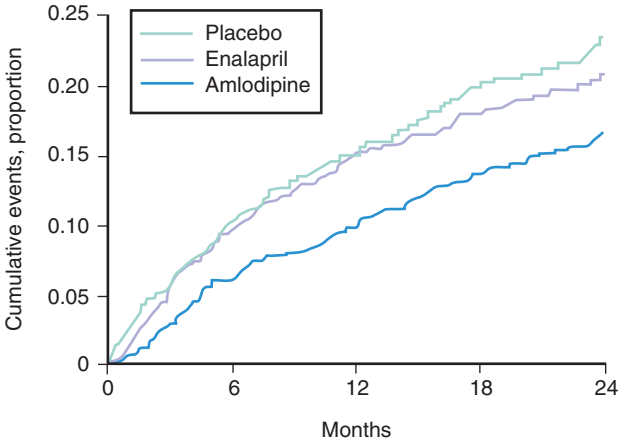
Recent Trials

Several antihypertensive trials of calcium-channel blockers have demonstrated similar outcomes with calcium-channel blockers compared with other agents. Some of these trials have enrolled patients with a history of MI and provide reassuring data.

The CAMELOT Trial

The Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study randomized 1991 patients with angiographically documented CAD (>20%) to amlodipine 5 to 10 mg daily, enalapril 10 to 20 mg daily, or to placebo.[51] Uniquely, these patients had "normal" blood pressure at baseline (~129/77). The primary outcome was incidence of adverse cardiovascular and cerebrovascular events that included cardiovascular death, resuscitated cardiac arrest, nonfatal MI, coronary revascularization, hospitalization for CHF, hospitalization for angina pectoris, stroke or transient ischemic attack (TIA), and any new diagnosis of peripheral vascular disease. The trial had an intravascular ultrasound (IVUS) substudy with the end point being percent change in atheroma volume. The mean age of the patients was about 57 years, and 38% of the entire population had a history of MI.

The primary end point occurred in 23.1% of placebo patients compared with 20.2% of enalapril patients and 16.6% of amlodipine patients, with significant differences between both the enalapril and amlodipine groups compared with placebo (Fig. 14-4). The amlodipine group had a statistical trend for fewer cardiovascular events compared with the enalapril group (HR, 0.81; 95% CI, 0.63 to 1.04; $P = .10$), and amlodipine treatment resulted in significantly fewer hospitalizations for angina (HR, 0.59; 95% CI, 0.42 to 0.84; $P = .003$). Of interest, amlodipine also displayed a trend for reduced atheroma progression compared with placebo ($P = .12$); also, amlodipine-treated patients with baseline blood pressures above mean had significantly reduced atheroma progression compared with placebo ($P < .001$).



No. at risk					
Placebo	655	588	558	525	488
Enalapril	673	608	572	553	529
Amlodipine	683	623	599	574	535

FIGURE 14-4 Cumulative events in the CAMELOT trial.

The INVEST Trial

The International Verapamil-Trandolapril Study (INVEST) compared a calcium-channel blocker strategy to a non–calcium-channel blocker strategy for treatment of hypertension in CAD patients.[52] The trial randomized patients to baseline therapy of long-acting verapamil or atenolol. Patients not meeting Joint National Committee VII (JNC-7) blood pressure goals received trandolapril and/or hydrochlorothiazide. The primary end point was incidence of death, MI, or stroke.

The 22,576 enrolled patients all had documented CAD, and about 32% had a history of MI. Because secondary hypertensive therapy was not specified, secondary agents differed between the groups. The verapamil arm received more trandolapril than the atenolol arm (62.9% vs. 52.4%, $P < .001$) but received less hydrochlorothiazide (43.7% vs. 60.3%, $P < .001$). At a mean follow-up of 2.7 years, the primary end point did not differ between verapamil and atenolol arms (9.93% for verapamil vs. 10.17% for atenolol; RR, 0.98; 95% CI, 0.90 to 1.06, $P = 0.57$). Also, the primary end point did not differ according to treatment arm for patients with a history of MI (13.67% for verapamil vs. 14.38% for atenolol; RR, 0.95; 95% CI, 0.85 to 1.07).

Thus the INVEST and CAMELOT trials confirm that long-term calcium-channel blockade is safe and efficacious in high-risk patients, even those with a history of MI. The JNC-7 guidelines recommend that post-MI patients receive ACE inhibitors and beta-blockers; calcium-channel blockers have been given a "compelling indication" for patients with diabetes or high CAD risk. Most patients, of course, require multiple medications for blood pressure control, and all these data suggest that calcium-channel blockers are a reasonable part of the treatment plan.[53] Moreover, any concerns about an interaction with other agents, such as clopidogrel via the cytochrome P-450 enzymes, appear unfounded.[54]

Percutaneous Coronary Intervention

As an adjunct to PCI, calcium-channel blockers have shown beneficial effects on myocardial perfusion, particularly during a no-reflow state, and on restenosis. No-reflow phenomenon is slow epicardial flow and inadequate myocardial perfusion despite a patent epicardial vessel. Although the mechanisms of the no-reflow phenomenon are incompletely understood, many investigators believe that it occurs because of widespread microvascular dysfunction from overwhelming thromboembolism and reperfusion injury.

Because calcium-channel blockers are potent coronary vasodilators, investigators have used these agents in no-reflow states in hopes of opening the plugged microvasculature. Small studies support this idea. In a single-center, nonrandomized study, Hang and colleagues[55] administered IC verapamil to 50 acute MI patients undergoing primary PCI and compared these patients with 50 historic controls. Myocardial perfusion, as measured by thrombolysis in myocardial infarction (TIMI) perfusion grade, significantly differed with verapamil administration. Specifically, 42% of verapamil-treated patients had TIMI grade 3 flow compared with only 14% of control subjects ($P = .004$). Moreover, verapamil treatment was an independent predictor of TIMI grade (OR, 0.26; 95% CI, 0.12 to 0.58; $P = .001$).

Umemura and colleagues[56] confirmed this benefit of verapamil in patients with acute MI undergoing primary PCI. They performed Tc99m tetrofosmin single photon emission computed tomographic (SPECT) imaging before, immediately after, and 1 month after PCI in 101 acute MI patients. A no-reflow state occurred in 32 patients (31%). Verapamil administration independently predicted not only post-PCI TIMI grade 3 flow (OR, 22.4; $P = .002$) but also lower infarct size by 1 month according to SPECT imaging.

Corroborating both of these studies, Huang and colleagues[57] randomized 102 patients with no-reflow phenomenon in primary PCI to receive IC diltiazem, verapamil, or nitroglycerin and found more complete ST-segment resolution at 3 hours and a lower peak troponin T

level with diltiazem or verapamil compared with nitroglycerin. Finally, a recent meta-analysis found a lower 30-day wall motion index score and 2-month major adverse cardiac event (MACE) rate in ACS patients given IC verapamil during PCI.[58]

In addition to improving no-reflow states, calcium-channel blockers might also lower the incidence of restenosis. Although thus far the most effective agents for reducing neointimal hyperplasia have been sirolimus and paclitaxel, some data do exist for a beneficial effect of calcium-channel blockers in reducing restenosis. For example, recent data for benidipine, a dihydropyridine calcium-channel blocker, showed that proliferation of vascular smooth muscle cells (VSMCs) in culture was significantly reduced by benidipine.[59]

The reduction in VSMC proliferation may lead to less neointimal hyperplasia. Yamazaki and colleagues[60] showed this by randomizing 63 patients after successful coronary intervention with bare-metal stents to amlodipine 5 mg/day or quinapril 10 mg/day. Investigators performed quantitative coronary angiography before and immediately after stenting and 3 to 6 months later. Approximately 50% of each group also received IVUS at follow-up. Amlodipine-treated patients had a significantly larger minimal lumen diameter at follow-up (1.52 ± 0.53 vs. 1.88 ± 0.64 mm, $P < .01$) and a significantly smaller neointimal area (1.9 ± 0.5 vs. 2.7 ± 0.8 mm^2, $P < .01$).

This reduction in neointimal proliferation appears to lead to fewer clinical events, as demonstrated by the most recent clinical trial of calcium-channel blockade after PCI, the Verapamil Slow-Release for Prevention of Cardiovascular Events After Angioplasty (VESPA) trial.[61] The VESPA investigators randomized 700 patients after PCI using bare-metal stents to verapamil 240 mg twice daily for 6 months or placebo. Most patients (83%) received stents, and follow-up was excellent: 95% had complete clinical follow-up, and 94% received angiography at 6 months. The primary end point—a composite of death, MI, or target-vessel revascularization (TVR) by 1 year—was 19.3% for placebo patients compared with 29.3% for verapamil patients (RR, 0.66; 95% CI, 0.48 to 0.89; $P = .002$). The end point was driven by a lower risk of TVR (26.2% for placebo vs. 17.5% for verapamil; RR, 0.67; 95% CI, 0.49 to 0.93; $P = .006$). Furthermore, verapamil reduced the incidence of restenosis by 75% or more (13.7% vs. 7.8%; RR, 0.57; 95% CI, 0.35 to 0.92; $P = .014$). Despite these promising animal and clinical data, they are limited, and VESPA is a single small trial; furthermore, the advent of drug-eluting stents has significantly dampened enthusiasm for systemic therapies such as calcium-channel blockade.

Angiotensin-Converting Enzyme

Angiotensin-converting enzyme (ACE) plays an important role in the renin-angiotensin-aldosterone system. When the kidneys sense a decrease in blood volume, the juxtaglomerular apparatus secretes renin, which catalyzes the conversion of angiotensinogen (hepatically produced) to angiotensin I. ACE, secreted by pulmonary and renal endothelial cells, converts angiotensin I to angiotensin II and also degrades bradykinin and other vasoactive peptides. Angiotensin II increases sympathetic activity, promotes aldosterone and antidiuretic hormone (ADH) release, and increases arteriolar vasoconstriction. Although these actions are helpful counterregulatory mechanisms (e.g., acute blood loss), chronic activation of this system promotes atherosclerosis, cardiomyopathy, and nephropathy.[62]

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors decrease the production of angiotensin II and prevent the degradation of bradykinin. Reduction of angiotensin II lowers arteriolar resistance, which lowers blood pressure and increases stroke volume and cardiac output. In addition to direct hemodynamic effects, ACE inhibitors have pleiotropic actions that promote favorable ventricular remodeling. For example, ACE-I inhibition prevents hypertrophy and apoptosis of cardiac myocytes and decreases myocardial fibrosis through lower collagen type 1 production and altered matrix metalloproteinase activity.[63]

Percutaneous Coronary Intervention

As an adjunctive agent to PCI, ACE inhibitors might reduce periprocedural injury according to some small trials. For example, Mangiacapra and colleagues[64] randomly assigned 40 patients undergoing elective PCI to IC enalaprilat or placebo. Patients pretreated with enalaprilat had lower peak troponin T levels. However, the small scale of this trial limits generalizing the findings.

Experimental animal models suggest that ACE inhibitors might reduce restenosis after coronary intervention with bare-metal stents,[65] although few clinical data exist to support this benefit. For example, Okimoto and colleagues[66] randomized 253 patients after coronary intervention to quinapril or placebo. Binary angiographic restenosis occurred in 34.3% of the quinapril group compared with 47.7% of the placebo group ($P < .05$). Similarly, Deftereos and colleagues[67] randomized 86 patients to quinapril or placebo after PCI and found a reduction in restenosis (9.3% vs. 25.6%, $P = .047$). Conversely, in the largest randomized trial of ACE inhibition after PCI, investigators found no reduction in restenosis.[68] With the introduction of drug-eluting stents, quality evidence regarding the true efficacy of ACE inhibitors in reducing restenosis will remain elusive.

Acute Myocardial Infarction

Numerous trials have demonstrated benefit of ACE inhibitors after MI. More than two decades ago, several investigators provided evidence that ACE inhibitors greatly attenuate unfavorable remodeling after MI. For instance, Pfeffer and colleagues[69] showed decreased end-diastolic volumes and pressures in patients given captopril after anterior MI, and large clinical trials confirmed benefit in a wide range of patients after MI.

The Survival and Ventricular Enlargement (SAVE) trial[70] randomized 2231 patients with an LVEF of 40% or less to captopril or placebo within 3 to 16 days of MI. Captopril significantly reduced recurrent MI (RR, 25%; 95% CI, 5 to 40; $P = .015$), severe heart failure (RR, 22%; 95% CI, 4 to 37; $P = .019$), and all-cause mortality (20% vs. 25%, $P = .019$). The Chinese Cardiac Study (CCS-1) also randomized patients ($N = 14,962$) after acute MI to captopril or placebo.[71] Captopril significantly reduced death or heart failure (21.5% vs. 23.1%, $P = .02$). Confirming a class effect for ACE inhibitors, the Acute Infarction Ramipril Efficacy (AIRE) trial demonstrated that ramipril reduced mortality (RR, 27%; 95% CI, 11 to 40; $P = .002$).[72] Similarly, the Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico (GISSI-3), Survival of Myocardial Infarction Long-Term Evaluation (SMILE), and Trandolapril Cardiac Evaluation (TRACE) trials demonstrated comparable benefits of lisinopril, zofenopril, and trandolapril, respectively.[73-75]

Complementing these trials was the largest and most definitive trial, ISIS-4. In this extraordinary trial, 58,050 patients within 24 hours of MI (median 8 hours) were randomized in a $2 \times 2 \times 2$ factorial study to controlled-release mononitrate versus placebo, IV magnesium versus placebo, and 1 month of oral captopril (6.25 mg titrated up to 50 mg twice daily).[76] At 5 weeks, captopril reduced mortality significantly (7.19% vs. 7.69%, $P = .02$). Although the absolute benefit for the entire cohort was modest, higher-risk groups, such as those presenting with heart failure or a history of previous MI, benefited more (up to 10 fewer deaths per 1000 treated).

Although ACE inhibitors remain the first-line therapy in the angiotensin pathway to treat patients after MI, angiotensin-receptor blockers (ARBs) are important alternatives. In the VALIANT trial, 14,808 patients with recent MI and LV dysfunction were randomized to captopril, the ARB valsartan, or both. The primary end point, all-cause mortality, did not differ between captopril and valsartan, and combining the two conferred no additional benefit.[77]

CONCLUSION

Although the COMMIT trial suggests caution for acute IV beta-blockade after MI, the data are strong for the benefit of beta-blockers

in the subacute and chronic treatment of patients with MI. Indeed, strong recommendations can be made for using beta-blockers in all post-MI patients, particularly those with LV dysfunction. Similarly, in stable patients after MI, calcium-channel blockers can be a useful adjunct for hypertension and angina treatment. Finally, overwhelming evidence supports routine administration of ACE inhibitors after MI, particularly in those with LV dysfunction. Coupling these therapies with other well-established ones, such as antiplatelet agents and statins, is important for maximizing benefit for the patient and the public.

REFERENCES

1. Brodde OE, Bruck H, Leineweber K: Cardiac adrenoceptors: physiological and pathophysiological relevance. *J Pharmacol Sci* 100:323–337, 2006.
2. Emorine LJ, Marullo S, Briend-Sutren MM, et al: Molecular characterization of the human beta 3-adrenergic receptor. *Science* 245: 1118–1121, 1989.
3. Collins S, Cao W, Robidoux J: Learning new tricks from old dogs: beta-adrenergic receptors teach new lessons on firing up adipose tissue metabolism. *Mol Endocrinol* 18:2123–2131, 2004.
4. Aragon JP, Condit ME, Bhushan S, et al: Beta3-adrenoreceptor stimulation ameliorates myocardial ischemia-reperfusion injury via endothelial nitric oxide synthase and neuronal nitric oxide synthase activation. *J Am Coll Cardiol* 58:2683–2691, 2011.
5. Arner P: The beta 3-adrenergic receptor–a cause and cure of obesity? *N Engl J Med* 333:382–383, 1995.
6. Begin-Heick N: Of mice and women: the beta 3-adrenergic receptor leptin and obesity. *Biochem Cell Biol* 74:615–622, 1996.
7. Biery AJ, Ebbesson SO, Shuldiner AR, Boyer BB: The beta(3)-adrenergic receptor TRP64ARG polymorphism and obesity in Alaskan Eskimos. *Int J Obes Relat Metab Disord* 21:1176–1179, 1997.
8. Elbein SC, Hoffman M, Barrett K, et al: Role of the beta 3-adrenergic receptor locus in obesity and non–insulin-dependent diabetes among members of Caucasian families with a diabetic sibling pair. *J Clin Endocrinol Metab* 81:4422–4427, 1996.
9. Garcia-Rubi E, Calles-Escandon J: Insulin resistance and type 2 diabetes mellitus: its relationship with the beta 3-adrenergic receptor. *Arch Med Res* 30:459–464, 1999.
10. Gettys TW, Harkness PJ, Watson PM: The beta 3-adrenergic receptor inhibits insulin-stimulated leptin secretion from isolated rat adipocytes. *Endocrinology* 137:4054–4057, 1996.
11. Kadowaki H, Yasuda K, Iwamoto K, et al: A mutation in the beta 3-adrenergic receptor gene is associated with obesity and hyperinsulinemia in Japanese subjects. *Biochem Biophys Res Commun* 215:555–560, 1995.
12. Keen RW, Samaras K, Richens KL, et al: Beta 3-adrenergic receptor gene polymorphisms and determination of adiposity and fat distribution in normal female twins. *Diabetologia* 40:122–123, 1997.
13. Kim-Motoyama H, Yasuda K, Yamaguchi T, et al: A mutation of the beta 3-adrenergic receptor is associated with visceral obesity but decreased serum triglyceride. *Diabetologia* 40:469–472, 1997.
14. Lowe WL, Jr, Rotimi CN, Luke A, et al: The beta 3-adrenergic receptor gene and obesity in a population sample of African Americans. *Int J Obes Relat Metab Disord* 25:54–60, 2001.
15. Sasaki N, Uchida E, Niiyama M, et al: Anti-obesity effects of selective agonists to the beta 3-adrenergic receptor in dogs. II. Recruitment of thermogenic brown adipocytes and reduction of adiposity after chronic treatment with a beta 3-adrenergic agonist. *J Vet Med Sci* 60:465–469, 1998.
16. Petrikova M, Jancinova V, Nosal R, et al: Antiplatelet activity of carvedilol in comparison to propranolol. *Platelets* 13:479–485, 2002.
17. Ndrepepa G, Braun S, Schomig A, Kastrati A: Impact of therapy with statins, beta-blockers and angiotensin-converting enzyme inhibitors on plasma myeloperoxidase in patients with coronary artery disease. *Clin Res Cardiol* 100:327–333, 2011.
18. Gottlieb SO, Weisfeldt ML, Ouyang P, et al: Effect of the addition of propranolol to therapy with nifedipine for unstable angina pectoris: a randomized, double-blind, placebo-controlled trial. *Circulation* 73:331–337, 1986.
19. Early treatment of unstable angina in the coronary care unit: a randomised, double blind, placebo controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both. Report of The Holland Interuniversity Nifedipine/Metoprolol Trial (HINT) Research Group. *Br Heart J* 56:400–413, 1986.
20. Hohnloser SH, Meinertz T, Klingenheben T, et al: Usefulness of esmolol in unstable angina pectoris. European Esmolol Study Group. *Am J Cardiol* 67:1319–1323, 1991.
21. Brunner M, Faber TS, Greve B, et al: Usefulness of carvedilol in unstable angina pectoris. *Am J Cardiol* 85:1173–1178, 2000.
22. Ellis K, Tcheng JE, Sapp S, et al: Mortality benefit of beta blockade in patients with acute coronary syndromes undergoing coronary intervention: pooled results from the EPIC, EPILOG, EPISTENT, CAPTURE and RAPPORT Trials. *J Interv Cardiol* 16:299–305, 2003.
23. Miller CD, Roe MT, Mulgund J, et al: Impact of acute beta-blocker therapy for patients with non-ST-segment elevation myocardial infarction. *Am J Med* 120:685–692, 2007.
24. Sharma SK, Kini A, Marmur JD, Fuster V: Cardioprotective effect of prior beta-blocker therapy in reducing creatine kinase-MB elevation after coronary intervention: benefit is extended to improvement in intermediate-term survival. *Circulation* 102:166–172, 2000.
25. Chan AW, Quinn MJ, Bhatt DL, et al: Mortality benefit of beta-blockade after successful elective percutaneous coronary intervention. *J Am Coll Cardiol* 40:669–675, 2002.
26. Jackson JD, Muhlestein JB, Bunch TJ, et al: Beta-blockers reduce the incidence of clinical restenosis: prospective study of 4840 patients undergoing percutaneous coronary revascularization. *Am Heart J* 145:875–881, 2003.
27. Serruys PW, Foley DP, Hofling B, et al: Carvedilol for prevention of restenosis after directional coronary atherectomy: final results of the European carvedilol atherectomy restenosis (EUROCARE) trial. *Circulation* 101:1512–1518, 2000.
28. Wang FW, Osman A, Otero J, et al: Distal myocardial protection during percutaneous coronary intervention with an intracoronary beta-blocker. *Circulation* 107:2914–2919, 2003.
29. Uretsky BF, Birnbaum Y, Osman A, et al: Distal myocardial protection with intracoronary beta blocker when added to a Gp IIb/IIIa platelet receptor blocker during percutaneous coronary intervention improves clinical outcome. *Catheter Cardiovasc Interv* 72:488–497, 2008.
30. Park H, Otani H, Noda T, et al: Intracoronary followed by intravenous administration of the short-acting beta-blocker landiolol prevents myocardial injury in the face of elective percutaneous coronary intervention. *Int J Cardiol* 167:1547–1551, 2013.
31. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group. *Lancet* 2:57–66, 1986.
32. The MIAMI Trial Research Group: Metoprolol in acute myocardial infarction (MIAMI). A randomised placebo-controlled international trial. *Eur Heart J* 6:199–226, 1985.
33. Ibanez B, Macaya C, Sanchez-Brunete V, et al: Effect of early metoprolol on infarct size in ST-segment-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial. *Circulation* 128:1495–1503, 2013.
34. Chen ZM, Pan HC, Chen YP, et al: Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 366:1622–1632, 2005.
35. Park KL, Goldberg RJ, Anderson FA, et al: Beta-blocker Use in ST-segment Elevation Myocardial Infarction in the Reperfusion Era (GRACE). *Am J Med* 127:503–511, 2014.
36. Freemantle N, Cleland J, Young P, et al: Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 318:1730–1737, 1999.
37. Dargie HJ: Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 357:1385–1390, 2001.
38. Califf RM, Lokhnygina Y, Velazquez EJ, et al: Usefulness of beta blockers in high-risk patients after myocardial infarction in conjunction with captopril and/or valsartan (from the VALsartan In Acute Myocardial Infarction [VALIANT] trial). *Am J Cardiol* 104:151–157, 2009.
39. Lanfear DE, Jones PG, Marsh S, et al: Beta2-adrenergic receptor genotype and survival among patients receiving beta-blocker therapy after an acute coronary syndrome. *JAMA* 294:1526–1533, 2005.
40. Cresci S, Dorn GW, 2nd, Jones PG, et al: Adrenergic-pathway gene variants influence beta-blocker-related outcomes after acute coronary syndrome in a race-specific manner. *J Am Coll Cardiol* 60:898–907, 2012.
41. Terra SG, Hamilton KK, Pauly DF, et al: Beta1-adrenergic receptor polymorphisms and left ventricular remodeling changes in response to beta-blocker therapy. *Pharmacogenet Genomics* 15: 227–234, 2005.
42. McLean RC, Hirsch GA, Becker LC, et al: Polymorphisms of the beta adrenergic receptor predict left ventricular remodeling following acute myocardial infarction. *Cardiovasc Drugs Ther* 25: 251–258, 2011.
43. Cresci S, Jones PG, Sucharov CC, et al: Interaction between PPARA genotype and beta-blocker treatment influences clinical outcomes following acute coronary syndromes. *Pharmacogenomics* 9:1403–1417, 2008.
44. Beitelshees AL, Finck BN, Leone TC, et al: Interaction between the UCP2-866 G>A polymorphism, diabetes, and beta-blocker use among patients with acute coronary syndromes. *Pharmacogenet Genomics* 20:231–238, 2010.
45. Gao H, Wang F, Wang W, et al: Ca(2+) influx through L-type Ca(2+) channels and transient receptor potential channels activates pathological hypertrophy signaling. *J Mol Cell Cardiol* 53: 657–667, 2012.
46. Held PH, Yusuf S, Furberg CD: Calcium channel blockers in acute myocardial infarction and unstable angina: an overview. *BMJ* 299:1187–1192, 1989.
47. Comparison of the effects of beta blockers and calcium antagonists on cardiovascular events after acute myocardial infarction in Japanese subjects. *Am J Cardiol* 93:969–973, 2004.
48. Braunwald E, Antman EM, Beasley JW, et al: ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction–summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol* 40:1366–1374, 2002.
49. Kaplan NM: The calcium channel blocker controversy. *Hypertens Res* 19:57–64, 1996.
50. Opie LH: Calcium channel blockers in hypertension: reappraisal after new trials and major meta-analyses. *Am J Hypertens* 14: 1074–1081, 2001.
51. Nissen SE, Tuzcu EM, Libby P, et al: Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA* 292:2217–2225, 2004.
52. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al: A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA* 290:2805–2816, 2003.
53. Chobanian AV, Bakris GL, Black HR, et al: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 289:2560–2572, 2003.
54. Olesen JB, Gislason GH, Charlot MG, et al: Calcium-channel blockers do not alter the clinical efficacy of clopidogrel after myocardial infarction: a nationwide cohort study. *J Am Coll Cardiol* 57:409–417, 2011.
55. Hang CL, Wang CP, Yip HK, et al: Early administration of intracoronary verapamil improves myocardial perfusion during percutaneous coronary interventions for acute myocardial infarction. *Chest* 128:2593–2598, 2005.
56. Umemura S, Nakamura S, Sugiura T, et al: The effect of verapamil on the restoration of myocardial perfusion and functional recovery in patients with angiographic no-reflow after primary percutaneous coronary intervention. *Nucl Med Commun* 27:247–254, 2006.
57. Huang D, Qian J, Ge L, et al: REstoration of COronary flow in patients with no-reflow after primary coronary interVEntion of acute myocaRdial infarction (RECOVER). *Am Heart J* 164:394–401, 2012.
58. Su Q, Li L, Liu Y: Short-term effect of verapamil on coronary no-reflow associated with percutaneous coronary intervention in patients with acute coronary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Clin Cardiol* 36:E11–E16, 2013.
59. Arakawa E, Hasegawa K: Benidipine, a calcium channel blocker, regulates proliferation and phenotype of vascular smooth muscle cells. *J Pharmacol Sci* 100:149–156, 2006.
60. Yamazaki T, Taniguchi I, Kurusu T, et al: Effect of amlodipine on vascular responses after coronary stenting compared with an angiotensin-converting enzyme inhibitor. *Circ J* 68:328–333, 2004.
61. Bestehorn HP, Neumann FJ, Buttner HJ, et al: Evaluation of the effect of oral verapamil on clinical outcome and angiographic restenosis after percutaneous coronary intervention: the randomized, double-blind, placebo-controlled, multicenter Verapamil Slow-Release for Prevention of Cardiovascular Events After Angioplasty (VESPA) Trial. *J Am Coll Cardiol* 43:2160–2165, 2004.
62. Ferrario CM, Strawn WB: Role of the renin-angiotensin-aldosterone system and proinflammatory mediators in cardiovascular disease. *Am J Cardiol* 98:121–128, 2006.
63. Gajarsa JJ, Kloner RA: Left ventricular remodeling in the post-infarction heart: a review of cellular, molecular mechanisms, and therapeutic modalities. *Heart Fail Rev* 16(1):13–21, 2011.
64. Mangiacapra F, Peace AJ, Di Serafino L, et al: Intracoronary EnalaPrilat to Reduce MICROvascular Damage During Percutaneous Coronary Intervention (ProMicro) study. *J Am Coll Cardiol* 61:615–621, 2013.
65. Muller D, Ellis S, Topol E: Experimental models of coronary artery restenosis. *J Am Coll Cardiol* 19:418–432, 1992.
66. Okimoto T, Imazu M, Hayashi Y, et al: Quinapril with high affinity to tissue angiotensin-converting enzyme reduces restenosis after percutaneous transcatheter coronary intervention. *Cardiovasc Drugs Ther* 15:323–329, 2001.

67. Deftereos S, Giannopoulos G, Kossyvakis C, et al: Effect of quinapril on in-stent restenosis and relation to plasma apoptosis signaling molecules. *Am J Cardiol* 105:54–58, 2010.
68. Smalling RW: Redoubtable restenosis. *Circulation* 86:325–327, 1992.
69. Pfeffer M, Lamas G, Vaughan D, et al: Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. *N Engl J Med* 319:80–86, 1988.
70. Pfeffer M, Braunwald E, Moyé L, et al: Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 327:669–677, 1992.
71. Chinese Cardiac Study (CCS-1) Collaborative Group: Oral captopril versus placebo among 14,962 patients with suspected acute myocardial infarction: a multicenter, randomized, double-blind, placebo controlled clinical trial. *Chin Med J* 110: 834–838, 1997.
72. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators: Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 342:821–828, 1993.
73. Amborsioni E, Borghi C, Magnani B: The effect of the angiotensin-converting enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. *N Engl J Med* 332:80–85, 1995.
74. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and togther on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. *Lancet* 343:1115–1122, 1994.
75. Kober L, Torp-Pedersen C, Carlsen J, et al: A clinical trial of the angiotensin-converting enzyme trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med* 333: 1670–1676, 1995.
76. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,5050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet* 345:669–685, 1995.
77. Pfeffer MA, McMurray JJ, Velazquez EJ, et al: Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 349:1893–1906, 2003.

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15 The History of Balloon Angioplasty

BERNHARD MEIER

KEY POINTS

- Coronary balloon angioplasty has stood the test of time. The world's first patient is still enjoying good health with no need for coronary bypass surgery after more than 37 years.
- The slow start of balloon angioplasty was due more to the use of coronary angiography at a late stage in the disease state, which typically revealed advanced triple-vessel disease not well suited for catheter-based treatment then or today.
- The most important adjunct to the balloon, guiding catheter, and guidewire trio was the coronary stent. It drastically reduced the risk for abrupt closure and, in its drug-eluting version, the restenosis risk.
- Coronary balloon angioplasty did not initiate catheter-based cardiac therapy but transformed it into a commodity that fostered other such therapies, including electrophysiologic ablation, shunt closure, and valve treatments and culminating in the current spectacular era of percutaneous valve implantations.
- Coronary balloon angioplasty has also facilitated catheter-based treatments in a variety of other disciplines, such as gastroenterology, gynecology, neurology, and urology.
- Coronary balloon angioplasty has provided the basis for the most important clinical, educational, and industrial medical segment of modern therapy in the Western world.

Coronary balloon angioplasty, currently referred to as *plain old balloon angioplasty* (POBA), ushered in catheter-based cardiac treatment as a commodity. When POBA was introduced in 1977, it was not the first such therapy (Table 15-1), but it placed itself on top of a list of therapeutic interventions that became routine in catheterization laboratories around the world. The only three clinically relevant techniques prior to that were atrial septostomy (first reported in 1966), closure of a patent ductus arteriosus (1966), and closure of an atrial shunt (1974). Other important techniques prompted and fostered by POBA are ablations in electrophysiology (1982), mitral valve balloon dilation (1984), coronary stenting (1986), left atrial appendage closure (2001), percutaneous aortic valve replacement (2002), and (potentially) percutaneous mitral valve replacement (2012).

HISTORY OF CORONARY BALLOON ANGIOPLASTY

Serendipity led a young and ambitious physician, Andreas Roland Grüntzig (Fig. 15-1), not only to invent balloon angioplasty when hardly anybody else was even contemplating it but also to go about it in a cautious and methodological way that was hard to criticize.

The long history of the development of cardiac catheterization started with the Egyptians inserting tubes into the urethra.[1] In 1844, live cardiac catheterization was first performed by Claude Bernard in France with a thermometer inserted through the carotid artery into the left ventricle of a horse. The development of x-rays by Wilhelm Röntgen in 1895 and Werner Forssmann's self-experimentation in 1929, when he advanced a urologist's plastic tube through a cut-down in his left arm to his right atrium, are the backbones of modern human cardiac catheterization; both happened in Germany. In the United States, André Cournand and Dickinson Richards subsequently began to use cardiac catheterization for diagnostic purposes by performing invasive measurements. Coronary angiography was brought about from the United States by a fortuitous selective contrast medium injection into a right coronary artery by Mason Sones in 1958. It was perfected in the United States by Kurt Amplatz and, in particular, by Melvin Judkins, who developed a truly nonsurgical percutaneous approach benefitting from the elegant vessel access described by Sven Seldinger in Sweden.[2] The first catheter-based therapeutic procedures for arteries were performed in the early sixties by Charles Dotter in the United States.[3] He dilated stenoses in leg vessels by telescoping increasing catheter diameters through the narrowing. Eberhard Zeitler imported the technique to Germany and accumulated a significant number of patients successfully treated within a few years. He introduced Grüntzig to catheter-based vascular therapy when he hosted him for a short visit in Engelskirchen, Germany, in 1971.

The Man Behind Coronary Angioplasty

Andreas Grüntzig, whose early life and career is detailed in Box 15-1, spent a year at the Zürich University Hospital radiology department, from August 1971 to July 1972, and transferred from the angiology unit to the cardiology unit in October 1973. There he was promoted to chief resident in cardiology in March 1974 and to staff cardiologist in August 1974 by Wilhelm Rutishauser, the unit chief (see Table 15-2). This likely represents the fastest and most successful fellowship in cardiology of all time. The next promotion to senior staff cardiologist had to wait until 1980, shortly before Grüntzig left for Emory University in Atlanta, Georgia, in the United States. Grüntzig was finally nominated as full professor of cardiology and radiology there. Before in Zürich, he had been mobbed (the term had yet to be defined in that context) by jealous peers and envious superiors; this had slowed down but not stopped the evolution of POBA.

The shortcomings of the Dotter technique were its relative crudeness and the fact that the arterial entry hole of the catheter had to be as large as the final lumen achieved. This dismayed Grüntzig, so he experimented with balloons—the logical concept to introduce something small and delicate that became large and aggressive only where and when needed. Latex used for balloons at that time did not allow pressure to build up; instead, the balloons simply gained volume. Werner Porstmann experimented with balloons to the same end in Berlin, East Germany, at that time and tried to overcome this problem by "inflating" a latex balloon with liquid within a longitudinally sliced

TABLE 15-1 Evolution of Interventional Cardiology

Year	Physician	Procedure
1953	Rubio-Alvarez	Pulmonary wire valvuloplasty
1966	Rashkind	Atrial septostomy
1966	Porstmann	Patent ductus arteriosus closure
1972	Galiano	Coronary wire recanalization in acute myocardial infarction
1974	King	Atrial septal defect closure
1975	Gianturco	Coil occlusion of shunt
1977	**Grüntzig**	**Percutaneous coronary intervention (PCI)**
1979	Semb	Pulmonary balloon valvuloplasty
1981	Singer	Coarctation angioplasty
1982	Gallagher	His bundle ablation
1983	Lababidi	Aortic balloon valvuloplasty
1984	Inoue	Mitral balloon valvuloplasty
1986	Puel	Coronary stent implantation
1987	Simpson	Coronary atherectomy (debulking)
1990	Palacios	Pericardial balloon fenestration
1994	Sigwart	Transluminal ablation of septal hypertrophy
1996	Condado	Brachytherapy against coronary restenosis
1997	Oesterle	Percutaneous transmyocardial laser revascularization
2000	Bonhoeffer	Percutaneous pulmonary valve replacement
2001	Sievert	Closure of left atrial appendage
2002	Cribier	Percutaneous aortic valve replacement
2003	Feldman	Percutaneous mitral valve repair
2012	Sondergaard	Percutaneous mitral valve replacement

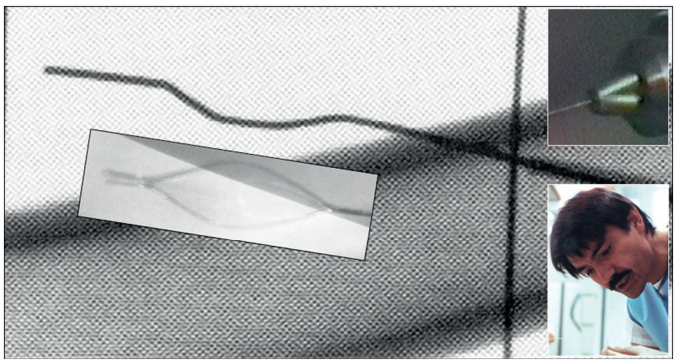

FIGURE 15-1 Rotational wire thrombectomy by Andreas Grüntzig (*right lower inset*). A household drill (*right upper inset*) rotated a wire with a C-bend. This formed a "thrashing olive" (*left inset*) that was pulled back through a thrombotic occlusion of a dog-leg artery, thereby achieving recanalization. (Courtesy Maria Schlumpf.)

BOX 15-1 Early Life and Career of Andreas Grüntzig

Andreas Grüntzig was born on June 25, 1939, in Dresden, Germany. Important stages of his life are detailed in Table 15-2.[4] His mother was a piano teacher and his father was a geographer and meteorologist, but his father's skills would be abused and his life wasted by the Third Reich before World War II was over. Grüntzig's mother, henceforth a widow, struggled to raise two talented and ambitious sons and planned a permanent emigration to Argentina. It turned out to be a rather short stay (1950-1952), and the family returned to Leipzig, East Germany. Both sons attended high school and allegedly were slated for blue collar professions by the East German regime, but that was not what their mother had in mind. In 1957, about 4 years before the Wall went up, the threesome fled the dull postwar German Democratic Republic to Heidelberg in West Germany, where the two sons studied medicine. Johannes, the elder son, became an academic ophthalmologist; Andreas attended medical school from 1958 through 1964 and became the father of balloon angioplasty.

Andreas Grüntzig planned to be an internist after training in Germany and England in a variety of specialties, including epidemiology. He applied at the Zürich University Hospital in Switzerland to train under Robert Hegglin, one of the leading clinicians in Europe at the time and the author of the then most coveted textbook of internal medicine in the German language. Hegglin was impressed by the young applicant, and a contract was issued. However, just 3 weeks after Grüntzig started his job in Zürich in 1969, Hegglin succumbed to a ruptured aortic aneurysm, so one great man literally took over from another great man. A professional orphan, Grüntzig was "adopted" by Alfred Bollinger, head of the newly built unit for angiology, a discipline in some European countries that encompasses everything but open surgery for peripheral vessels, just as cardiology does for the heart. Grüntzig combined his knowledge in internal medicine and epidemiology with rapidly acquired skills in clinical angiology, oscillography, and plethysmography to become a prominent driving force in the angiology unit in no time.

Before embarking on catheter-based revascularization therapies, Grüntzig came up with a technique to quantify leg ischemia during exercise by correlating it with prolonged relaxation times of the Achilles tendon reflex.[4] The photometric technique he used had been developed to diagnose and assess hypothyroidism, but he adapted it for peripheral artery disease. He called this diagnostic tool *claudicometry*. It did not make its way into everyday practice. Oscillography and the upsurging Doppler ankle pressure measurements were more practical and more appealing; however, claudicometry was the basis of later studies on the contractility of the heart muscle under exercise stress.

In 1971, in an effort to recanalize arteries, Grüntzig shaped a C-bend on a straight wire close to its tip, passed it through a dog's hind leg artery obstructed by an injected thrombus, and removed the thrombus by swirling the wire with the help of a household drill attached to its outside end (see Fig. 15-1). The rapidly rotating C-bend on the wire looked on fluoroscopy like an olive commensurate in size with the vessel diameter. It hashed the thrombus on pull-back, sending innocuous tiny fragments to the periphery. The vessel was subsequently recanalized and looked normal. Some initial experiments with laser equipment followed in 1975 but could not compete with the self-made balloon catheters already in clinical use at the time.

catheter, which contained the balloon during inflation.[5] However, at deflation, the closing slits of the catheter tended to catch on the vessel wall or dissection flaps, leading to deleterious effects in the form of an unintended atherectomy when withdrawing the catheter. Grüntzig found the solution with the help of retired plastics expert Heinrich Hopff, who still worked part-time at the Technical University just across the street from Grüntzig's office at the Zürich University Hospital (then called Cantonal Hospital). Grüntzig was quite resourceful in picking the brains of professionals and getting their practical help: he soon learned that polyvinyl chloride (PVC) can be heat-treated such that it remains constant in form, which preserves the cylindrical shape even under increasing pressure; the initial double-lumen catheters were partially constructed at home by Grüntzig, his assistant Maria Schlumpf, and their respective spouses Michaela and Walter. It is noteworthy that Hopff died in 1977, the year of the first clinical percutaneous coronary intervention (PCI) case.

Late in 1973, Grüntzig performed the first clinical peripheral artery balloon angioplasty. As he already had moved from the angiology to the cardiology unit, he was understandably tempted to carry over the promising results of peripheral balloon angioplasty to the coronary field. Coronary artery disease (CAD) was as much in the focus of medicine then as it is today, with the possibility of revascularization by coronary artery bypass grafting (CABG) less than 10 years old at the time. Many considered the idea of tampering with the coronary arteries of the beating heart of an awake human as heresy. Besides the lack of logistic support from Grüntzig's superiors, there was a more important reason why PCI numbers picked up slowly: At the time in Europe

TABLE 15-2 Chronicle of Andreas Roland Grüntzig's Life (1939-1985)

June 25, 1939	Birth in Dresden, Germany
1945	Primary school, Rochlitz, East Germany
1950	Moved temporarily to Argentina
1952	High school and college, Leipzig, East Germany
1957	College graduation (classical languages), Leipzig, East Germany
1957	Escape to Heidelberg, West Germany
1957	College graduation, Heidelberg, West Germany
1958	Medical school, Heidelberg, West Germany
1964	Medical doctor degree, Heidelberg, West Germany
1964	Surgery, Mannheim, West Germany
1964	Gynecology, Hannover, West Germany
1965	Internal medicine, Bad-Harzburg, West Germany
1965	Vascular surgery, Ludwigshafen, West Germany
1966	Social medicine, Heidelberg, West Germany
1967	Epidemiology, London, United Kingdom
1968	Internal medicine, Darmstadt, West Germany
Zürich, Switzerland	
October 1969	Angiology
January 1971	Internal medicine
August 1971	Radiology
July 1972	Internal medicine
October 1973	Cardiology resident
March 1974	Cardiology chief resident
August 1974	Cardiology staff
May 1977	Traveled to San Francisco to perform the first intraoperative coronary balloon dilation
September 16, 1977	First-in-man PCI performed in Zürich, Switzerland
November, 1977	Private lecturer (associate professor)
August 1980	Senior staff
United States	
October 1980	Professor of cardiology and radiology, Atlanta, Georgia
October 27, 1985	Death as pilot in a plane crash, Forsyth, Georgia

Meier B: The first angioplasties in Zurich. In Bertrand ME, editor: *The evolution of cardiac catheterization and interventional cardiology,* St. Albans, UK, 2006, Latric Press and the European Society of Cardiology, pp 61-74.

as elsewhere, coronary angiography was considered indicated only for patients whose CAD had proved truly refractory to several antianginal drugs for an extended period of time. Hence coronary angiograms, once they were finally done, typically revealed triple-vessel disease with compromised left ventricular (LV) function. PCI initially targeted early disease.

For almost 2 years, Grüntzig was ready to start PCI but could not find a suitable patient. A couple of weeks after the first coronary balloon catheter had been delivered to him by the local Schneider company, producer of his peripheral balloon catheters in parallel to the American company Cook, a first PCI case was attempted on March 22, 1976.[4] But it did not get far. A 73-year-old man cared for in the intensive care unit for the better of 2 weeks for refractory unstable angina with recurrent myocardial infarction (MI) was presented to Grüntzig. Cardiac surgery had turned him down for good for poor general health, including advanced triple-vessel CAD, poor LV function, and complete occlusion of the descending aorta. Although far from what Grüntzig considered a good first case, he reluctantly agreed to an attempt with PCI. Having to access through an arm artery with the bulky guiding catheter of the time, he failed to properly cannulate the left main stem coronary artery, and a balloon catheter was never introduced. The patient succumbed to his untreatable disease 2 days later.

During his quest to find a suitable first patient, Grüntzig traveled to San Francisco, California, in May of 1977, where he joined the team of Richard Myler, an invasive cardiologist, and Elias Hanna, a cardiac surgeon, to perform four cases of intraoperative balloon dilations, the first one on May 9, 1977. Subsequent angiograms proved patent, both the dilated segments and the simultaneously placed bypass grafts. Myler had invited Grüntzig after being intrigued by a poster Grüntzig had presented at the November 1976 American Heart Association meeting. It portrayed coronary balloon angioplasty in eight closed-chest dogs with promising follow-up histology.

First-in-Man Coronary Angioplasty

It took another 6 months until the ideal patient was finally found. Grüntzig had just returned from another week in San Francisco, looking in vain for a patient on whom to perform the first-in-man PCI there, when I presented him with a patient his age (38 years): a heavy smoker in good general health who suddenly had been caught by exertional and rest angina episodes that were poorly controlled by nitrates and beta-blockers prescribed at a peripheral hospital. He was transferred to Grüntzig's hospital in Zürich on September 13, 1977, and underwent an exercise stress test (a test avoided nowadays in such an unstable situation). It showed transient, massive anterior ST-segment elevation accompanied by chest pain. On September 14, 1977, coronary angiography revealed a tight proximal stenosis of the left anterior descending (LAD) coronary artery.

Grüntzig looked at the coronary angiogram I presented to him, beamed at me, and took me straight to the patient to talk to him. Today this would be called gaining "informed consent." Both the patient and I recall that Grüntzig was quite frank about the possibility that the proposed world premiere PCI procedure could end up with the need for emergency CABG. In fact, the patient had been informed the day before that CABG was going to be his treatment, and he literally jumped at the chance to avoid it. Sharing a room with patients who had undergone CABG, he had been frightened by their tales of postoperative sufferings and scars. The PCI procedure was slated for the following day, September 16, 1977. The support of Åke Senning, the chief of cardiac surgery and a pioneer in his own right; Marko Turina, Senning's associate; and Walter Siegenthaler, Grüntzig's supreme boss, had remained valid since the go-ahead granted more than a year prior. And there was no such thing as a medical ethical committee to bother with at that time in the country of Switzerland.

About 10 people, just about twice as many as usual, crowded the catheterization laboratory. The roller pump to perfuse the central lumen of the balloon catheter was readied. It was not going to be used for this case or for any elective PCI case ever. The lesion was easily crossed, and the balloon inflation that lasted for just seconds was tolerated without any symptoms or change in heart rhythm or systemic pressure. Looking at the fuzzy contrast injection run on fluoroscopy with the poor resolution of the time following the world's first therapeutic coronary balloon inflation, someone in the room pointed out a stenosis of the first diagonal branch taking off immediately distal to the lesion (Fig. 15-2). Grüntzig, pleased with the nice distal pressure recorded at the tip of the nonsteerable balloon catheter (Fig. 15-3), thought to see it, too, and retracted and readvanced the balloon catheter. Its soft wire tip effortlessly entered the diagonal branch. There Grüntzig executed another inflation. Only when the 35-mm film was processed did he realize that there had been absolutely no need for this. Although this case was not only the birth of PCI but also of surgical standby, there was no permanent presence of a surgeon in the room. Three different cardiac surgeons did drop in and out, hardly realizing that what they were witnessing was going to be bigger than CABG.

The case was over in virtually no time, and the angiographic result looked appealing (see Fig. 15-2), but two odd things are worth noting: First, the patient left the catheterization laboratory with a right bundle

branch block in the electrocardiogram (ECG) and only reverted to his normal ECG pattern several hours later. Second, an exercise stress test performed 2 days later still revealed transient ST-segment elevations in the anterior leads, albeit less pronounced than before the procedure. People, including Grüntzig, thought that right bundle branch block and ST-segment elevations during the early exercise stress test came with the technique; however, both findings turned out to be exquisite rarities.

The patient was discharged on anti–vitamin K oral anticoagulation and a beta-blocker, notably one with intrinsic mimetic activity since withdrawn from the market; acetylsalicylic acid was not yet in the game. Routine follow-up coronary angiographies were done about 1 month later and on the day 10 years later. A clinically prompted coronary angiography occurred 23 years later (3 instances) and 37 years later (see Fig. 15-2). In fact, the patient was going to quit smoking immediately after his historic treatment in 1977 but also decided to stop all his medications after a few months. His was of the conviction that medications taken for a long time lose their effect. When symptoms recurred for the first time after 23 years, he restarted medication, this time with acetylsalicylic acid and a statin. However, having lost his symptoms after a repeat intervention, he again stopped the medication. After his third PCI 37 years later, he appeared quite agreeable to stay on a platelet inhibitor (prasugrel) and a statin (rosuvastatin) for good, although we have yet to see the last of this.

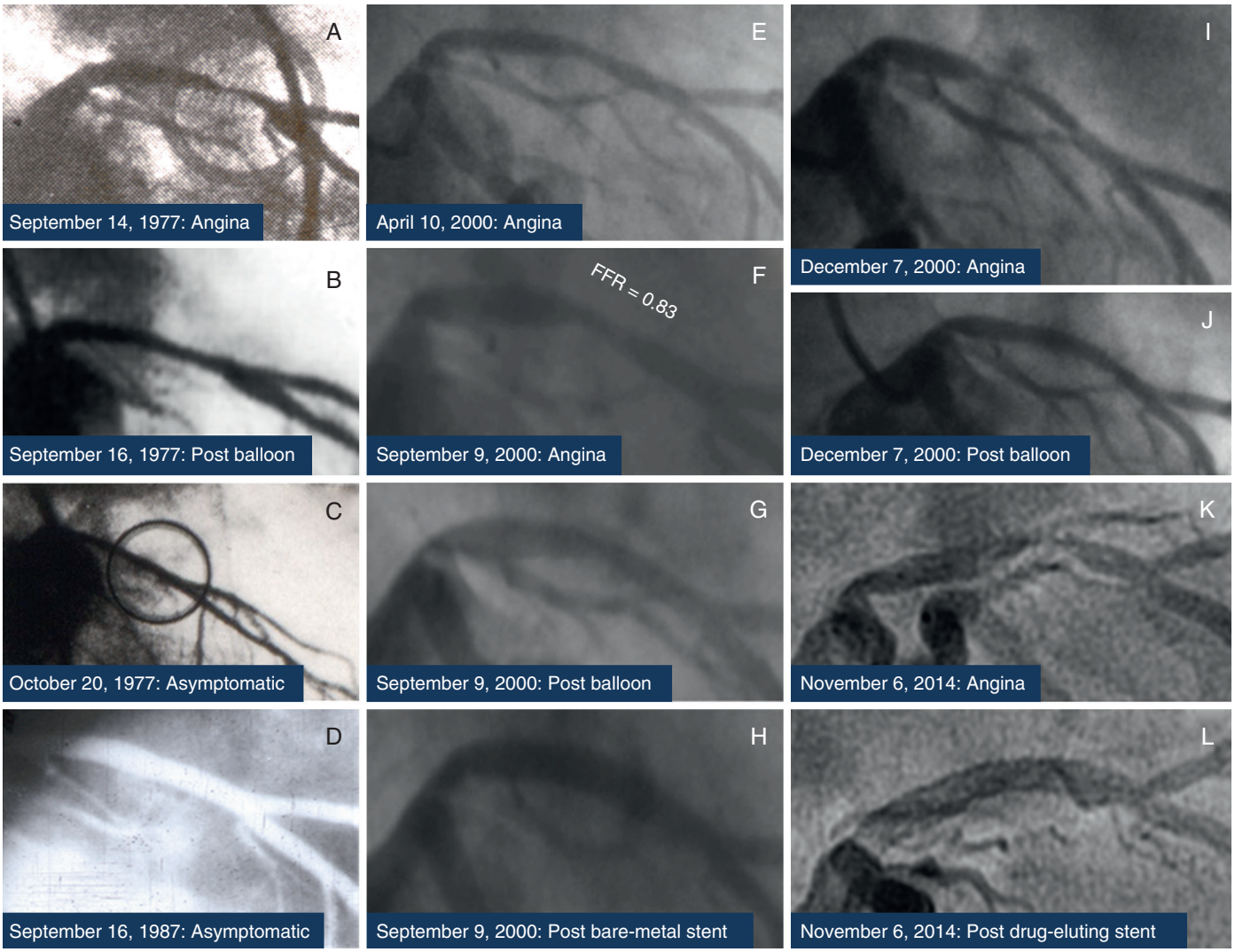

FIGURE 15-2 The world's first coronary artery lesion treated by percutaneous coronary intervention (PCI) and its 37-year follow-up, right anterior oblique projection. **A,** Lesion before the first intervention (*circle*). **B,** Result after the balloon angioplasty. **C,** Preplanned elective follow-up 1 month later showing a good result (*circle*). **D,** On the very day of the 10-year anniversary of the initial intervention, elective follow-up performed by Spencer King in Atlanta with a 4-Fr multipurpose catheter showed a good long-term result. **E,** Coronary angiogram performed in Bern, Switzerland, because of recurrent chest pain 23 years after the initial intervention. A lesion that appears to be insignificant lies just proximal to the initial one. In part not to spoil the immaculate follow-up, the patient was reassured, and no intervention was done. **F,** Symptoms persisted and the patient requested another angiogram 5 months later. The new lesion still looked borderline, and fractional flow reserve (FFR) was normal. The patient insisted on treatment this time. **G,** Result after balloon angioplasty accepted by the operator, but not by the patient, who demanded a stent. **H,** Result after bare-metal stent placement (drug-eluting stents were not yet available). **I,** Symptoms recurred after 2 months and were more severe than ever; repeat angiography at 3 months showed tight in-stent restenosis. **J,** Result after balloon angioplasty. **K,** New lesion at the proximal end of the stent led to typical exertional angina another 14 years later, now 37 years after the historical first intervention. **L,** Result after implantation of a drug-eluting stent covering the original lesion and the bare-metal stent placed in 2000.

During early follow-up, the patient, who had had a rather difficult childhood and was experiencing marriage troubles, changed spouse, profession, and lifestyle. He became some kind of a public figure in Switzerland. This was less because of his occasional television appearances as the world's first PCI patient and more because he made a remarkable career as a professional card game instructor and expert of Swiss country music. Figure 15-3 shows him around his first procedure in 1977 and the day after his (so far) last procedure in 2014, just coming out of a negative exercise stress test, the results of which are shown in Figure 15-4.

CLINICAL ADOPTION AND EVOLUTION OF PLAIN OLD BALLOON ANGIOPLASTY

The massive underestimation of the potential of POBA subsequently turning into PCI with default stenting is best exemplified by the fact that Grüntzig's first abstract on the clinical use of PCI submitted to the 1978 annual convention of the Swiss Society of Cardiology would have been rejected had it not been for Wilhelm Rutishauser, a tutor of Grüntzig's who happened to preside over the society at that time. Moreover, Grüntzig himself estimated that PCI might someday attain a share of some 15% of coronary revascularization patients, leaving 85% to CABG. Today that relation is just about reversed. Many erroneously assume that this exclusively testifies to the great development of PCI from a primitive and limited procedure to an elegant and widely applicable one. In fact, the dominance of PCI over CABG in numbers is more due to the change in the indications for invasive workup of a suspicion of CAD. In the 1970s, around the world coronary angiography was considered dangerous, expensive, and a last resort in CAD management, but this has gradually and drastically changed. The advent of PCI certainly helped to render coronary angiography a readily available first-line diagnostic tool for CAD. Using it in a timely manner typically reveals situations amenable to PCI. The technique itself has basically maintained the same indications over almost four decades: a few isolated lesions with at the most one chronic total occlusion. Add to this the inoperable patients for general health or age. In fact, world case number two—performed by Grüntzig in Frankfurt, Germany, together with Martin Kaltenbach on October 18, 1977—and world case number four were patients with left main coronary artery stenoses. This indication projected a technically easy approach (proximal lesion) for the nonsteerable fixed-wire balloon of the time. It would have prevailed in selected cases had it not been for the fact that two of the early left main patients died during the first months of follow-up. Their autopsies showed no left main occlusion, which is in keeping with the fact that there were virtually no follow-up lesion occlusions after POBA (with the exception of recanalized previous total occlusions). Nonetheless, it disqualified left main stenosis for PCI in most centers for almost two decades; stenting put it back on the agenda.

Attempts at expanding the indication range to advanced triple-vessel disease never went far. Before stents, the risk of an abrupt closure (about 7% per lesion) accumulated unacceptably if too many lesions were approached simultaneously. This was drastically curbed by stents. Yet, even with drug-eluting stents, the most recent randomized trial proved PCI inferior to CABG in advanced triple-vessel disease,[6] particularly in diabetic patients.[7] Of course, complex cases can be performed more swiftly and successfully today, compared with what was possible with the initial relatively crude equipment. The fact that single-vessel PCI still amounts for about three quarters of all PCI procedures worldwide underscores that early and simple CAD cases remain the backbone of PCI.

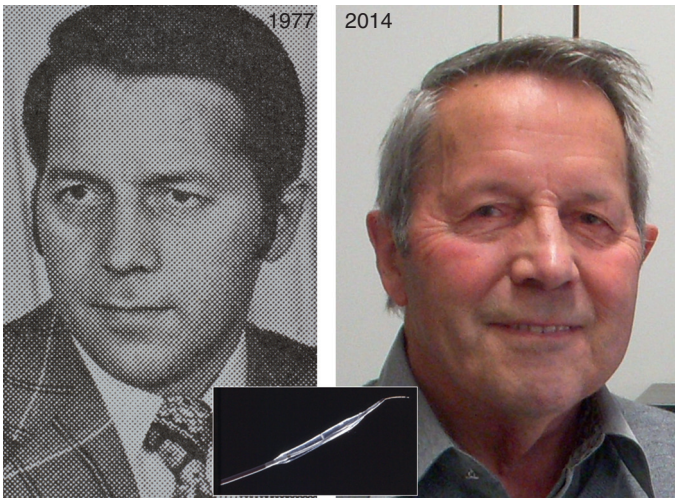

FIGURE 15-3 The world's first percutaneous coronary intervention (PCI) patient at the time of the procedure in 1977 (age 38 years) and 37 years later, the day after his most recent PCI (age 75 years). The inset shows the original Grüntzig coronary artery dilation balloon used.

A B

FIGURE 15-4 Maximal exercise stress test the day after implantation of a drug-eluting stent into the lesion at the historic site in the proximal left anterior descending coronary artery and into an additional lesion in the proximal right coronary artery. **A,** Resting electrocardiogram (ECG) depicts the right bundle branch block that temporarily appeared 37 years earlier as a consequence of the historic first procedure and relapsed for good about 30 years later. **B,** Computer rendering of two ECG leads at increasing exercise (*top three rows*) and during recovery (*bottom row*) reveals no signs of ischemia.

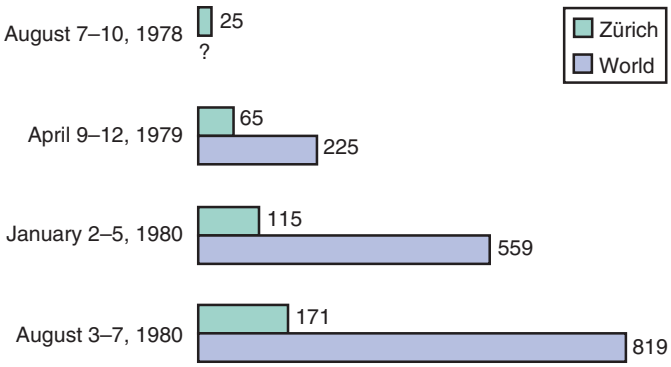

FIGURE 15-5 Live courses on coronary angioplasty in Zürich, Switzerland, and respective worldwide recorded cases from 1978 through 1980. (From Rutishauser W: A Swiss perspective of percutaneous coronary interventions: historic aspects. *Cardiovasc Med* 4:293-306, 2001.)

POBA spread to other countries quite rapidly; the first cases were performed in the United States on March 1, 1978, simultaneously by Richard Myler in San Francisco and Simon Sterzer in New York City.[8] The skeptical attitude of referring physicians, and cardiac surgeons and internists in particular, resulted in slow growth for PCI. Grüntzig performed just over 170 procedures in the first 3 years at the University Hospital of Zürich. Notably, none of these patients died in the hospital, although a number of patients, close to 10% initially, required emergency CABG, starting with patient number seven.

From its infancy, POBA brought about new terms such as *surgical standby, coronary restenosis,* and *live demonstration*. The latter referred to courses given by Grüntzig, first all by himself in Zürich and later with peers and at different locations, demonstrating the PCI cases from A to Z. The first PCI courses in Zürich took place on August 7 through 10, 1978 (28 participants), April 9 through 12, 1979 (104 participants), January 2 through 5, 1980 (171 participants), and August 3 through 7, 1980 (212 participants). On that last occasion, the combined world experience with POBA was estimated at about 800 cases (Fig. 15-5).[9] The first PCI live video broadcast from one city to another—from Atlanta, Georgia (USA) to Geneva, Switzerland—occurred on June 23, 1992, after Grüntzig's death.

Technical Modifications

It is worth noting that in the 1970s, the only place to buy a coronary balloon catheter in the world was the Schneider Medintag Company, a tiny shop at 62 Clausiusstrasse in Zürich, Switzerland. In the years preceding the introduction of the coronary stent by Jacques Puel in France in 1986,[10,11] some significant technical improvements to the three essential components—guiding catheter, balloon catheter, and guidewire—occurred, and the clinical data were scrutinized by registries and even in some randomized trials. Grüntzig had performed all his peripheral balloon angioplasties with balloons inserted over a guidewire and continued to do so after the initiation of PCI. While miniaturizing the equipment for coronary use, he anticipated from experiences with dog experiments—and from advice he received from one of his mentors, Wilhelm Rutishauser—that continuous distal perfusion with arterial blood during balloon inflation would be necessary to prevent ventricular fibrillation and death. Hence a central lumen of the catheter reserved for this was required, and it could not be blocked by a guidewire. The solution was to attach a guidewire stub to the tip of the balloon and reserve the balloon shaft for two separate channels. The first one was used for balloon filling and emptying, the second one for injecting arterial blood harvested from an artery (the opposite femoral artery was planned for this in patients) or for distal pressure measurements. The latter purpose prevailed after it had been proved that arterial perfusion was not required for short coronary occlusions in human beings. Fluoroscopy at the time provided poor resolution, and the deficient live-picture quality was a significant challenge for PCI. Early video recorders lacked any usable still-frame capability, and replay produced angiographic runs even more fuzzy than the live ones. During PCI intervention it was virtually impossible to optically assess the result after balloon dilation. Waiting repeatedly for 20 minutes or more to process the cine films was impractical. Hence, the catheter lumen initially designed for arterial perfusion was exclusively used to assess the pressure distal to the lesion before and, more importantly, after PCI. A distal pressure of less than 20 mm Hg inferior or equal to the proximal pressure (obtained from the guiding catheter tip) documented an adequate hemodynamic result. Moreover, watching this pressure for 10 or more minutes showed either a stable situation or an insidiously dropping distal pressure. The latter was a harbinger of an obstructive dissection (rarely visible on the hazy fluoroscopy pictures) with a cul-de-sac slowly filling up with blood. Overall, abrupt closures amounted to about 7% after POBA (not all of them clinically relevant because of collaterals or preinfarcted myocardium), but the risk of abrupt closure approached 50% in lesions with obviously decreasing distal pressure at the end of balloon dilation. The only thing that could be done about it was reinflating the balloon for a longer period. Long inflations were often not well tolerated by the patient because of angina, dropping blood pressure, or malignant arrhythmia. Perfusion balloons were used in such cases.[12-14] The autoperfusion principle was enabled with proximal sideholes in the balloon catheter shaft, through which blood crossed the balloon to perfuse the distal territory through the hole in the tip.

The guiding catheters of the time were 9 Fr (1 Fr = 1 Charrière unit, or 0.3 mm). The initial balloon catheter shafts were bulky and required space because of their double-lumen construction. This left little room in the guiding catheter, and contrast medium injections were difficult. Manufacturers succeeded in diminishing the balloon catheter shaft diameters, and the guiding catheter sizes could then be progressively reduced, first to 8 Fr, then to 7 Fr, and finally to 6 Fr, the current standard (Fig. 15-6). Coronary ostial obstruction (wedging) often required sideholes in 7- to 9-Fr catheters to avoid flow obstruction in the cannulated coronary artery. All major manufacturers offered prefabricated sideholes, or such holes were made by hand (Fig. 15-7). This problem virtually disappeared with 6-Fr guiding catheters. The size reduction of the equipment did not end there, rather it culminated around 1990 in PCIs performed through a diagnostic 4-Fr coronary catheter using a fixed-wire balloon (Fig. 15-8).[15]

Initially, more often than not, the balloon catheter had to be removed from the guiding catheter to obtain adequate contrast visualization of the treated lesion. With the initial fixed-wire Grüntzig balloon catheter, if another inflation was needed, the lesion had to be renegotiated with this unsteerable instrument. John Simpson used an over-the-wire system in PCI,[16] and after the introduction of truly steerable guidewires,[17] complete removal of the balloon catheter out of the guiding catheter while maintaining the guidewire position using a long guidewire (first suggested by Martin Kaltenbach[18]) was possible. Tassilo Bonzel[19] and Paul Yock came up with the idea of running only the distal portion of the balloon catheter over the guidewire exiting the balloon catheter shaft through a sidehole. The Monorail system—as I named it, referring to the Monorail train concept fashionable in the eighties (Fig. 15-9)—has since become the default technology for practically all PCI equipment. It allows the interventionalist to easily remove or exchange balloon catheters over a normal-length coronary guidewire kept in place across the lesion.

An important safety feature was the introduction of soft-tip catheters by Robert van Tassel[20] (Fig. 15-10). Another advance was the increasing selection of preshaped guiding catheters (Fig. 15-11), which reduced the common need for shaping guiding catheters with a hot-air gun or hot-water steam. Continuous improvements and simplifications were made in the indeflator device used for pressure filling and voiding of coronary balloons.[21] The pressure gauges were initially limited to 20 bar or less but later had to be adapted to balloons withstanding up to 40 bar.

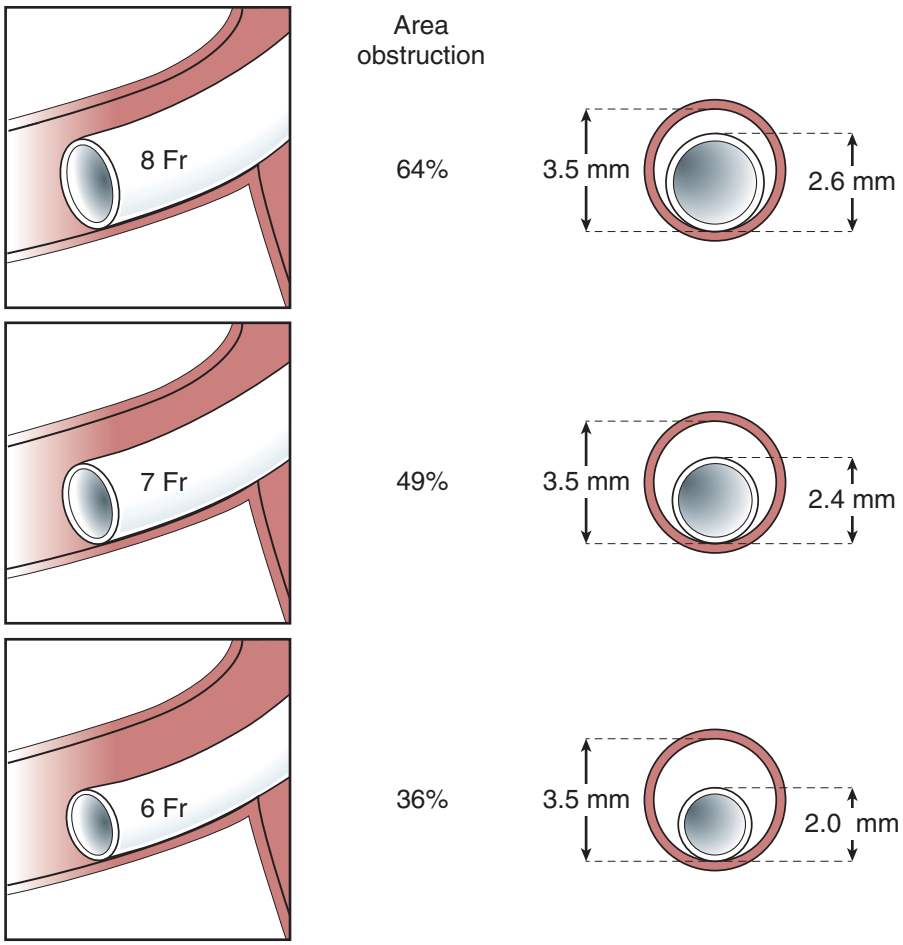

FIGURE 15-6 Decremental size of guiding catheters in French (Fr) size over time and its relation to a typical coronary artery ostial diameter of 3.5 mm.

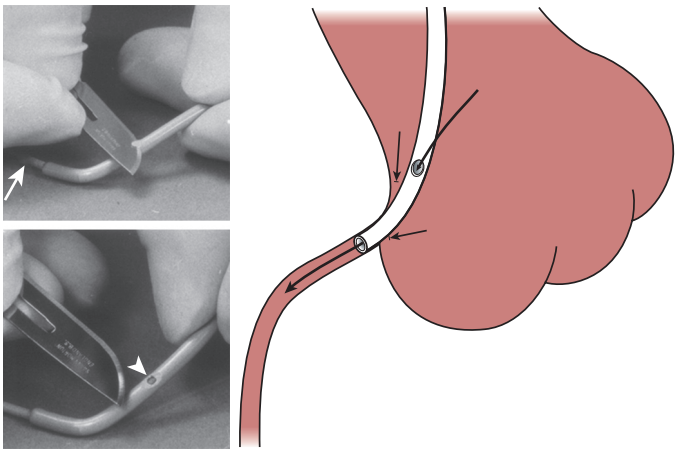

FIGURE 15-7 Sidehole carving. Holes could be produced with a simple blade (*left panels*) to avoid flow obstruction in a coronary artery because of wedging of the guiding catheter (*right panel*).

Attempts to make the tip of a fixed wire on a balloon shapeable from the outside during coronary negotiation were abandoned for lack of success.[22] A similar fate befell tapered and step-up balloon silhouettes, tandem balloons placed serially on a single catheter, and cutting balloons eqiupped with longitudinal cutting blades. One ingenious but unsuccessful balloon modification, called the *Fogarty linear extrusion balloon,*[23] used an invaginated balloon placed proximal to a stenosis; the balloon was filled under pressure, thereby making it extrude while creeping through the lesion and dilating it.

For patient surveillance during PCI, the distal pressure measurements fell into oblivion as fluoroscopy improved and high-resolution still frames became available. The replacement of urographin by low-osmolar nonionic contrast media not only improved patient safety but virtually eliminated dye-induced bradycardia. The initially mandatory right heart catheterization for monitoring of the pulmonary artery pressure and rapid access to pacing, if needed, was also abandoned over time. For swift pacing accessibility, coronary pacing was described,[24] but most operators still prefer to use right heart pacing on the rare occasions that it becomes necessary. The idea of recording the intracoronary ECG from the guidewire to depict ischemia more conspicuously and specifically[24] was proposed but never became standard. Femoral puncture closure devices (Fig. 15-12)[25,26] made life easier for operators and patients, albeit without significantly impacting safety.[27-29]

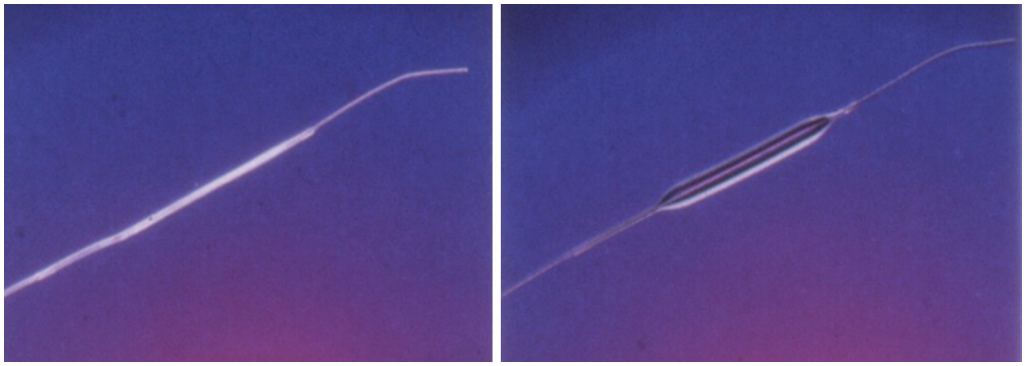

FIGURE 15-8 Ace balloon. Fixed-wire balloon enables percutaneous coronary intervention through a 4-Fr diagnostic catheter. (From Moles VP, Meier B, Urban P, et al: Percutaneous transluminal coronary angioplasty through 4 French diagnostic catheters. *Cathet Cardiovasc Diagn* 25:98-100, 1991.)

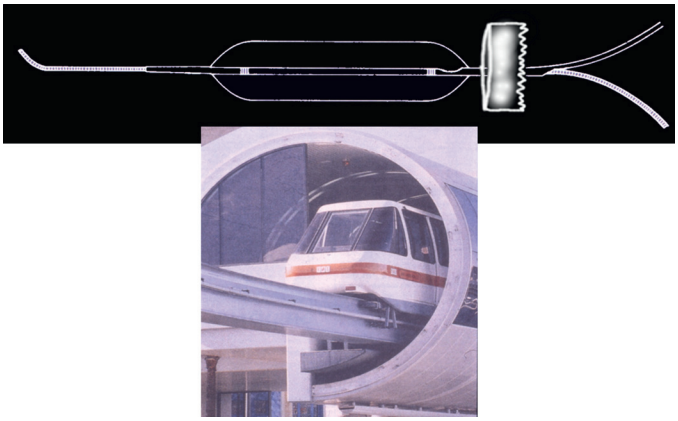

FIGURE 15-9 Monorail balloon shaft and guidewire concept (*top panel*) and its analogy to the Monorail train (*bottom panel*).

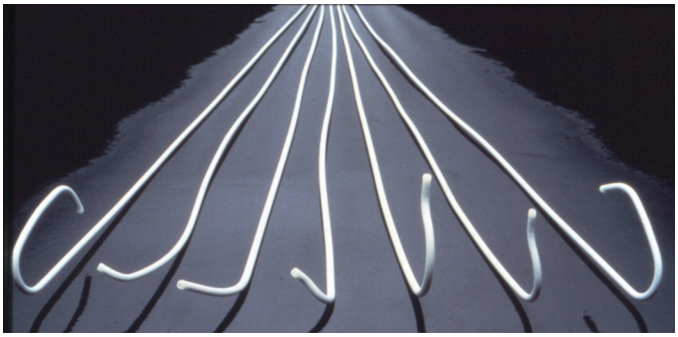

FIGURE 15-11 Typical and ever-growing array of guiding catheter shapes. (Courtesy Angiomed, Karlsruhe, Germany.)

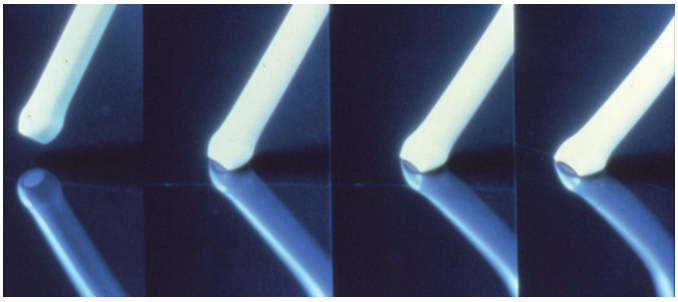

FIGURE 15-10 Soft-tip coronary catheters minimize the risk of ostial dissection. (From Van Tassel R, Gobel F, MacCarter D, Vlodaver Z. Histologic evidence of angiographic catheter-induced vascular trauma: a comparison of conventional and deformable soft-tip catheters. *Tex Heart Inst J* 15(1):39-43, 1988.)

Surgical Standby

Surgical standby, meaning that cardiac surgery had to be preinformed about a PCI case and available at any time during the case, was a sine qua non for decades and has remained one even up to now in some institutions. However, even before the coronary stent, it was proved that surgical standby does not significantly enhance overall safety.[30] Not infrequently, patients were sent to emergency surgery for a small area of ischemia produced by a failed PCI attempt. The added surgery did not salvage that area because of the time elapsed until revascularization, and surgical complications were added to the hospital course. By the time coronary stents were introduced, which reduced acute vessel occlusion during PCI from about 7% to 1%, the percentage of patients going to emergency surgery after failed PCI had already fallen to 1% to 2%; currently, it is less than 0.5%. Eliminating the organized surgical standby requirement tremendously facilitated the organization of a busy catheterization unit and reduced quarrels among teams (invasive cardiology, cardiac surgery, anesthesiology, and intensive care unit) to those rare cases where a patient had to be rushed to surgery at a difficult time. The so-called heart team was laid to rest until the recent revival in the realm of percutaneous valve replacement.

Clinical Results

The success rate, defined as improvement of the lesion without important complication, increased from the initial 70%[31] to over 95% with improved material and experience in selecting patients. These data were monitored initially by registries.[32-36]

Restenosis

The problem of restenosis was a major blemish that would be partially alleviated by stents and practically eliminated by drug-eluting stents. Many drug regimens were tried in vain. The restenosis rates, initially between 20% and 30%, got worse as busy operators began to dilate more stenoses less, compared with their initial practice, to dilate less stenoses more. POBA operators knew that if the patient left the hospital without an abrupt closure, it was extremely unlikely that he or she

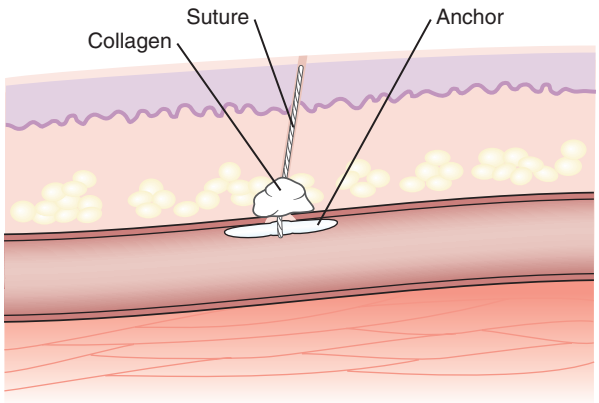

FIGURE 15-12 Graphic depiction of the concept of the AngioSeal device (St. Jude Medical, St. Paul, MN), designed by Kenneth Kensey and one of the first to be successfully applied for percutaneous femoral arterial puncture site closure. The anchor provides counterforce to squeeze a collagen plug, which is threaded over a suture onto the puncture hole in the artery. The suture is cut off at the skin surface and is resorbable, as are the remainder of the implanted parts. (From Aker UT, Kensey KR, Heuser RR, et al: Immediate arterial hemostasis after cardiac catheterization: initial experience with a new puncture closure device. *Cathet Cardiovasc Diagn* 31:228-332, 1994.)

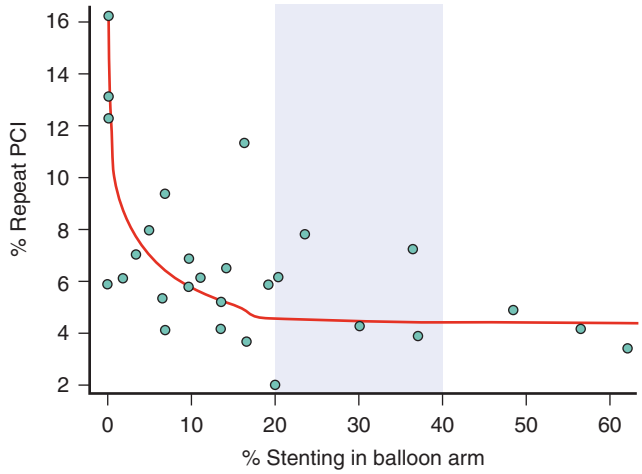

FIGURE 15-13 Need for reintervention (repeat percutaneous coronary intervention [PCI]) in the balloon arm of 29 randomized trials that comprised 9918 patients and compared plain old balloon angioplasty to bare-metal stenting according to the percentage of stents used. Whereas it is 16% with no stents used, this rapidly drops to less than 10% with less than 20% stenting. The authors conclude that "the ideal rate of stenting is difficult to determine, but our analysis suggests diminishing returns once a provisional stenting rate exceeds approximatively 20% to 40%" (*shaded area*). (From Brophy JM, Belisle P, Joseph L: Evidence for use of coronary stents. A hierarchical bayesian meta-analysis. *Ann Intern Med* 138:777-786, 2003.)

would suffer a later vessel occlusion, even in the event of restenosis. Restenosis was not a resurgence of the original plaque; rather it was lumen loss by neointimal growth. Neointima had no tendency whatsoever for spontaneous rupture and vessel thrombosis. This fact led to the suggestion to also treat mild lesions with balloon angioplasty to promote plaque sealing.[37] This concept was based on the fact that abrupt closure of mild lesions was extremely rare, and late closures were practically inexistent. Moreover, after POBA of mild lesions, restenosis was rare. The initial bare-metal stents had a thrombosis rate over the first year of 1% to 2% followed by close to 1% per year for several years. Currently, with a stent thrombosis record of modern drug-eluting stents of less than 1% over the first 4 years, the plaque-sealing concept is back in discussion.

When the restenosis rate of POBA was initially compared with that of the new bare-metal stents, the worst POBA restenosis rates (30% to 50%) were typically used to exaggerate the difference to the typical 10% of bare-metal stents. In reality, the need for reintervention had already been in the single digits before the advent of stents, at least when looking at the selected patients of the randomized stent trials (Fig. 15-13).[38]

Considering the shortcomings of POBA, it was understandable that many, including Grüntzig, were avidly searching for improvements or replacements of the technique. Parallel with the coronary stent that finally became a default complement to balloon angioplasty, a number of other techniques were clinically evaluated[39] that included directional atherectomy,[40] rotablation,[41] and low-[42] or high-speed[43-46] rotational atherectomy. All the techniques meant to remove material were subsumed under the term *debulking techniques*. The most complex of these used laser energy (called hot tips when used for chronic total occlusions).[47-50] Ultrasound heat was also tried,[51] but neither method prevailed.

Initially, new devices were considered superior to stenting for all the wrong reasons. The stent was typically used only as a bail-out technique when POBA or any of the other new devices had failed. Hence the results of stented patients yielded an infarction rate of 20% or more and thus looked noncompetitive. Other new devices had produced results that were comparable to, albeit not better than, those of POBA; yet they were only used in selected elective cases. Early attempts at setting straight the skewed general opinion about new devices and stenting went unheard at first,[52,53] but to date the stent reigns supreme, whereas the other new devices have all but disappeared. The sole exception is rotablation, which still solves an occasional case in which sleek modern balloons cannot pass or their tolerated pressure of 40 bar or more cannot crack the lesion. Radiofrequency heated balloons, meant mainly to curb restenosis, never made it to clinical use.[54] Local catheter-based radiotherapy (brachytherapy) did make it to clinical use[55] but has largely been replaced by drug-eluting stents.

Comparison to Bypass Surgery

Comparisons with CABG,[56] some randomized,[57,58] were accumulating; one of these focused on patients with diabetes.[59] Such comparisons invariably showed inferiority of PCI mostly because of an increased need for reintervention; however, this did not appreciably slow down the conquest of PCI.

Special Subgroups

Two subgroups were looked at separately, POBA for acute MI and POBA for chronic total occlusion.

Acute Myocardial Infarction

The heavy logistics, in particular those imposed by the need for surgical standby, were the main reason that PCI recanalization of an occluded coronary artery during acute MI (primary PCI) was not attempted or was at least not published. Finally, reports using PCI instead, as a complement, or as a bail-out procedure in conjunction with intracoronary or systemic thrombolysis emerged.[60-64] Three of them were randomized trials.[65-67] Two of them had warned against PCI as an adjunct to systemic thrombolysis, then the gold standard treatment for acute MI.[66,67] They seemed to put acute PCI to permanent rest much to the relief of interventional cardiologists on night duty (or their spouses for that matter), until data from Geoffrey Hartzler rekindled the interest and showed that POBA for acute MI had indeed been buried alive.[68-71] Ever since, PCI has all but supplanted thrombolysis wherever catheterization laboratories are at hand.

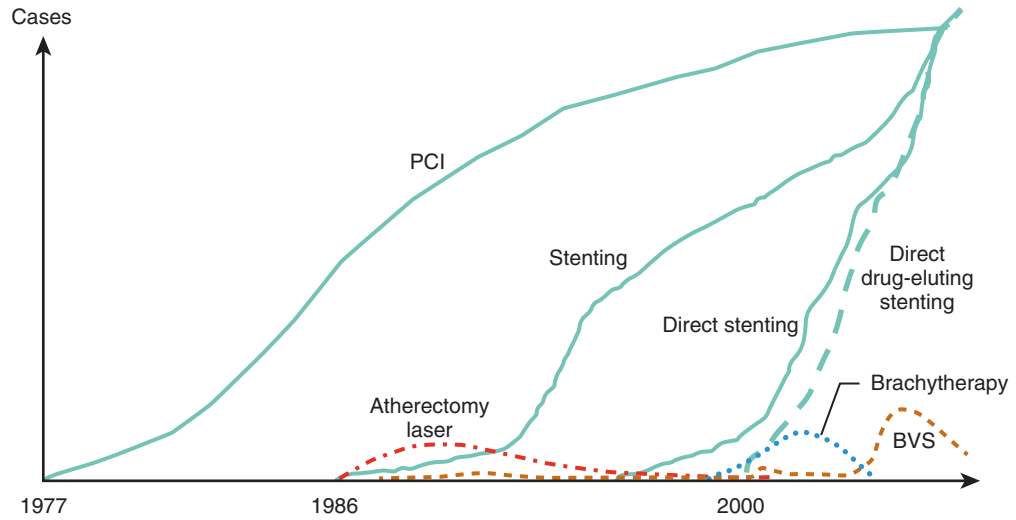

FIGURE 15-14 Evolution of percutaneous coronary intervention (PCI) from the first case with hypothetic extrapolations for the future. *BVS,* Bioabsorbable vascular scaffold.

Chronic Total Occlusion

The first chronic total occlusions (CTOs) were tackled by Grüntzig with his primitive balloon, when patients with an initial stenosis came in for PCI at the end of a long waiting period, with progression to a silent occlusion having occurred in the meantime. Because these occlusions were relatively fresh, technical success was quite rewarding. By attempts at older occlusions with steerable wires, it became evident that technical success was at best 50%. On the other hand, complications were quite rare; the most common problem of POBA at that time was abrupt vessel closure, hardly an issue with a vessel that was closed at the start. Indications were logically restricted to occlusions with visible collaterals to the distal bed. The debate is ongoing as to how long such collaterals remain recruitable in cases of reocclusion after successful opening of a CTO. Some reports on massive infarction after reocclusion of a recanalized CTO are one of the reasons to discourage operators to attempt them in the first place. In my experience, this can only happen when significant collaterals were severed during the process, which is more common with stenting, in which intimal flaps get pasted to the wall and may plug up collateral entrances. The introduction of hydrophilic guidewires and more sophisticated technical approaches, such as retrograde recanalizations through collaterals, has boosted the technical success rate but has also increased cost and risk.

Today, some subspecialized PCI operators attempt difficult CTOs with all the available new gear, while most restrict themselves to recent and short CTOs. Registries and randomized trials vary in their conclusions: some attest no clinical benefit to PCI of CTOs,[72] whereas others document benefit.[73] On top of the benefit of perfusing normally subtended viable myocardium is the potential of reversed collaterals from the recanalized vessel in case of later occlusion of the initial donor vessel.

CONCLUSION

PCI in the form of POBA got off the ground quite laboriously. Nonetheless, it has matured to become not only one of the most common medical interventions worldwide but also an important industrial, educational, and even a health-politics factor. The stent was instrumental to its success (Fig. 15-14). Notably, an initial randomized trial showed that default stenting was clinically inferior to POBA (Fig. 15-15).[74] This did not hinder the conversion of PCI into default stenting and the results of current drug-eluting stents are outstanding. I am quite sure that although Grüntzig may have frowned on stents briefly, he ultimately would have signed on as he had signed on to the launch of PCI, a gargantuan medical achievement.

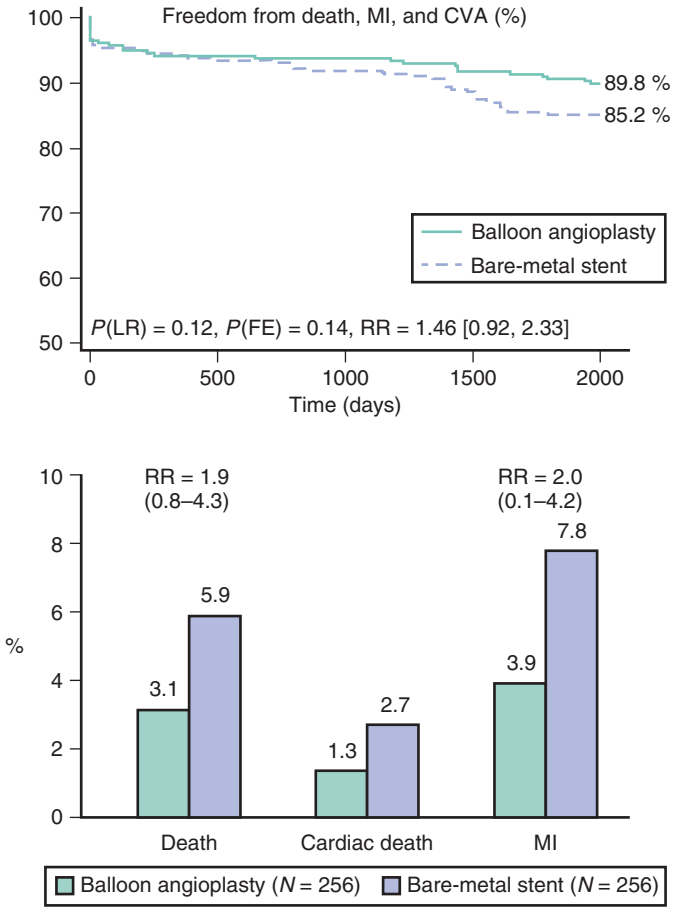

FIGURE 15-15 Five-year clinical follow-up of the BeNeStent (Belgium Netherlands Stent) I randomized comparison of coronary balloon angioplasty or bare-metal stenting. The results point to inferiority of stenting. *CVA,* Cerebrovascular accident; *FE,* Fisher exact test; *LR,* log rank test; *MI,* myocardial infarction; *RR,* relative risk. (From Kiemeneij F, Serruys PW, Macaya C, et al: Continued benefit of coronary stenting versus balloon angioplasty: five-year clinical follow-up of Benestent-I trial. *J Am Coll Cardiol* 37:1598-1603, 2001.)

REFERENCES

1. Alegria J, Holmes D: History of coronary balloon angioplasty and current indications. In Topol EJ, editor: *Textbook of interventional cardiology*, ed 6, Philadelphia, 2012, Elsevier Saunders, pp 203–208.
2. Seldinger SI: Catheter replacement of the needle in percutaneous arteriography: a new technique. *Acta Radiol* 39:368–376, 1953.
3. Dotter CT, Judkins MP: Transluminal treatment of arteriosclerotic obstruction: description of a new technic and a preliminary report of its application. *Circulation* 3:654–670, 1964.
4. Meier B: The first angioplasties in Zurich. In Bertrand ME, editor: *The evolution of cardiac catheterization and interventional cardiology*, St. Albans, UK, 2006, Latric Press and the European Society of Cardiology, pp 61–74.
5. Porstmann W: [A new corset balloon catheter for Dotter's transluminal recanalization with special reference to obliterations of the pelvic arteries]. *Rad Diagn* [Article in German] 14:239–244, 1973.
6. Head S, Davierwala P, Serruys P, et al: Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial. *Eur Heart J* 35:2821–2830, 2014.
7. Dangas GD, Farkouh ME, Sleeper LA, et al: Long-term outcome of PCI versus CABG in insulin and non-insulin-treated diabetic patients: results from the FREEDOM trial. *J Am Coll Cardiol* 64:1189–1197, 2014.
8. Myler RK, Sterzer SH: Coronary and peripheral angioplasty: historical perspective. In Topol EJ, editor: *Textbook of interventional cardiology*, ed 4, Philadelphia, 1990, Saunders, pp 187–198.
9. Rutishauser W: A Swiss perspective of percutaneous coronary interventions: historic aspects. *Cardiovasc Med* 4:293–306, 2001.
10. Puel J, Joffre F, Rousseau H, et al: [Self-expanding coronary endoprosthesis in the prevention of restenosis following transluminal angioplasty. Preliminary clinical study]. *Arch Mal Coeur* [Article in French] 8:1311–1312, 1987.
11. Sigwart U, Puel J, Mirkovitch V, et al: Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med* 316:701–706, 1987.
12. Busch U, Erbel R, Clas W, et al: [Improved occlusion tolerance time by continuous coronary perfusion with a modified Grüntzig coronary angioplasty catheter]. *Z Kardiol* [Article in German] 74:435–439, 1985.
13. Stack RS, Quigley P, Collins P, Phillips HR: Perfusion balloon catheter. *Am J Cardiol* 61:77G–80G, 1988.
14. Quigley PJ, Hinohara T, Phillips HR, et al: Myocardial protection during coronary angioplasty with an autoperfusion balloon catheter in humans. *Circulation* 78:1128–1134, 1988.
15. Moles VP, Meier B, Urban P, et al: Percutaneous transluminal coronary angioplasty through 4 French diagnostic catheters. *Cathet Cardiovasc Diagn* 25:98–100, 1991.
16. Simpson JB, Baim DS, Robert EW, Harrison DC: A new catheter system for coronary angioplasty. *Am J Cardiol* 49:1216–1222, 1982.
17. Grüntzig AR, Meier B: Current status of dilatation catheters and guiding systems. *Am J Cardiol* 53:92C–93C, 1984.
18. Kaltenbach M: The long-wire technique: a new technique for steerable balloon catheter dilatation of coronary artery stenoses. *Eur Heart J* 5:1004–1009, 1984.
19. Bonzel T, Wollschläger H, Just H: [A new catheter system for mechanical dilatation of coronary artery stenosis with exchangeable intracoronary catheters, fast flow of the contrast agent, and improved control]. *Biomed Technik* [Article in German] 31:195–200, 1986.
20. Van Tassel R, Gobel F, MacCarter D, Vlodaver Z: Histologic evidence of angiographic catheter-induced vascular trauma: a comparison of conventional and deformable soft-tip catheters. *Tex Heart Inst J* 15:39–43, 1988.
21. Cragg A, Kotula F, Castaneda-Zuniga W, Amplatz K: A simple mechanical device for inflation of dilating balloons. *Radiology* 147:273, 1983.
22. Hamm CW, Kupper W, Kuck KH, et al: Recanalization of chronic, totally occluded coronary arteries by new angioplasty systems. *Am J Cardiol* 66:1459–1463, 1990.
23. Fogarty TJ, Kinney TB: Intraoperative coronary artery balloon-catheter dilatation. *Am Heart J* 107:845–851, 1984.
24. Meier B, Rutishauser W: Coronary pacing during percutaneous transluminal coronary angioplasty. *Circulation* 71:557–561, 1985.
25. De Swart H, Dijkman L, Hofstra L, et al: A new hemostatic puncture closure device for the immediate sealing of arterial puncture sites. *Am J Cardiol* 72:445–449, 1993.
26. Aker UT, Kensey KR, Heuser RR, et al: Immediate arterial hemostasis after cardiac catheterization: initial experience with a new puncture closure device. *Cathet Cardiovasc Diagn* 31:228–332, 1994.
27. Duffin DC, Muhlestein JB, Allisson SB, et al: Femoral arterial puncture management after percutaneous coronary procedures: a comparison of clinical outcomes and patient satisfaction between manual compression and two different vascular closure devices. *J Invasive Cardiol* 13:354–362, 2001.
28. Lasic Z, Nikolsky E, Kesanakurthy S, Dangas G: Vascular closure devices: a review of their use after invasive procedures. *Am J Cardiovasc Drugs* 5:185–200, 2005.
29. Schulz-Schüpke S, Helde S, Gewalt S, et al: Comparison of vascular closure devices vs manual compression after femoral artery puncture: the ISAR-Closure Randomized Clinical Trial. *J Am Med Assoc* 312:1981–1987, 2014.
30. Meier B, Urban P, Dorsaz PA, Favre J: Surgical standby for coronary balloon angioplasty. *J Am Med Assoc* 268:741–745, 1992.
31. Grüntzig AR, Senning A, Siegenthaler WE: Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med* 301:61–68, 1979.
32. Kent KM, Bentivoglio LG, Block PC, et al: Long-term efficacy of percutaneous transluminal coronary angioplasty (PTCA): report from the National Heart, Lung, and Blood Institute PTCA Registry. *Am J Cardiol* 53:27C–31C, 1984.
33. Detre K, Holubkov R, Kelsey S, et al: Percutaneous transluminal coronary angioplasty in 1985–1986 and 1977–1981. The National Heart, Lung, and Blood Institute Registry. *N Engl J Med* 318:265–270, 1988.
34. Detre KM, Holmes DR, Jr, Holubkov R, et al: Incidence and consequences of periprocedural occlusion. The 1985-1986 National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *Circulation* 82:739–750, 1990.
35. King SB, 3rd, Yeh W, Holubkov R, et al: Balloon angioplasty versus new device intervention: clinical outcomes: a comparison of the NHLBI PTCA and NACI registries. *J Am Coll Cardiol* 31:558–566, 1998.
36. Kelsey SF, James M, Holubkov AL, et al: Results of percutaneous transluminal coronary angioplasty in women. 1985-1986 National Heart, Lung, and Blood Institute's Coronary Angioplasty Registry. *Circulation* 87:720–727, 1993.
37. Meier B: Plaque sealing by coronary angioplasty. *Heart* 90:1395–1398, 2004.
38. Brophy JM, Belisle P, Joseph L: Evidence for use of coronary stents. A hierarchical bayesian meta-analysis. *Ann Intern Med* 138:777–786, 2003.
39. Waller BF: Crackers, brakers, stretchers, drillers, scrapers, shavers, burners, welders, and melters—the future treatment of atherosclerotic coronary artery disease? A clinical-morphologic assessment. *J Am Coll Cardiol* 13:969–987, 1989.
40. Simpson JB: How atherectomy began: a personal history. *Am J Cardiol* 72:3E–5E, 1993.
41. Fourrier JL, Bertrand ME, Auth DC, et al: Percutaneous coronary rotational angioplasty in humans: preliminary report. *J Am Coll Cardiol* 14:1278–1282, 1989.
42. Kaltenbach M, Vallbracht C: Reopening of chronic coronary artery occlusions by low speed rotational angioplasty. *J Interven Cardiol* 2(3):137–145, 1989.
43. Kensey KR, Nash JE, Abrahams C, Zarins CK: Recanalization of obstructed arteries with a flexible, rotating tip catheter. *Radiology* 165:387–389, 1987.
44. Warth DC, Leon MB, O'Neill W, et al: Rotational atherectomy multicenter registry: acute results, complications and 6-month angiographic follow-up in 709 patients. *J Am Coll Cardiol* 24:641–648, 1994.
45. Webb J, Carere R, Lau E, et al: Pullback atherectomy with the Arrow-Fischell atherectomy device. *Cathet Cardiovasc Diagn* 42:79–83, 1997.
46. Meany TB, Friedman HZ, O'Neill WW: Coronary rotational atherectomy: clinical application. *J Invasive Cardiol* 3:19–24, 1991.
47. Grundfest WS, Litvack F, Forrester JS, et al: Laser ablation of human atherosclerotic plaque without adjacent tissue injury. *J Am Coll Cardiol* 5:929–933, 1985.
48. Sanborn TA, Faxon DP, Kellett MA, Ryan TJ: Percutaneous coronary laser thermal angioplasty. *J Am Coll Cardiol* 8:1437–1440, 1986.
49. Sanborn TA: Laser angioplasty. What has been learned from experimental studies and clinical trials? *Circulation* 78:769–774, 1988.
50. Litvack F, Eigler N, Margolis J, et al: Percutaneous excimer laser coronary angioplasty: results in the first consecutive 3,000 patients. The ELCA Investigators. *J Am Coll Cardiol* 23:323–329, 1994.
51. Siegel R, Fishbein M, Forrester JS, et al: Ultrasonic plaque ablation. A new method for recanalization of partially or totally occluded arteries. *Circulation* 78:1443–1448, 1998.
52. Chatelain P, Meier B, De la Serna F, et al: Success with coronary angioplasty as seen at demonstrations of procedure. *Lancet* 340:1202–1205, 1992.
53. Meier B: New devices for coronary angioplasty: the emperor's new clothes revisited. *Am J Med* 98:429–431, 1995.
54. Lee BI, Becker GJ, Waller BF, et al: Thermal compression and molding of atherosclerotic vascular tissue with use of radiofrequency energy: implications for radiofrequency balloon angioplasty. *J Am Coll Cardiol* 13:1167–1175, 1989.
55. Condado JA, Waksman R, Gurdiel O, et al: Long-term angiographic and clinical outcome after percutaneous transluminal coronary angioplasty and intracoronary radiation therapy in humans. *Circulation* 96:732–737, 1997.
56. Hannan EL, Racz MJ, McCallister BD, et al: A comparison of three-year survival after coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 33:63–72, 1999.
57. King SB, 3rd, Lembo NJ, Weintraub WS, et al: A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST). *N Engl J Med* 331:1044–1050, 1994.
58. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators: Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 335:217–225, 1996.
59. Detre KM, Guo P, Holubkov R, et al: Coronary revascularization in diabetic patients: a comparison of the randomized and observational components of the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 99:633–640, 1999.
60. Meyer J, Merx W, Schmitz H, et al: Percutaneous transluminal coronary angioplasty immediately after intracoronary streptolysis of transmural myocardial infarction. *Circulation* 66:905–913, 1982.
61. Papapietro SE, MacLean WA, Stanley AW, Jr, et al: Percutaneous transluminal coronary angioplasty after intracoronary streptokinase in evolving acute myocardial infarction. *Am J Cardiol* 55:48–53, 1985.
62. Hartzler GO, Rutherford BD, McConahay DR, et al: Percutaneous transluminal coronary angioplasty with and without thrombolytic therapy for treatment of acute myocardial infarction. *Am Heart J* 106:965–973, 1983.
63. Pepine CJ, Prida X, Hill JA, et al: Percutaneous transluminal coronary angioplasty in acute myocardial infarction. *Am Heart J* 197:820–822, 1984.
64. Prida XE, Holland P, Feldman RL, et al: Percutaneous transluminal coronary angioplasty in evolving myocardial infarction. *Am J Cardiol* 57:1069–1074, 1986.
65. O'Neill W, Timmis GC, Bourdillon PD, et al: A prospective randomized clinical trial of intracoronary streptokinase versus coronary angioplasty for acute myocardial infarction. *N Engl J Med* 314:812–818, 1986.
66. Topol EJ, Califf RM, George BS, et al: A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. *N Engl J Med* 317:581–588, 1987.
67. Simoons ML, Arnold AE, Betriu A, et al: Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous coronary angioplasty. *Lancet* 1(8579):197–203, 1988.
68. Kahn JK, Rutherford BD, McConahay DR, et al: Usefulness of angioplasty during acute myocardial infarction in patients with prior coronary artery bypass grafting. *Am J Cardiol* 65:698–702, 1990.
69. Kahn JK, Rutherford BD, McConahay DR, et al: Results of primary angioplasty for acute myocardial infarction in patients with multivessel coronary artery disease. *J Am Coll Cardiol* 16:1089–1096, 1990.
70. Kahn JK, Rutherford BD, McConahay DR, et al: Catheterization laboratory events and hospital outcome with direct angioplasty for acute myocardial infarction. *Circulation* 82:1910–1915, 1990.
71. Meier B: Balloon angioplasty for acute myocardial infarction. Was it buried alive? *Circulation* 82:2243–2245, 1990.
72. Hochman JS, Lamas GA, Buller CE, et al: Coronary intervention for persistent occlusion after myocardial infarction. *N Engl J Med* 355:2395–2407, 2006.
73. Khattab A, Meier B: Chronic total occlusion. In Topol E, Teirstein P, editors: *Textbook of interventional cardiology*, ed 6, Philadelphia, 2012, Saunders, pp 312–322.
74. Kiemeneij F, Serruys PW, Macaya C, et al: Continued benefit of coronary stenting versus balloon angioplasty: five-year clinical follow-up of Benestent-I trial. *J Am Coll Cardiol* 37:1598–1603, 2001.

16 Bare-Metal and Drug-Eluting Coronary Stents

TULLIO PALMERINI | AJAY J. KIRTANE | GREGG W. STONE

KEY POINTS

- Bare-metal stents (BMSs) overcome many of the drawbacks of balloon angioplasty but are limited by restenosis, which develops in 20% to 40% of cases.
- Drug-eluting stents (DESs) consist of a metallic stent coated with a drug carrier vehicle, usually a polymer, that controls the dose and timing of the elution of an antiproliferative agent, and they have been shown to significantly reduce in-stent late loss, resulting in reduced rates of angiographic and clinical restenosis.
- First-generation DESs, including sirolimus- and paclitaxel-eluting stents, have resulted in similar rates of mortality and myocardial infarction (MI) as BMSs in a broad spectrum of patients and lesions; however, concern over an increased rate of late stent thrombosis led to reliance on extended dual-antiplatelet therapy (DAPT), and studies have demonstrated an increase in stent thrombosis and MI beyond 1 year with these devices.
- Second-generation DESs have been developed to overcome the drawbacks of their predecessors, principally by using improved stent platforms with thinner struts and enhanced deliverability and more biocompatible or bioabsorbable polymers compared with first-generation devices.
- Not only have second-generation DESs been shown to be safer and more effective than first-generation DESs, they may also be safer than BMSs. The enhanced safety of these second-generation stents is especially apparent in specific high-risk and complex situations, including acute MI, bifurcation lesions, chronic total occlusions, diabetic patients, and saphenous vein grafts. The utility of DESs compared with bypass surgery has also become accepted in some but not all cases of left main and multivessel disease.
- The improved safety profile of second-generation DESs has challenged the notion of prolonged DAPT after DES implantation. Evidence has emerged that in low-risk patients, 3- or 6-month DAPT after second-generation DES implantation may be as effective as and safer than DAPT continued for 1 year. However, in patients with a low risk of bleeding and high risk of atherothrombotic events, prolonged DAPT for several years or longer after stent implantation may reduce the ongoing risk of very late stent thrombosis and may prevent MI arising from untreated atherosclerosis.
- Even with the improvements with current generation DESs, adverse ischemic events that arise from the stent site continue to accrue at late follow-up because of neoatherosclerosis, strut fractures, compliance mismatch, and altered vascular physiology. In this regard, fully bioabsorbable stents may further improve long-term outcomes, a hypothesis being tested in several ongoing large-scale randomized trials.

The history of percutaneous coronary intervention (PCI) can be described as a series of transformative steps that began with the introduction of coronary balloon angioplasty. Development of the implantable metallic stent enabled PCI to become a durable approach for the vast majority of patients with coronary artery disease (CAD) and one that most operators can apply safely. From balloons to atherectomy to lasers to bare-metal and now drug-eluting stents, the evolution of interventional cardiology has progressively and uncompromisingly advanced through the insights and inventions of thousands of physicians and scientists, coupled with the recognition of the importance of optimal adjunctive pharmacotherapy, on the foundation of thousands of randomized controlled trials (RCTs) and registries from around the world, which provide an unparalleled evidence base for daily clinical decision making. This chapter will trace the evolution and development of the coronary stent from its initial applications to treat balloon angioplasty failures to its widespread global adoption for the treatment of patients with ischemic coronary heart disease.

BARE-METAL STENT OVERVIEW

Limitations of Balloon Angioplasty and Development of the Coronary Stent

The performance of the first successful balloon angioplasty by Andreas Grüntzig on September 16, 1977, in Zurich, Switzerland, was a landmark event that heralded the inception of percutaneous management of obstructive CAD. Although this initial procedure set the stage for the millions of PCI procedures that have taken place since, stand-alone balloon angioplasty was a highly unpredictable experience. Although the majority of vessels tolerate the focal plaque dissections caused by balloon dilation and heal sufficiently to result in an adequate lumen, the injury to the vessel wall may unpredictably result in severe dissections, which along with acute recoil and chronic constrictive remodeling result in balloon angioplasty's two major limitations: *abrupt closure,* which occurs acutely or within the first several days after angioplasty; and *restenosis,* which occurs later—within months and even years, albeit rarely, after the procedure. The coronary stent was thus devised as an endoluminal scaffold to create a larger initial lumen to seal dissections and resist recoil and late vascular remodeling, thereby improving upon the early and late results of balloon angioplasty.

The first implantation of stents in human coronary arteries occurred in 1986 when Ulrich Sigwart, Jacques Puel, and colleagues[1] placed the Wallstent sheathed self-expanding metallic mesh scaffold (Medinvent, Lausanne, Switzerland) in the peripheral and coronary arteries of eight patients. Further experience with this device demonstrated high rates of thrombotic occlusion and late mortality,[2] although patients without thrombosis had a 6-month angiographic restenosis rate of only 14%, suggesting for the first time that stenting could improve late patency in addition to stabilizing the acute results obtained after conventional balloon angioplasty. Contemporaneously, Cesare Gianturco and Gary Roubin developed a balloon-expandable coil stent that consisted of a wrapped stainless steel wire resembling a clamshell. Completion of a phase II study using the Gianturco-Roubin stent to reverse postangioplasty acute or threatened vessel closure[3] led to U.S. Food and Drug Administration (FDA) approval for this indication in June 1993. However, high rates of restenosis with this device relegated its use mainly for bailout of occlusive dissections and recoil after balloon angioplasty.

While these stents were being developed and tested, in 1984, Julio Palmaz designed a balloon-expandable stainless steel slotted-tube stent. In this stent design, rectangular slots were cut into a 15-mm long thin-walled stainless steel tube, such that balloon inflation within the stent deformed these rectangular slots into diamond-shaped windows, or "cells." Although this design allowed for relatively straightforward

deployment and greater resistance to recoil than the clamshell design, the rigidity of this stent made it difficult to deliver in the coronary vasculature.

The first coronary Palmaz-Schatz stent was placed in a patient by Eduardo Sousa in São Paulo, Brazil in 1987. In 1989, a design modification was suggested by Richard Schatz that consisted of the placement of a 1-mm central articulating bridge to connect two rigid 7-mm slotted segments,[4] thus creating the 15-mm Palmaz-Schatz stent (Johnson & Johnson Interventional Systems, Warren, NJ; Fig. 16-1). The Palmaz-Schatz stent was subsequently investigated in two landmark randomized trials to compare balloon angioplasty with elective stenting. In the Stent Restenosis Study (STRESS)[5] and the Comparison of Balloon-Expandable-Stent Implantation With Balloon Angioplasty in Patients With Coronary Artery Disease (BENESTENT-1) study,[6] routine use of the Palmaz-Schatz stent was associated with a 20% to 30% reduction in clinical and angiographic restenosis within 6 to 12 months compared with conventional balloon angioplasty (Fig. 16-2). The Palmaz-Schatz stent also resulted in markedly improved initial angiographic results, with a larger postprocedural minimal luminal diameter and fewer residual dissections, which translated into a lower rate of subacute vessel closure. These results led to approval of the Palmaz-Schatz stent by the U.S. Food and Drug Administration (FDA) in 1994. Long-term follow-up up to 15 years has subsequently demonstrated a low (but not zero) rate of clinical and angiographic recurrences from years 1 to 5 after coronary stent implantation,[7,8] with slight and progressive decrements in luminal size thereafter that extend beyond 10 years.[9] The mechanisms of this late progression of disease are not entirely known, but as will be discussed later, it is usually described as "atherosclerotic transformation of neointimal hyperplasia," otherwise known as *neoatherosclerosis.*

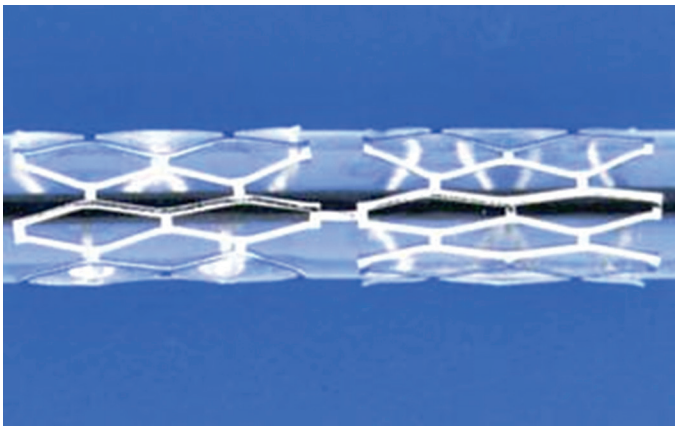

FIGURE 16-1 The Palmaz-Schatz stent. Note the articulation between the two slotted tubes.

Despite the success of the Palmaz-Schatz stent in improving the early and late results of conventional balloon angioplasty, widespread adoption of stent technology was initially hindered by high rates of subacute stent thrombosis (ST) that necessitated an intense antithrombotic and antiplatelet regimen consisting of aspirin, dextran, dipyridamole, heparin, and warfarin. Further refinements in the stent procedure and in periprocedural pharmacotherapy regimens were thus required. Colombo and colleagues[10] demonstrated reduced rates of ST with more aggressive intravascular ultrasound (IVUS)-guided deployment techniques including routine high-pressure adjunctive dilatation (>14 atmospheres), along with the use of aspirin and a second antiplatelet agent (the thienopyridine ticlopidine) rather than prolonged warfarin therapy. These modifications significantly reduced the incidence of ST to approximately 1% to 2%, along with a marked reduction in bleeding and femoral arterial complications.[11] The confirmation of these initial findings in several RCTs definitively established the superiority of DAPT with aspirin and ticlopidine over anticoagulation with warfarin for prevention of ST, and this facilitated widespread adoption of coronary stenting by the late 1990s.[12-15]

STENT DESIGN: IMPACT ON PERFORMANCE AND CLINICAL OUTCOMES

Classification

Coronary stents may be classified based on their *composition,* such as metallic or polymeric; *configuration,* slotted tube versus coiled wire for example; *bioabsorption,* either inert (biostable or durable) or degradable (bioabsorbable); *coatings,* either none or such passive coatings as heparin or polytetrafluoroethylene (PTFE) or bioactive coatings such as those that elute rapamycin or paclitaxel; and *mode of implantation,*

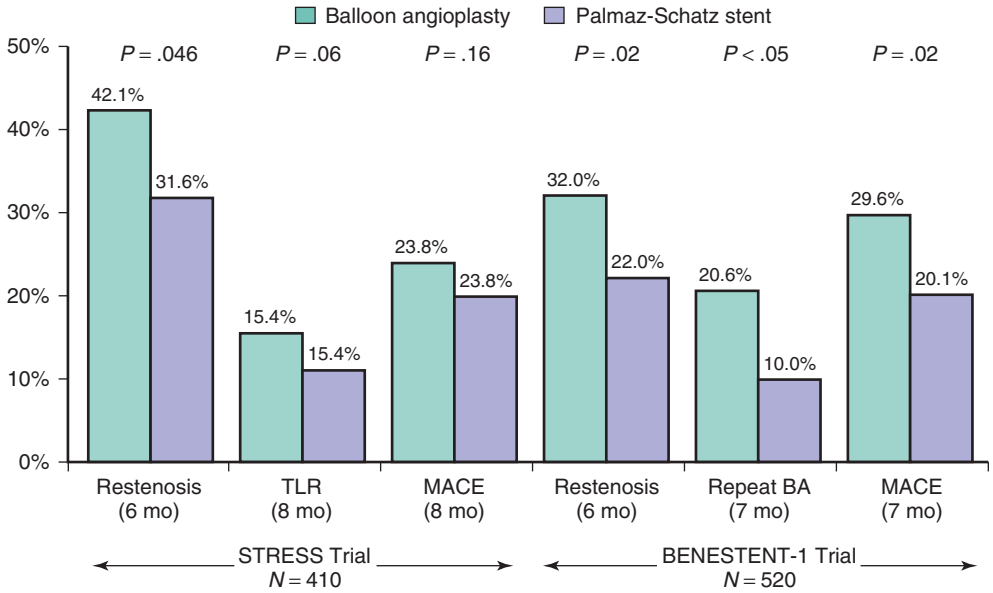

FIGURE 16-2 The pivotal early stent versus percutaneous transluminal coronary angioplasty studies. *BA,* Balloon angioplasty; *MACE,* major adverse cardiovascular event; *TLR,* target-lesion revascularization.

that is, whether the stent is self-expanding or balloon expandable. In theory, the ideal coronary stent would be made of a nonthrombogenic material and would have sufficient flexibility in its unexpanded state to allow passage through small guiding catheters and tortuous vessels. It would also have an expanded configuration to provide uniform scaffolding of the vessel wall with low recoil and maximal radial strength, and it would be conformable on bends. In addition, the ideal stent would be sufficiently radiopaque to allow fluoroscopic visualization to guide accurate placement and management should restenosis occur, but it would not be so opaque as to angiographically obscure important vascular details.

Stent Composition

In the early stent experience, the most widely used material was 316L stainless steel. More recently, cobalt-chromium and platinum-chromium alloys have been used to allow lower-profile thin stent struts (75 to 82 μm vs. 100 to 150 μm in most stainless steel stents) that maintain strength and visibility. Most self-expanding stents utilize nitinol, a nickel-titanium alloy, which after being baked at a high temperature maintains shape memory for a predetermined size and configuration.

Other than gold, which has been shown to increase restenosis, little evidence suggests that thrombosis or restenosis rates vary with the specific stent metal, although the final stages of surface finishing, smoothing, and purification or passivation may affect early thrombotic and late restenotic processes.[16] Interest is growing in polymeric and metallic fully biodegradable stents (bioabsorbable stents), which theoretically offer the advantages of increased longitudinal flexibility, compatibility with noninvasive imaging, and complete bioresorption over a period of months to a year or longer with the potential to restore underlying vascular reactivity (see Chapter 34, Bioabsorbable Stents).

Stent Configuration and Design

Stents can be assigned to one of three distinct subcategories based on design and construction elements: (1) wire coils, (2) slotted tubes/multicellular structures, and (3) modular designs. The vast majority of stents in current use are either slotted tube/multicellular or modular in design. Within these subcategories, stents are often classified as having open cells or closed cells based upon the design of the connecting links between adjacent stent struts. *Open-cell designs* tend to have varying cell sizes and shapes, which provide increased flexibility, deliverability, and side-branch access with staggered cross-linking elements to provide radial strength. *Closed-cell designs* typically incorporate a repeating unicellular element that provides more uniform wall coverage with less tendency for plaque prolapse, but this is done at the expense of flexibility and side-branch access.

Stent design may significantly impact acute and late vascular responses. Stents that possess better conformability, less rigidity, and greater circularity experimentally produce less vascular injury, thrombosis, and neointimal hyperplasia.[17,18] Clinical studies have suggested that thin stent struts may be associated with reduced neointimal hyperplasia and lower rates of restenosis.[19] In addition, an experimental study using an ex vivo modified Chandler loop to generate pulsatile flow found that thick-strutted stents (162 μm) are significantly more thrombogenic than otherwise identical thin-strutted stents (81 μm).[20] Stent design may also significantly impact longitudinal integrity of the stent, which principally depends on the number of connectors between hoops.[21] Longitudinal distortion may manifest as length change, strut overlap, or strut separation, which can obstruct the lumen and predispose to ST or restenosis.[22]

Stent Coatings

A variety of coatings have been used to attempt to reduce the thrombogenicity or restenosis of metallic stents (Table 16-1). Experimental studies have demonstrated that coating stents with inert polymers may reduce surface reactivity and thrombosis,[18] although until recently, most polymers used were found to provoke intense inflammatory reactions.[23] With the advent of drug-eluting stents came a renewed interest in the study of stent coatings, primarily to act as drug-carrier vehicles. However, concerns regarding the long-term safety of DESs and the requirement for extended duration DAPT have led to the development of new stent coatings that are either more biocompatible or are bioabsorbable. Finally, covered stents—that is, metallic stents covered by a distensible, microporous PTFE membrane—are of unquestioned clinical utility in treating life-threatening perforations. They are also used for excluding giant aneurysms, pseudoaneurysms, and clinically significant fistulae (see Chapter 28, Procedural Complications of Percutaneous Coronary Intervention). More recent is the application of polyethylene terephthalate (PET) mesh–covered stents (MGuard, Inspire MD, Tel Aviv, Israel) to minimize the risk of distal embolization in patients with ST-segment elevation myocardial infarction (STEMI; see Chapter 20, Percutaneous Coronary Intervention in Acute ST-Segment Elevation Myocardial Infarction).

TABLE 16-1 Stent Coatings Designed to Reduce Thrombogenicity

Heparin
• Multiple formulations that incorporate heparin bonding through covalent or ionic bonds or heparin complexes (Carmeda BioActive Surface [CBAS] covalently heparin-bonded Palmaz-Schatz and Bx Velocity stents, Jomed Corline Heparin surface [CHS], heparin-coated Jostent)
Carbon
• Turbostratic (Sorin Carbostent) • Silicon carbide (Biotronik Tenax) • Diamond-like films (Phytis Diamond and PlasmaChem BioDiamond)
Phosphorylcholine
• Biocompatibles' BiodivYsio stent • Medtronic's Endeavor drug-eluting stent
Other Technologies
• Ionic oxygen penetration into stent (Iberhospitex Bioinert) • CD34 antibody to capture endothelial progenitor cells (Orbus-Neich Genous technology) • Trifluoroethanol (Polyzene-F coated stent) • Nanolayer protein coating (SurModics Finale coating on the Protex stent) • Nitric oxide scavengers, including titanium-nitric oxide (Hexacath Titan stent) • Single-knitted polyethylene terephthalate (PET) fiber mesh (MGuard) • BioLinx polymer (Medtronic Resolute drug-eluting stent) • Abciximab and other glycoprotein IIb/IIIa inhibitors • Activated protein C • Hirudin and bivalirudin • Prostacyclin • Gold

BALLOON-EXPANDABLE VERSUS SELF-EXPANDING STENTS

Balloon-expandable stents (BESs) are mounted onto a delivery balloon and delivered into the coronary artery in their collapsed state. Once the stent is in the desired location, inflation of the delivery balloon expands the stent against the arterial wall, after which the stent delivery system is removed. Almost all stents implanted in human coronary arteries are balloon expandable. *Self-expanding stents* incorporate either specific geometric designs or nitinol shape-retaining metal to achieve a preset diameter and are released from a resisting sheath once placed in position. Whereas self-expanding stents are more flexible than their balloon-expandable counterparts, greater rates of restenosis have been observed with this design, presumably from chronic vascular injury, and this limits their use in coronary arteries.[24] Recently, a renewed interest in self-expanding stents with reduced outward

expansion force for the treatment of patients with acute coronary syndromes or vulnerable plaque has surfaced.[25-27]

INDICATIONS FOR CORONARY STENTING AND COMPARISON WITH BALLOON ANGIOPLASTY

Stenting After Failed Balloon Angioplasty

Stents may be used either on a routine (planned) basis or after failed balloon angioplasty for acute or threatened vessel closure ("bail-out" stenting). One of the major benefits of stenting—indeed, the initial reason for the genesis of stents—is the ability to reverse abrupt closure due to dissection and recoil, thus eliminating the need for high-risk emergency bypass surgery.[28] These data—coupled with the fact that compared with balloon angioplasty, routine stent implantation provides superior acute results and greater event-free survival in almost every patient and lesion subtype studied to date—have for the most part relegated balloon dilation to the rare lesion that is too small to stent (<2.0 mm), or to which a stent cannot be delivered because of excessive vessel tortuosity or calcification, or in patients who cannot tolerate thienopyridines or when those are contraindicated.

Routine Stenting During Percutaneous Coronary Intervention

The utility of routine stent implantation as a modality to reduce acute vessel closure and late restenosis was first demonstrated in the STRESS and BENESTENT-1 trials, which enrolled patients undergoing PCI of discrete, focal lesions.[5,6] As a result, the types of lesions treated in these trials—discrete de novo lesions coverable by one stent, with a reference vessel diameter (RVD) of 3.0 to 4.0 mm—became known as "Stress/Benestent" lesions to differentiate them from more complex stenoses. Despite initial concerns regarding diminished safety and efficacy of coronary stents, which were also more costly than balloon angioplasty alone, and with more generalized use of these devices,[29] numerous randomized trials and observational studies that compared stenting with balloon angioplasty demonstrated an advantage to coronary stenting over conventional balloon angioplasty across a wide range of patient and lesion subsets.[30-32]

DRUG-ELUTING STENTS: OVERVIEW

Limitations of Bare-Metal Stenting

By the late 1990s, stent implantation had become the predominant treatment for most patients with CAD as a result of more predictable acute and late angiographic results compared with those of conventional balloon angioplasty, atherectomy, and laser therapy. Improvements in procedural technique, including IVUS guidance, more effective antiplatelet regimens, and the introduction of increasingly lower profile, more flexible, more deliverable devices additionally contributed to the ascendancy of stenting. With improvements in stent deliverability and reductions in rates of subacute ST to less than 1%, restenosis emerged as the major persistent limitation of coronary stenting. Although coronary stents increase acute luminal diameters to a greater extent than balloon angioplasty, with greater acute gain, the greater vascular injury caused by stent implantation compared with balloon angioplasty elicits an exaggerated degree of neointimal hyperplasia that results in greater decreases in luminal diameter (i.e., late loss [LL]).[5,6] Of note, however, comparing stents with balloon angioplasty, the mean incremental gain in luminal dimensions with stenting is statistically greater than the mean incremental increase in LL, resulting in a larger net gain in minimal luminal dimensions. This observation led Kuntz and colleagues[33,34] to formulate the "bigger is better" concept: the greater the acute gain, the greater the late gain and the lower the ultimate rate of restenosis. Nonetheless, even with optimal stent implantation, restenosis after BMS implantation still occurred in approximately 20% to 40% of patients within 6 to 12 months, in part because more complex patient and lesion subsets were treated than in the balloon angioplasty era. As such, coronary restenosis became known as the "Achilles heel" of coronary stenting, with significant resources devoted to its prevention and treatment (see Chapter 33, Restenosis).

DESs maintain the mechanical advantages of a BMS while delivering an antirestenotic pharmacologic therapy locally to the arterial wall, and they have been shown to effectively and safely reduce the amount of in-stent tissue that accumulates after stent implantation, resulting in significantly reduced rates of clinical and angiographic restenosis. These devices were designed specifically to prevent the neointimal hyperplasia that results after conventional BMS placement, and they have been highly successful in this regard. In numerous randomized trials, the reduction in neointimal hyperplasia that occurs with a DES, compared with a BMS, has been shown to result in a 50% to 75% reduction in binary angiographic restenosis and target-lesion revascularization (TLR).[35-37] The initial results of the pivotal randomized trials that led to device approval have been replicated and validated in numerous subsequent trials and real-world registries across the spectrum of disease and lesion subtypes.[38,39]

Components of Drug-Eluting Stents

The three critical components of a DES that must be optimized to ensure its safety and efficacy are (1) the stent itself, including its delivery system; (2) the pharmacologic agent being delivered; and (3) the drug carrier vehicle, which controls the drug dose and pharmacokinetic release rate (Fig. 16-3).

Drug-Eluting Stent Designs

The stent component of early DES platforms was typically that of the predicate BMS without design modifications; that is, relatively thick strut designs composed of stainless steel. Indeed, first-generation DES designs often appropriated approved and "off-the shelf" stent designs in order to expedite device development and regulatory approval. Subsequent DESs have incorporated newer materials, thinner struts, and more flexible designs with resultant improvements in device delivery and performance.[40,41] Additionally, newer dedicated DES designs have included modifications aimed at either optimizing local drug delivery while reducing total drug dose (e.g., drug delivery limited to the abluminal direction) or modifying the stent surface to facilitate direct drug delivery and/or arterial healing following implantation (without a drug carrier vehicle per se). The latest evolution has been the introduction of drug-eluting bioabsorbable stents, wherein the stent frame is composed of a bioabsorbable polymer or metal that provides a scaffolding function for 6 to 12 months and then completely resorbs over the next 1 to 2 years, recapitulating the underlying vessel anatomy and physiology.

Basic Drug-Eluting Stent Pharmacology

Following promising cell culture and in vitro development, the antirestenotic properties of a wide range of pharmacologic agents have been tested in humans (Fig. 16-4). Among these, the two most clinically effective classes of agents are the *rapamycin analogue family* of drugs

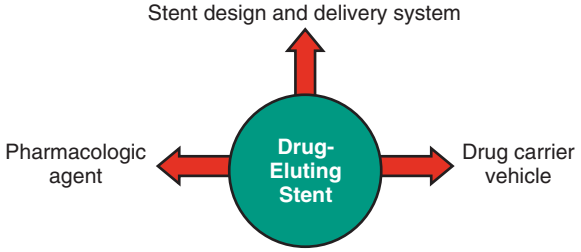

FIGURE 16-3 Components of a drug-eluting stent.

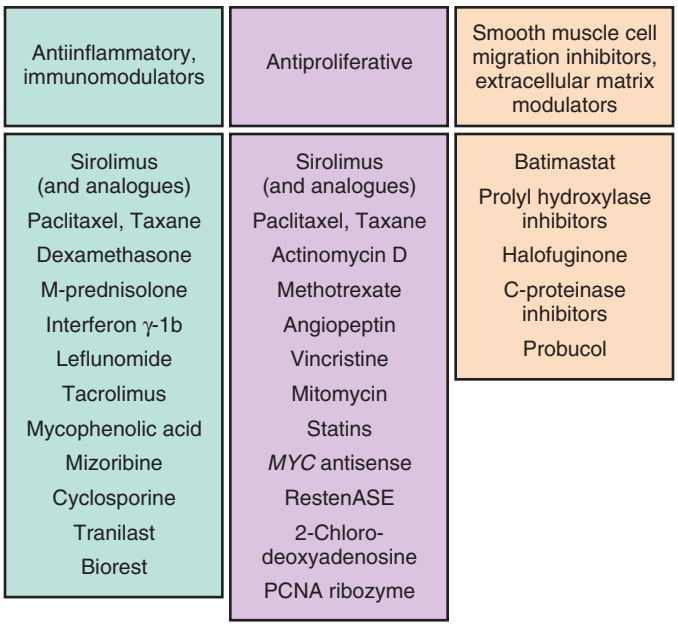

FIGURE 16-4 Potential antirestenotic agents for use with a drug-eluting stent. *PCNA,* Proliferating cell nuclear antigen. (Modified from Baim and Grossman).

and paclitaxel. The principal mechanism of action of rapamycin, also known as *sirolimus,* and its analogues—including zotarolimus, everolimus, biolimus A9, and novolimus—is inhibition of the mammalian target of rapamycin (mTOR), which prevents cell-cycle progression from the G1 to the S phase.[42] Also, mTOR is localized on platelet membranes, where it mediates platelet activation and aggregation. Inhibition of mTOR by sirolimus analogues has been shown to inhibit platelet aggregation and prevent platelet spreading on fibrinogen that coats the cover slips, and it produces platelet diasaggregation under shear flow conditions.[43] In addition, rapamycin or rapamycin analogues are able to inhibit mTOR-dependent clot retraction.[44] Although they vary somewhat in lipophilicity and potency, most rapamycin analogues have been clinically comparable in their safety and efficacy profiles. Two other rapamycin analogues that have in the past (but not the present) been used on DES platforms, tacrolimus and pimecrolimus, have a different mechanism of action: they bind directly to FK-binding protein (BP) 506 (FKBP506) and thereby inhibit the calcineurin receptor with downregulation of cytokines and inhibit smooth muscle cell activity[45]; unlike the mTOR inhibitors, these agents have not shown significant antirestenotic potential.

The other agent that has been used effectively not only in DESs but also on drug-eluting balloons (DEBs) is paclitaxel. By interfering with microtubule function, paclitaxel has multifunctional antiproliferative and antiinflammatory properties, it prevents smooth muscle migration, blocks cytokine and growth factor release and activity, interferes with secretory processes, is antiangiogenic, and impacts signal transduction.[46-48] At low doses similar to those in DES applications, paclitaxel affects the G0-G1 and G1-S phases of the cell cycle (G1 arrest), resulting in cytostasis without cell death.[46,49]

Drug-Eluting Stent Polymers and Drug Carrier Systems

The inability to predictably deliver a specific dose of active drug over the right time frame to the arterial wall led to the failure of early DES programs.[50] To ensure accurate drug dosing, a *drug delivery vehicle* became necessary, which for most first-generation stents was a durable (nonerodable) polymer. A wide range of polymer systems have since been developed and are DES specific; these are discussed in subsequent sections of this chapter. Whereas the polymer is instrumental in regulating the pharmacokinetics of drug delivery to the arterial wall, which is necessary for reduced neointimal hyperplasia, the polymer may elicit deleterious vascular responses. Specifically, histopathologic studies have demonstrated hypersensitivity and eosinophilic inflammatory reactions and delayed endothelialization with DES use that were not previously seen with BMSs.[51-53] Whether these maladaptive vascular responses are directly related to the polymer and/or to toxic reactions from the drug itself is speculative, but in animal models these effects can be attenuated by modification of the polymer vehicle.[54] It is believed that in selected patients, excessive inflammation and delayed endothelialization play a role in the development of late stent malapposition, aneurysm formation, ST, and restenosis.[51,55] For these reasons, great interest has been shown in the development of inert and biocompatible polymers, bioabsorbable polymers (BPs), and even polymer-free DESs. For example, fluorinated copolymers that coat some second-generation DESs have been shown to possess thrombosis-resistant properties in blood-contact applications and have also been shown to reduce platelet adhesion compared with an otherwise identical BMS.[20,56] On the other hand, optimizing bioresorbable polymer (BP) performance entails consideration of biocompatibility, composition, and degradation time of the polymer, which can be affected by the use of long polymer chains, decreased polymer hydrophobicity, and greater polymer crystallinity.[57] Polymer degradation can also be associated with significant inflammatory reactions and a persistent immune-mediated response to monomer breakdown product.[58]

Generational Classification of Drug-Eluting Stents

Given the rapid evolution of DES technologies, DESs are often classified into several generations of development (Table 16-2). *First-generation devices* include the two DESs that were initially approved for clinical use by most regulatory bodies, each of which utilized an early thick-strut stainless steel stent platform—which would be suboptimal by today's standards—with a durable polymer not specifically designed for biocompatibility (and prone to inflammation) to deliver either sirolimus or paclitaxel. *Second-generation devices*, currently used in the majority of DES procedures, have incorporated more deliverable, thinner-strut stents mostly made from cobalt-chromium or platinum-chromium alloys with more biocompatible polymers that elute, in most cases, rapamycin analogues. In addition, a variety of BP-based DESs have been developed that are widely used in Europe and Asia but that have not yet been approved for use in the United States. *Future-generation devices* will continue to undergo iteration, with further modifications of the base stent, delivery polymers, and use of biodegradable/bioabsorbable or polymer-free drug delivery vehicles. Finally, more than 50,000 patients outside the United States have undergone implantation of an everolimus-eluting stent with a poly-L-lactic acid (PLLA) backbone, and large-scale trials are ongoing to compare these devices to metallic DESs.

First-Generation Drug-Eluting Stents

The Cypher Sirolimus-Eluting Stent

Although the Cypher stent (Cordis/Johnson & Johnson) was the first important DES, the interest in this device is mainly historic because of discontinuation of its manufacture in 2011. The Cypher sirolimus-eluting stent (SES) was initially approved in Europe in 2002 and in the United States in 2003. Sirolimus is a highly lipophilic, naturally occurring macrocyclic lactone first isolated from *Streptomyces hygroscopicus* found in a soil sample from Easter Island, and it was initially developed as an antifungal agent. Shortly thereafter it was discovered that sirolimus also possessed potent immunosuppressive properties, and it was initially approved by the FDA as Rapamune (Pfizer, New York) for prevention of renal transplant rejection in 1999. The primary mechanism of action of sirolimus's inhibition of neointimal hyperplasia is thought to be related to its ability to bind to FKBP12 in cells; the sirolimus-FKBP12 complex then binds to and inhibits activation of mTOR, thus preventing progression of the cell cycle from the late G1

TABLE 16-2 Generational Classification of Major Durable Polymer–Based Drug-Eluting Stents

Generation	Drug	Polymer	Stent
First	**Sirolimus or Paclitaxel**	**Not Specifically Designed for Biocompatibility**	**Early BMS Platforms**
Cypher	Sirolimus	Biostable mix of poly-n-butyl methacrylate and polyethylene–vinyl acetate	Bx Velocity (stainless steel)
Taxus Express	Paclitaxel	Styrene-isobutylene-styrene	Express (stainless steel)
Taxus Liberté	Paclitaxel	Styrene-isobutylene-styrene	Liberté (stainless steel)
Second	**Rapamycin Analogues**	**Biocompatible Polymers**	**More Flexible, Thinner Strut BMS**
Endeavor	Zotarolimus	Phosphorylcholine	Driver (cobalt-chromium alloy)
Resolute	Zotarolimus	BioLinx polymer (hydrophobic and hydrophilic trilayer)	
Integrity (cobalt-chromium alloy)			
Xience V, Xience Prime, Xience Expedition	Everolimus	Vinylidene fluoride and hexafluoropropylene	Vision (cobalt-chromium alloy)
Promus Element, Promus Premier	Everolimus	Vinylidene fluoride and hexafluoropropylene	Omega (platinum-chromium alloy)

BMS, Bare-metal stent.

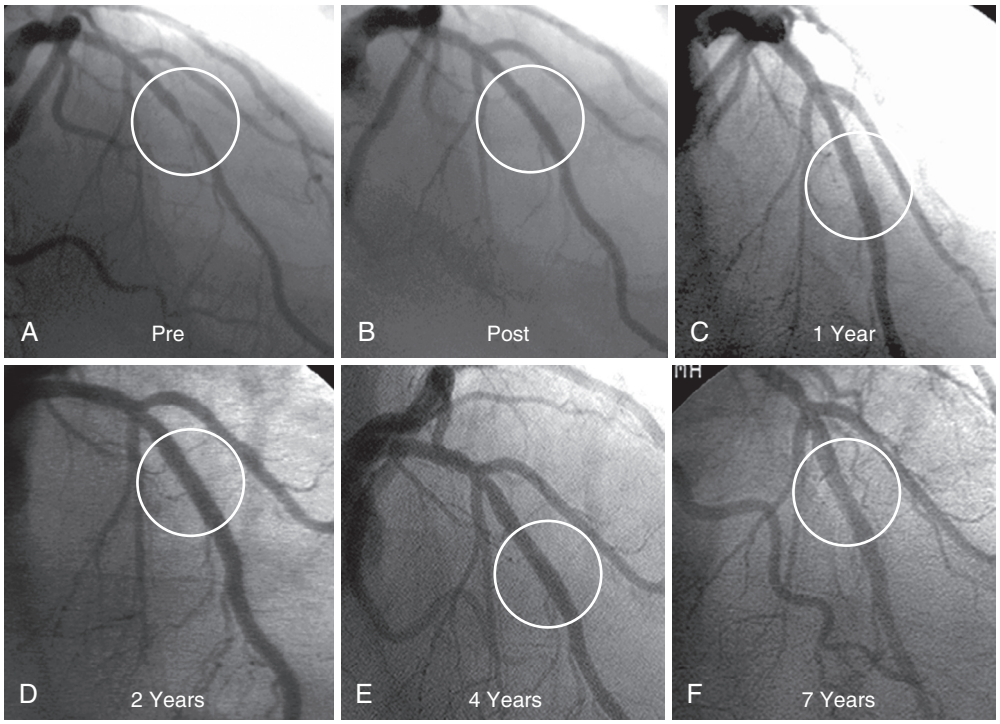

FIGURE 16-5 Seven-year follow-up of one of the initial sirolimus-eluting stent (SES) implantations from the Instituto Dante Pazzanese de Cardiologia in São Paulo, Brazil.

to the S phase.[42] The SES was demonstrated to have a marked effect on suppression of neointimal hyperplasia with low toxicity following implantation in initial small and large animal studies.[59,60]

The base stent platform for the Cypher SES was the Bx Velocity stent, a slotted tube with a closed-cell design constructed from 316L stainless steel. Human experience with the Cypher SES was reported from the first-in-man (FIM) study initiated in 1999 in 45 patients with symptomatic de novo lesions less than 18 mm in length with a reference vessel diameter (RVD) of 3.0 to 3.5 mm in native coronary arteries at the Instituto Dante Pazzanese de Cardiologia in São Paulo, Brazil, and at the Thoraxcenter in Rotterdam, The Netherlands. In this study, SES demonstrated marked suppression of neointimal hyperplasia as measured by intravascular ultrasound (IVUS) and quantitative coronary angiography (QCA) at 4 months and at 1, 2, and 4 years.[61] Serial angiography and IVUS have now been performed at 7 years and have shown continued vessel patency without further late loss (Fig. 16-5).

Following the success of SES in this initial study, several RCTs (Table 16-3),[36,62,63] meta-analyses,[38] and observational registries[64] comparing Cypher with its BMS counterpart have been performed across a wide range of patient indications and lesion subsets. In April of 2003, following the completion of the pivotal randomized Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Coronary Artery Lesions (SIRIUS) trial,[36] the Cypher SES became the first DES approved by the FDA. To date, this stent has been one of the most studied devices in modern history, with at least 20 randomized trials performed to compare the use of a commercialized Cypher SES to bare-metal stenting across a range of

TABLE 16-3 Randomized Controlled Trials Comparing Sirolimus-Eluting Stents With Bare-Metal Stents

Trial/Authors	Study Cohort	Number Randomized (Planned Angiographic Follow-Up)	Latest Follow-Up to Date	Principal Findings
RAVEL[62]	Single de novo native coronary lesions	238 (all)	5 years	At 6 months, late loss was significantly lower with the SES than with the BMS (–0.01 mm vs. 0.80 mm, $P < .001$); no restenosis was seen in the SES group at 6 months.
SIRIUS[36]	Single de novo native coronary lesions	1058 (~850)	5 years	The 9-month rate of TVF was significantly reduced with the SES versus the BMS (8.6% vs. 21.0%, $P < .001$) driven by a reduction in TLR. At 5 years, this reduction was maintained with the SES (9.4% vs. 24.2%, $P < .001$) with similar rates of death, MI, and ST.
C-SIRIUS[63]	Single de novo native coronary lesions	100 (all)	5 years (in pooled analyses)	SES was associated with greater 8-month in-stent minimum lumen diameter (2.46 mm with SES use vs. 1.49 mm with a BMS, $P < .001$).
E-SIRIUS[401]	Single de novo native coronary lesions	352 (all)	5 years (in pooled analyses)	At 8 months, minimum lumen diameter was greater with the SES than with the BMS (2.22 mm vs. 1.33 mm, $P < .001$).
MULTI-STRATEGY[191]	STEMI	745 (none)	8 months	At 8 months, the SES was associated with a reduction in TVR compared with the BMS (3.2% vs. 10.2%, $P < .001$); no differences were observed between stent types in death or MI.
TYPHOON[192]	STEMI	712 (200)	1 year	One-year TVF was lower with the SES versus the BMS (7.3% vs. 14.3%, $P = .004$). No differences were found between the SES and BMS with respect to death, MI, or ST.
MISSION![193]	STEMI	310 (all)	3 years	The SES was associated with lower in-segment late lumen loss at 9 months compared with the BMS (0.12 mm vs. 0.56 mm, $P < .001$). At 3 years, differences in TLR were attenuated (6.3% vs. 12.5%, $P = .06$).
SESAMI[194]	STEMI	320 (all)	3 years	SES was associated with lower 1-year binary restenosis compared with BMS (9.3% vs. 21.3%, $P = .032$). TLR was lower at 3 years, with no differences in death, MI, or ST.
PASEO[202]	STEMI	270 (90 PES; none)	4 years	Compared with the BMS, the SES was associated with lower TLR at 1 year (14.4% vs. 3.3%, $P = .016$) that was maintained at 4 years.
STRATEGY[195]	STEMI	175 (all)	5 years	At 8 months, TLR was lower with the SES compared with the BMS (6% vs. 20%, $P = .006$). This benefit was maintained at 5-year follow-up with no excess in ST with the SES.
Diaz de la Llera[402]	STEMI	120 (none)	1 year	SES use was associated with a nonsignificantly different rate of the primary end point of cardiac death, MI, or TLR compared with use of a BMS (6.7% vs. 11.%, $P = .40$).
SCORPIUS[403]	Diabetic patients	200 (all)	1 year	In-segment late lumen loss was lower with the SES compared with the BMS (0.18 mm vs. 0.74 mm, $P < .001$) and had lower MACE rates.
DIABETES[303]	Diabetic patients	160 (all)	2 years	SES use was associated with lower late lumen loss at 9 months (0.06 mm vs. 0.47 mm, $P < .001$). At 2 years, the SES was associated with a lower rate of TLR compared with the BMS (7.7% vs. 35.0%, $P < .001$).
DECODE[404]	Diabetic patients	83 (all)	1 year	Mean in-stent late lumen loss at 6 months was lower with the SES compared with the BMS (0.23 mm vs. 1.10 mm, $P < .001$).
SCANDSTENT[405]	Complex CAD	322 (all)	3 years	SES use was associated with greater MLD at 6 months than BMS use (2.48 mm vs. 1.65 mm, $P < .001$). At 3 years, TLR was significantly reduced with the SES (4.9% vs. 33.8%, $P < .001$).
PRISON II[256]	CTO	200 (all)	4 years	The SES had significantly lower 6-month binary in-segment restenosis rates than the BMS (7% vs. 36%, $P < .001$). At 4 years, significant reductions in TLR were maintained with the SES.
SES SMART[406]	Small vessels	257 (all)	2 years	At 8 months, binary in-segment restenosis was lower with the SES compared with the BMS (9.8% vs. 53.1%, $P < .001$). At 2 years, lower rates of TLR and MI were observed with the SES compared with the BMS.
RRISC[270]	SVG	75 (all)	3 years	Six-month in-stent late lumen loss was lower with the SES compared with BMS (0.38 mm vs. 0.79 mm, $P = .001$). At 3 years, similar rates of TVR were observed with both stent types, with 11 deaths observed with the SES versus no deaths with the BMS.

TABLE 16-3 Randomized Controlled Trials Comparing Sirolimus-Eluting Stents With Bare-Metal Stents—cont'd

Trial/Authors	Study Cohort	Number Randomized (Planned Angiographic Follow-Up)	Latest Follow-Up to Date	Principal Findings
Pache et al[407]	Unselected	500 (all)	1 year	SES had lower angiographic restenosis rates than a thin-strut BMS (8.3% vs. 25.5%, $P < .001$) with a lower incidence of TVR.
Ortolani et al[408]	Unselected	104 (all)	1 year	SES had lower in-stent late loss compared with a thin-strut cobalt-chromium BMS (0.18 mm vs. 0.51 mm, $P < .001$). At 1 year, rates of TLR were lower with the SES but were not statistically different.

BMS, Bare-metal stent; *CAD,* coronary artery disease; *CTO,* chronic total occlusion; *MACE,* major adverse cardiovascular event; *MI,* myocardial infarction; *MLD,* mean luminal diameter; *PES,* paclitaxel-eluting stent; *SES,* sirolimus-eluting stent; *ST,* stent thrombosis; *STEMI,* ST-segment elevation myocardial infarction; *SVG,* saphenous vein graft; *TLR,* target-lesion revascularization; *TVF,* target-vessel failure (cardiac death, MI, or TVR); *TVR,* target-vessel revascularization.

patient indications and lesion subsets. Collectively, these trials demonstrated that the Cypher SES resulted in a near abolition of in-stent late lumen loss (averaging ~0.15 mm across studies, compared with 0.8 mm to 1.0 mm with most BMSs), with an approximate 70% to 80% reduction in angiographic restenosis and target lesion revascularization (TLR) compared with bare-metal comparators. Longer-term follow-up with this device has extended to 5 years and beyond, particularly from the four major SES trials: SIRIUS, a Randomized Study With the Sirolimus-Eluting Velocity Balloon Expandable Stent (RAVEL), the Canadian Study of the Sirolimus-Eluting Stent in the Treatment of Patients With Long De Novo Lesions in Small Native Coronary Arteries (C-SIRIUS), and the Study of the Bx Velocity Stent in Patients With De Novo Coronary Artery Lesions (E-SIRIUS). In these analyses, treatment with SES has resulted in sustained reductions in clinical restenosis end points with similar rates of death and MI found in both SES and BMS arms,[65] although as discussed below, subsequent studies have shown an ongoing propensity for very late (>1 yr) ST with the Cypher DES.[66,67] This led to the development of safer second-generation DES and ultimately to the discontinuation of the Cypher stent.

The Taxus Paclitaxel-Eluting Stent

Paclitaxel, a highly lipophilic diterpenoid compound, was first isolated in 1963 from the Pacific yew tree (*Taxus brevifolia*) and was subsequently developed for its potent antineoplastic properties. Paclitaxel is insoluble in water and thus was combined with an intravenous (IV) oil-based Cremophor for IV injection as the oncologic compound Taxol. The principal action of paclitaxel is to interfere with microtubule dynamics and prevent depolymerization. Because microtubules are ubiquitous, paclitaxel has widespread multicellular and multifunctional activities with dose-dependent effects. Paclitaxel has antiproliferative and antiinflammatory properties and it prevents smooth muscle migration, blocks cytokine and growth factor release and activity, interferes with secretory processes, is antiangiogenic, and impacts signal transduction.[46-48] Although cytotoxic at high doses, at low doses similar to those in DES applications, paclitaxel affects the G0-G1 and G1-S phases of the cell cycle (G1 arrest) and results in cytostasis without cell death, probably via induction of *TP53/CDKN1A* tumor suppression genes.[46,49] Systemic paclitaxel was shown to inhibit restenosis in a rat carotid injury model at levels more than a hundredfold lower than that required for tumor cytotoxicity.[47] Neointimal area was greatly reduced in a rabbit balloon injury experiment using local paclitaxel administration,[46] and stent-based paclitaxel elution from polymer-based systems has been shown to profoundly reduce intimal hyperplasia in rabbit iliac arteries for up to 6 months with dose-dependent efficacy and toxicity.[68,69]

The Taxus (Boston Scientific, Natick, MA) paclitaxel-eluting stent (PES) consists of paclitaxel contained within a polyolefin derivative biostable polymer—styrene-isobutylene-styrene, referred to as *SIBS* (Translute; Boston Scientific)—originally coated on the Nir stent and subsequently on the Express open-cell slotted-tube stainless steel stent platform, the device from which most of the RCT data for this stent was derived. The base BMS for the current Taxus stent is the newer Liberté stent, a more flexible, thinner-strutted, open-cell stainless steel slotted-tube stent. Depending on the relative ratio of paclitaxel to polymer, the stent may be formulated with varying release kinetics. The clinically available formulation of the Taxus PES is the slow-release (SR) formulation, although the moderate-release (MR) formulation has also been tested in clinical trials. The SR stent has relatively more polymer to drug (paclitaxel concentration of 1 $\mu g/mm^2$), with a coating thickness of 18 μm and approximately 8% in vivo paclitaxel elution in 30 days. The drug is eluted in a rapid burst phase over the initial 48 hours, followed by a slow, sustained release for the next 10 to 30 days, with more than 90% of the drug sequestered in the bulk of the polymer matrix below the surface without pathways to the external environment and thus permanently retained on the stent. In a series of porcine experiments at 30, 90, 180, and 360 days involving a total of 350 swine and 800 stents, both SR and MR Taxus stent formulations were shown to be vasculocompatible, with early development of a thin, mature neointima with low levels of inflammation, microthrombi, and peristent amorphous material deposition and no evidence of cytotoxicity with complete healing and endothelialization within 90 days (data on file, Boston Scientific).

The clinical safety and efficacy of the Taxus PES compared with the BMS has been tested in at least 12 randomized trials (Table 16-4). Collectively, these trials have demonstrated consistent reductions in measures of neointimal hyperplasia as assessed by angiography and IVUS, with resultant reductions in clinical restenosis end points with PES compared with BMS. Longer-term follow-up with this device has extended to 5 years and beyond, particularly for the four major PES trials of the SR stent (TAXUS I, II, IV, and V). In these analyses, treatment with a PES resulted in sustained reductions in clinical restenosis end points with similar rates of death and MI found in both PES and BMS arms.[70] However, as with the Cypher, these and other studies have demonstrated an ongoing risk of ST beyond the first year after Taxus stent implantation.[66,67,71] The introduction of safer and more effective DESs has led to a marked decrease in Taxus use, currently in fewer than 10% of all worldwide implants. The currently available PES device is the Ion stent (Boston Scientific), which uses the same drug and polymer formulation as the Taxus Express SR but with an improved stent platform. It is most commonly used in small vessels and to treat restenosis of rapamycin-analogue DESs.

Comparisons of First-Generation Drug-Eluting Stents

Following the approval of the Taxus PES for commercial use, a series of comparisons between the two approved devices, the Cypher SES and Taxus PES, ensued to determine whether superiority could be established for a particular DES. A total of 21 randomized comparisons of different sizes have been performed to date in numerous patient and lesion cohorts and have included a variety of IVUS, angiographic, and clinical end points (Table 16-5).

In summary, the totality of evidence appears to indicate similar performance of SESs and PESs in routine de novo coronary artery

TABLE 16-4 Randomized Controlled Trials to Compare Paclitaxel-Eluting Stents With Bare-Metal Stents

Trial/Authors	Study Cohort	Number Randomized (Planned Angiographic Follow-Up)	Latest Follow-Up to Date	Principal Findings
TAXUS I[409]	Single de novo or restenotic lesions	61 (all)	5 years (in pooled analyses)	Six-month percent diameter stenosis was lower with the PES compared with the BMS (13.6% vs. 27.3%, $P < .001$), with improvements in IVUS findings with the PES as well.
TAXUS II[410]	Single de novo native coronary lesions	536 (all)	5 years	Six-month net volume obstruction was lower with the slow-release PES versus the BMS (7.9% vs. 23.2%, $P < .001$) and the moderate-release PES compared with the BMS. Reductions in TLR were maintained at 5 years with both PES formulations, with no differences in death, MI, or ST.
TAXUS IV[70]	Single de novo native coronary lesions	1314 (732)	5 years	PES use was associated with lower TLR compared with the BMS at 9 months (4.7% vs. 12.0%, $P < .001$) and had lower rates of angiographic restenosis. Reductions in TLR were maintained at 5 years with no differences in death, MI, or ST.
TAXUS V[411]	Single lesions, including complex lesions	1156 (all)	5 years	PES reduced 9-month TVR compared with BMS (12.1% vs. 17.3%, $P = .02$), with reductions in angiographic restenosis overall and among patients with complex disease. At 5 years, reductions in clinical restenosis have been maintained with similar rates of death, MI, and ST.
TAXUS VI[412]	Single, long, complex lesions	448 (all)	5 years	9-month TVR was lower with the PES moderate-release design compared with the BMS (9.1% vs. 19.4%, $P = .0027$) with lower rates of angiographic restenosis. At 5 years, TVR rates were similar between stents, although TLR was lower with the PES moderate-release design.
HORIZONS-AMI[413]	STEMI	3006 (1800)	3 years	The PES was associated with lower rates of TLR compared with the BMS at 1 year (4.5% vs. 7.5%, $P = .002$), and binary restenosis at 13 months was lower (10.0% vs. 22.9%, $P < .001$). The reduction in TLR was maintained at 3 years with no significant differences in death, MI, or ST.
PASSION[196]	STEMI	619 (none)	2 years	Both the PES and the BMS were associated with nonsignificantly different rates of the primary end point of TLF (8.8% vs. 12.8%, $P = .09$) at 1 year, a finding that was maintained at 2 years.
PASEO[202]	STEMI	270 including 90 SESs (none)	4 years	The PES was associated with lower TLR at 1 year compared with the BMS (4.4% vs. 14.4%, $P = .023$), and this reduction was maintained at 4 years.
HAAMU-STENT[197]	STEMI	164 (all)	1 year	Angiographic end points were improved with the PES compared with the BMS, with a trend toward lower TVR at 1 year (3.7% vs. 11%, $P = .07$).
SELECTION[198]	STEMI	80 (all)	7 months	Volume of neointimal hyperplasia by IVUS was lower with the PES compared with the BMS (4.6% vs. 20%, $P < .01$) with no differences in late malapposition seen between the stent types.
Erglis et al[244]	Left main stenosis	103 (all)	6 months	PES use was associated with a lower rate of binary angiographic restenosis at 6 months compared with BMS use (6% vs. 22%, $P = .021$). IVUS measures were also improved with the PES.
SOS[271]	SVG	80 (all)	Median 1.5 years	Binary angiographic restenosis was lower with the PES compared with the BMS (9% vs. 51%, $P < .001$), although similar rates of MI and death were observed.

BMS, Bare-metal stent; *IVUS,* intravascular ultrasound; *MI,* myocardial infarction; *PES,* paclitaxel-eluting stent (slow-release); *SES,* sirolimus-eluting stent; *ST,* stent thrombosis; *STEMI,* ST-segment elevation myocardial infarction; *SVG,* saphenous vein grafts; *TLR,* target-lesion revascularization; *TLF,* target-lesion failure (cardiac death, MI, or TVR); *TVR,* target-vessel revascularization.

lesions despite less neointimal hyperplasia with SESs as assessed by IVUS and angiography.[72-75] Among pooled analyses of more complex or "higher-risk" lesion subsets, there may be a clinical benefit to the Cypher SES because of its more potent suppression of neointimal hyperplasia, but validation of these findings would be required in a large-scale, adequately powered clinical trial before being considered definitive.[76]

Limitations of First-Generation Drug-Eluting Stent

Although individual pivotal trials did not raise major safety issues related to first-generation DESs, subsequent studies revealed an ongoing propensity of these devices for an increased risk of very late ST.[77,78] This safety concern was initially raised by a report of four cases of angiographically confirmed ST late after elective implantation of an SES or PES,[79] and then it was ignited by a meta-analysis performed on aggregate data presented in 2006 during the European Society of Cardiology annual meeting in Barcelona.[80] That meta-analysis, in which data from trial programs comparing SESs or PESs with BMSs were pooled, suggested an increased risk of mortality and MI with first-generation DESs compared with BMSs.[80] This concern was further fueled by additional real-world studies that showed an increased risk of late ST and MI in patients treated with a first-generation DES after

TABLE 16-5 Randomized Controlled Trials Comparing Sirolimus-Eluting Stents and Paclitaxel-Eluting Stents

Trial/Authors	Study Cohort	Number Randomized (Planned Angiographic Follow-Up)	Latest Follow-Up to Date	Principal Findings
REALITY[72]	One to two de novo coronary lesions	1386 (all)	1 yr	Despite lower late loss with SES use, rates of binary angiographic restenosis were similar with the SES and PES (9.1% vs. 11.1%, $P = .31$), with similar rates of MACE at 1 year.
Zhang et al[414]	De novo coronary lesions	673 including 224 to Firebird stents (none)	1 yr	At 1 year, MACE rates were similar between the SES and PES (8.4% vs. 11.2%).
SORT OUT II[74]	Unselected	2098 (none)	1.5 yr	No significant differences were found between the SES and PES in MACE (9.3% vs. 11.2%) or other end points, including death, MI, or ST.
SIRTAX[415]	Unselected	1012 (~50%)	5 yr	SES use was associated with a lower MACE rate at 9 months compared with the PES (6.2% vs. 10.8%, $P = .009$). However, at 5 years, the rates were similar with an accrual of events in both stent groups.
TAXi[416]	Unselected	202 (none)	3 yr	The 6-month MACE rate was similar with the SES and PES (6% vs. 4%, $P = .8$) with similar findings at 3 years.
DES-DIABETES[73]	Diabetic patients	400 (all)	2 yr	Six-month in-segment restenosis was lower with the SES compared with the PES (3.4% vs. 18.2%, $P < .001$). At 2 years, TLR remained lower with the SES (3.5% vs. 11.0%, $P = .004$).
ISAR-DIABETES[220]	Diabetic patients	250 (all)	5 yr (in pooled analyses)	In-segment late lumen loss was lower with the SES compared with the PES (0.43 mm vs. 0.67 mm, $P = .002$), with nonsignificantly different rates of TLR at 9 months (6.4% vs. 12.0%, $P = .13$).
Kim et al[417]	Diabetic patients	169 (all)	6 mo	Late lumen loss was similar with the SES and PES (0.26 mm vs. 0.39 mm, $P = .36$), and rates of TLR were similar at 6 months.
DiabeDES[418]	Diabetic patients	153 (all)	8 mo	In-stent late lumen loss was lower with the SES compared with the PES (0.23 mm vs. 0.52 mm, $P = .025$). The rates of TLR and MACE were similar with both stents.
CORPAL[419]	Lesions at high risk for restenosis	652 (all)	15 mo	Angiographic restenosis rates were similar with the SES and PES, with similar rates of TLR.
ISAR–LEFT MAIN[245]	Left main stenosis	607 (all)	2 yr	Similar rates of angiographic restenosis were observed with the SES and PES (19.4% vs. 16.0%, $P = .30$), with no differences observed in death, MI, or TLR.
LONG DES II[420]	Long lesions	500 (all)	9 mo	In-segment binary restenosis was lower with the SES compared with the PES (3.3% vs. 14.6%, $P < .001$), with lower 9-month TLR.
Han et al[421]	Multivessel CAD	416 (all)	19.5 mo	MACE rates were similar with the SES and PES over the follow-up period (6.4% vs. 8.8%), with no differences in minimum lumen diameter.
ISAR-SMART 3[422]	Small vessels	360 (all)	5 yr (in pooled analyses)	Late lumen loss at 6 to 8 months was greater with the PES compared with the SES (0.56 mm vs. 0.25 mm, $P < .001$) with greater TLR (14.7% vs. 6.6%, $P = .008$).
Pan et al[423]	Bifurcation lesions	205 (all)	2 yr	SES use was associated with lower rates of binary angiographic restenosis, less late lumen loss, and lower TLR at 2 years compared with PES use (4% vs. 13%, $P < .021$).
Petronio et al[75]	Complex lesions	100 (all)	9 mo	By IVUS, the area of neointimal hyperplasia was significantly lower with the SES than with the PES (7.4% vs. 15.4%, $P < .001$) at 9 months.
Cervinka et al[424]	Complex CAD	70 (all)	6 mo	IVUS-assessed neointimal hyperplasia volume was lower with the SES compared with the PES (4.1 mm^3 vs. 17.4 mm^3, $P = .001$).
ISAR-DESIRE[384]	BMS restenosis	300 including 100 balloon angioplasty patients (all)	5 yr (in pooled analyses)	Angiographic restenosis was lower with both the SES (14.3%) and the PES (21.7%) compared with balloon angioplasty at 6 months (44.6%). TVR was lower with the SES compared with the PES (8% vs. 19%, $P = .02$).
ISAR-DESIRE-2[393]	SES restenosis	450 (all)	1 yr	No differences were found in late lumen loss (0.40 vs. 0.38, $P = .85$) or other angiographic or clinical end points with the SES or PES for the treatment of SES restenosis.
PROSIT[425]	STEMI	308 (all)	1 yr	In-segment restenosis was lower with the SES compared with the PES (5.9% vs. 14.8%, $P = .03$), with similar TLR and MACE rates.
PASEO[202]	STEMI	270 including 90 BMS (none)	4 yr	Similar reductions in TLR were seen with the SES and PES (relative to the BMS), and this was maintained throughout the follow-up period.

BMS, Bare-metal stent; *CAD,* coronary artery disease; *IVUS,* intravascular ultrasound; *MACE,* major adverse cardiovascular event; *MI,* myocardial infarction; *PES,* paclitaxel-eluting stent; *SES,* sirolimus-eluting stent; *ST,* stent thrombosis; *STEMI,* ST-elevation myocardial infarction; *TLR,* target-lesion revascularization.

TABLE 16-6 Meta-Analyses Comparing First-Generation Drug-Eluting Stents With Bare-Metal Stents

First Author	Stent Comparators	Number of Trials	*N*	Principal Findings
Ellis[83]	PES vs. BMS	4	3,445	No significant difference was apparent in the 3-year rates of death, MI, or ST between the PES and the BMS. However, in the period between 6 months and 3 years, PES use was associated with significantly higher rates of ST.
Kastrati[84]	SES vs. BMS	14	4,958	No significant difference was apparent in the risk of death, MI, or ST between the SES and the BMS after a follow-up ranging from 12 to 58 months.
Spaulding[86]	SES vs. BMS	4	1,748	No significant difference was apparent in the 4-year rates of death, MI, or ST between the PES and the BMS. Compared with the BMS, SES use was associated with an increased risk of mortality in diabetic patients.
Stone[87]	SES vs. BMS PES vs. BMS	4 5	1,748 3,513	No significant difference was found in the 4-year rates of death, MI, or ST between the PES versus the BMS or the SES versus the BMS; rates of very late ST were higher with the PES and the SES compared with the BMS.
Mauri[85]	SES BMS	4 4	1,748	No significant difference was apparent in the 4-year rates of death, MI, or stent thrombosis between PES vs. BMS or SES vs. BMS.
Stettler[426]	SES vs. PES vs. BMS	38	18,023	No differences in rates of mortality or ST were found between any DES and BMS. PES use was associated with higher rates of late definite ST compared with the SES and the BMS. SES use was associated with lower rates of MI compared with the PES and the BMS.
Kirtane[38]	DES vs. BMS	22 RCT 34 observational studies	9,470 182,901	In RCTs, no significant difference in mortality or MI was found between the DES and the BMS at long-term follow-up. However, in observational studies, DES use was associated with significantly lower rates of death or MI compared with BMS use.

BMS, Bare-metal stents; *DES,* drug-eluting stents; *MI,* myocardial infarction, *PES,* paclitaxel-eluting stent; *RCT,* randomized controlled trial; *SES,* sirolimus-eluting stents; *ST,* stent thrombosis.

discontinuation of DAPT[77] and a steady accrual of ST at a rate of 0.6% per year with no evidence of plateau after 4-year follow-up.[67] In addition, human autopsy studies and pathologic studies in animal models suggested that the permanent polymer coating in first-generation DESs could be associated with chronic inflammation, chronic fibrin deposition, late hypersensitivity reactions, and delayed arterial healing, potentially increasing the risk of very late ST in some patients.[53,81] These findings entailed a dramatic reduction of DES utilization in the United States, which dropped from 90% before 2006 to 64% in the following years.[82]

In view of the rare incidence of ST and the conflicting evidence, several pooled analyses and meta-analyses were performed to address the safety of first-generation DESs (Table 16-6).[83-87] These studies collectively did not suggest an increased risk of mortality or MI with DESs compared with BMSs, but some of them confirmed an increased risk of late or very late ST with both SESs and PESs compared with BMSs.[83,87] Of note, SESs but not PESs were associated with a reduction of ST during the first year compared with BMSs, but this was offset by an increased risk of very late ST with SESs after the first year.[85] The slightly increased risk of ST with first-generation DESs likely offset any potential long-term benefit of these devices in improving MI and survival by reducing restenosis.[88]

Second-Generation Drug-Eluting Stents

Following the initial development and approval of the SES and the PES, further iterations in DES technology resulted from a desire to improve upon both the deliverability and efficacy of first-generation DESs and to address some of the safety limitations of these devices. In general, most second-generation DESs have incorporated superior stent platforms and more biocompatible durable polymers or BPs, principally with rapamycin-analogue drugs in comparison with first-generation DESs. Polymer-free stents have also been developed that offer the potential of controlled drug release without the vascular toxicity associated with the presence of the polymer. Finally, the introduction of bioabsorbable stents represents a new paradigm in the treatment of CAD, providing drug elution and a temporary vascular scaffolding function for 6 to 12 months, followed by complete bioresorption within 1 to 2 years, theoretically restoring the underlying coronary anatomy and physiology and preventing very late (>1 year) adverse reactions from polymers, neoatherosclerosis, and other mechanisms.

Durable Polymer-Based Second-Generation Drug-Eluting Stents

Pivotal randomized trials have been completed with four second-generation, permanent, polymer-based DESs: the Xience V, Xience Prime, and Xience Expedition (Abbott Vascular, Santa Clara, CA), which are cobalt-chromium stents that elute everolimus from a fluorinated copolymer (CoCr-EES); the Promus Element and Promus Premier (Boston Scientific, Natick, MA), which are platinum-chromium stents that elute everolimus from a fluorinated copolymer (PtCr-EES); the Endeavor (Medtronic, Santa Rosa, CA), a phosphorylcholine polymer-based stent that elutes zotarolimus relatively rapidly, mostly over several weeks (PC-ZES); and the Resolute (Medtronic), which uses a composite BioLinx polymer that possesses hydrophilic and hydrophobic properties to release zotarolimus slowly over 4 months (Re-ZES). All four polymer-based stents release a rapamycin-analogue that binds to cytosolic FKBP12 and subsequently to mTOR, thereby blocking the stimulatory effects of growth factors and cytokines released after vascular injury. However, the underlying stent platform and polymers vary significantly, as do the drug pharmacokinetics and pharmacodynamics, which has resulted in the unique angiographic and clinical profiles of these devices.

Cobalt-Chromium Everolimus-Eluting Stents: Xience

In the CoCr-EES, everolimus (100 μg/cm^2) is released from a thin (7.8 μm), nonadhesive, durable, biocompatible fluorinated copolymer consisting of vinylidene fluoride and hexafluoropropylene monomers, coated onto a low-profile (81 μm strut thickness), flexible cobalt-chromium stent, which has additionally undergone several iterations. The release kinetics are similar to those seen with sirolimus from the

SES (~80% of the drug released at 30 days, with none detectable after 120 days). The polymer is elastomeric and experiences minimal bonding, webbing, or tearing upon expansion. Fluoropolymers have been demonstrated to resist platelet and thrombus deposition in blood-contact applications.[56,89] The EES fluoropolymer has also been demonstrated to be noninflammatory in porcine experiments. The low-profile stent struts facilitate rapid reendothelialization[90] and are fracture resistant. Preclinical studies have demonstrated more rapid coverage of the stent struts with functional endothelialization with a CoCr-EES compared with an SES, PES, or PC-ZES.[54]

To date, the CoCr-EES has been the second-generation DES that has received the most extensive investigation, with at least 34 RCTs performed and 45,298 randomized patients included (Table 16-7). The CoCr-EES was compared with the PES in six trials with 7313 randomized patients,[41,91-95] with the SES in 10 trials with 11,931 randomized patients,[96-105] with the Re-ZES in three trials with 4333 randomized patients,[106-108] with the PtCr-EES in two trials with 4515 randomized patients,[109,110] and with the BMS in four trials with 3037 patients.[100,111-113] In addition, the CoCr-EES is the only second-generation durable polymer–based DES that has been compared with BP-based DESs in RCTs powered for clinical end points, including three trials with 8233 patients in which the CoCr-EES was compared with BP-based biolimus-eluting stents (BP-BESs)[114-116] and five trials with 6103 patients in which the CoCr-EES was compared with different types of BP-based SESs.[117-121]

Cobalt-Chromium Everolimus-Eluting Stents Versus First-Generation Drug-Eluting Stents

Among the six trials to compare the CoCr-EES with a PES (see Table 16-7),[41,92-95] two large-scale trials sufficiently powered for clinical end points were conducted.[41,92] In the large-scale Prospective Randomized Trial of Everolimus-Eluting Stents Compared to Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease (SPIRIT IV),[41] 3687 patients with stable CAD undergoing PCI of up to three lesions in three vessels were randomized to CoCr-EES versus PES (Express platform). The primary end point of target-lesion failure (TLF; composite of cardiac death, target-vessel MI, or ischemia-driven TLR) at 1 year was reduced by 39% (3.9% vs. 6.6%, $P = .0008$). Compared with the PES, the CoCr-EES also reduced the 1-year rates of ST (0.3% vs. 1.1%, $P = .003$), MI (1.9% vs. 3.1%, $P = .02$), and TLR (2.3% vs. 4.5%, $P = .0008$). These results have been sustained at 3 years follow-up.[122] In the Randomized Controlled Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice (COMPARE),[92] 1800 unrestricted "all-comer" patients were randomized to the CoCr-EES versus the PES (Liberté platform). At 1 year, the primary end point of major adverse cardiovascular events (MACEs)—death, MI, or target-vessel revascularization (TVR)—was reduced by 31% with the CoCr-EES (6.2% vs. 9.1%, $P = .02$), driven by reductions in ST (0.7% vs. 2.6%, $P = .002$), MI (2.8% vs. 5.4%, $P = .007$), and TLR (1.7% vs. 4.8%, $P = .0002$). These results have been sustained up to 5-year follow-up.[123]

Among the 10 randomized trials to compare the CoCr-EES with the SES (see Table 16-7),[96-101,103-105,124] three large-scale trials have been conducted.[99,100,124] In the Scandinavian Organization for Randomized Trials With Clinical Outcome IV (SORT OUT IV) trial,[99] 2774 unselected patients in Denmark were randomized to a CoCr-EES versus an SES and were followed through the Danish Civil Registration System and Western Denmark Heart Registry. The primary 9-month end point of the composite of cardiac death, MI, definite ST, or TVR occurred in a comparable proportion of patients in both groups, although the overall event rates were lower than expected. Definite ST occurred in fewer CoCr-EES than SES patients (0.1% vs. 0.7%, $P = .05$). At 5-year follow-up, the CoCr-EES was associated with significantly lower rates of MACEs (4.8% vs. 7.0%, $P = .02$) and definite ST (0.4% vs. 2.0%, $P = .0004$) compared with the SES.[125] In the large-scale Real Safety and Efficacy of Three-Month Dual Antiplatelet Therapy Following Endeavor Zotarolimus-Eluting Stent Implantation (RESET)[124] trial, 3197 unselected patients were randomized to the CoCr-EES or the SES. At 1-year follow-up, use of the CoCr-EES resulted in nonsignificantly different rates of the primary end point of TLR (4.3% in the CoCr-EES group vs. 5.0% in the SES group). The cumulative incidence of definite ST was similarly low between the two groups (0.32% vs. 0.38%, $P = .77$). Finally, in the Basel Stent Kosten Effektivitäts Trial–Prospective Validation Examination II (BASKET-PROVE II) trial,[100] 2314 all-comer patients with lesions in coronary arteries with diameters of 3 mm or greater were randomly allocated to receive a CoCr-EES, SES, or BMS. At 2-year follow-up, no significant difference was apparent between the CoCr-EES and the SES in the rates of the primary end point (a composite of death or MI), as well as in the rates of TVR or ST.

In summary, in a broad cross section of patients undergoing PCI, the CoCr-EES has shown marked improvements in safety and efficacy outcomes compared with the PES, and it has shown modest improvements compared with the SES. In view of the limited power of these randomized trials in detecting differences in low-frequency end points, several meta-analyses have been performed. In a meta-analysis in which 13 RCTs with 17,101 patients were included, CoCr-EES use was associated with significant reductions in MI, TVR, and definite/probable ST compared with pooled PES, SES, and Re-ZES after a median follow-up of 21 months.[126] However, the treatment effects for each end point varied by DES comparator, with the largest difference being apparent for the CoCr-EES versus the PES; the difference was intermediate for the CoCr-EES versus the Re-ZES and was smallest for the CoCr-EES versus the SES. In another meta-analysis that included 11 trials with 16,775 patients and focused on time-related differences in the risk of definite ST, CoCr-EES use was associated with significantly lower rates of early, late, 1-year, and 2-year definite ST compared with pooled PES, SES, and Re-ZES use, with no interaction apparent between the overall relative risk of definite ST and any DES comparator.[127] These findings have been corroborated in a third meta-analysis that included eight trials with 11,167 patients in which follow-up ranged from 9 to 36 months.[128]

The reduced risk of ST apparent in these meta-analyses with the CoCr-EES, compared with a first-generation DES, has since been confirmed in real-world observational studies. Specifically, in 1342 propensity score–matched pairs of patients followed for a median of 1.5 years, the CoCr-EES was associated with significantly lower rates of definite ST and MI compared with the SES.[129] Moreover, in a large all-comers study that included 12,339 patients, the CoCr-EES was found to have significantly lower rates of definite ST than either the SES or PES up to a 4-year follow-up, with differences in ST being most pronounced beyond the first year after stent implantation.[130]

Cobalt-Chromium Everolimus-Eluting Stent Versus Bare-Metal Stent

When second-generation DESs reached the clinical arena, the natural comparator of these new devices were first generation DESs. As a consequence, few studies have compared second generation DESs with the BMS. However, the CoCr-EES has been compared with a BMS in four randomized controlled trials: the SPIRIT FIRST Clinical Trial of the Abbott Vascular Xience V Everolimus-Eluting Coronary Stent System, BASKET-PROVE, Xience or Vision Stents for the Management of Angina in the Elderly (XIMA), and Everolimus-Eluting Stent Versus Bare-Metal Stent in ST-Segment Elevation Myocardial Infarction (EXAMINATION).[100,111-113] In addition, the CoCr-EES has been compared with the BMS in the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) trial,[131] in which 2013 patients were randomly assigned to receive 6-month DAPT versus 12-month DAPT and either a CoCr-EES, BMS, PES, or PC-ZES. SPIRIT FIRST was a small randomized trial that showed significantly lower rates of restenosis and in-stent late loss with the CoCr-EES compared with the BMS at 6-month angiographic follow-up.[113] In the large-scale randomized BASKET-PROVE trial, 2-year rates of the primary end point of death or MI were 3.2% with a CoCr-EES and 4.8% with a BMS ($P = .37$).[100] However, rates of TVR were significantly higher with a BMS than with a CoCr-EES (10.3% vs. 3.7%, respectively, $P = .002$).

TABLE 16-7 Randomized Controlled Trials With Food and Drug Administration–Approved Second-Generation Drug-Eluting Stents

Study	Study Cohort	Number of Randomized Patients	Latest Follow-Up to Date	Principal Findings
CoCr-EES Versus PES				
COMPARE[92,123]	All comers	1800	5 yr	Comparison of the CoCr-EES and PES showed in lower 1-year rates of the primary end point, a composite of death, MI, or TVR (6.2% vs. 9.1%, $P = .02$). CoCr-EES use also resulted in lower rates of MI, ST, and TLR. At 5 years, the primary composite end point occurred in 18.4% of CoCr-EES patients versus 25.1% of PES patients ($P = .0005$).
EXECUTIVE[93]	MVD, otherwise noncomplex CAD	200	9 mo	Compared with the PES, the CoCr-EES showed lower 9-month rates of angiographic in-stent late loss (0.11 ± 0.27 mm vs. 0.36 ± 0.39 mm, $P = .008$).
SPIRIT II[94,427]	Noncomplex CAD; up to two lesions	300	5 yr	Compared with the PES, the CoCr-EES showed lower 6-month rates of angiographic in-stent late loss (0.11 ± 0.27 mm vs. 0.36 ± 0.39 mm, $P < .0001$).
SPIRIT III[95,346]	Noncomplex CAD; up to two lesions	1002	5 yr	Compared with the PES, the CoCr-EES showed lower 8-month rates of angiographic in-segment late loss (0.14 ± 0.41 mm vs. 0.28 ± 0.48 mm, $P = .004$), noninferior 9-month rates of TVF (7.2% vs. 9.0%, $P = .31$), and reduced MACE rates at 1 year (5.7% vs. 9.9%, $P = .01$) and 5 years (13.2% vs. 20.7%, $P = .007$).
SPIRIT IV[41,122]	Noncomplex CAD; up to three lesions	3687	3 yr	Compared with the PES, the CoCr-EES showed lower 1-year rates of TLF (3.9% vs. 6.6%, $P = .0008$) and ischemia-driven TLR (2.3% vs. 4.5%, $P = .0008$) with noninferior rates of cardiac death or target-vessel MI (2.2% vs. 3.2%, $P = .09$). CoCr-EES use also resulted in lower rates of MI and ST. At 3 years, TLF occurred in 9.2% of CoCr-EES patients versus 11.7% of PES patients ($P = .02$).
SPIRIT V DIABETIC[91]	Diabetes mellitus	324	1 yr	Compared with the PES, the CoCr-EES resulted in lower 9-month rates of angiographic in-stent late loss (0.19 ± 0.37 mm vs. 0.39 ± 0.49 mm, $P = .0001$).
CoCr-EES Versus SES				
CIBELES[103]	Chronic total occlusion	207	9 mo	Noninferiority was present for the primary end point of in-segment late loss at 9 months (CoCr-EES 0.19 ± 0.69 mm vs. SES 0.29 ± 0.60 mm, $P_{NI} < .01$). Binary restenosis occurred in 10.8% of patients treated with an SES and in 9.1% of patients treated with a CoCr-EES.
EXCELLENT[105]	Noncomplex CAD	1443	9 mo	Noninferiority was present for the primary end point of in-segment late loss at 9 months (CoCr-EES 0.10 ± 0.36 mm vs. SES 0.05 ± 0.34 mm, $P_{NI} = .02$). MACEs occurred in only ~3.0% of patients in both groups at 9 months.
ESSENCE DIABETES[101]	Diabetes	300	1 yr	Compared with the SES, the CoCr-EES showed lower 8-month angiographic in-segment late loss (mean 0.23 mm vs. 0.37 mm, $P = .02$) and lower binary restenosis (0.9% vs. 6.5%, $P = .04$).
ISAR-TEST-4[97,428]	Simple and complex CAD	1304	3 yr	Compared with the SES, the CoCr-EES showed nonsignificantly different rates of in-segment late loss at 24 months (0.29 ± 0.51 mm vs. 0.31 ± 0.58 mm, $P = .59$). TLF at 3 years was not significantly different between the CoCr-EES and the SES (19.6% vs. 22.3%, $P = .26$), although TLR tended to be less frequent with the CoCr-EES (12.8% vs. 15.5%, $P = .15$).
LONG DES III[104]	Long lesion (≥25 mm)	450	9 mo	In-segment late loss was significantly greater with the CoCr-EES than with the SES (0.17± 0.41 mm vs. 0.09 ± 0.30 mm, $P_{NI} = .96$, $P_{SUP} = .04$). However, in-stent late loss (0.22 ± 0.43 mm vs. 0.18 ± 0.28 mm, $P = .29$) was similar between the two. The incidence of death, MI, ST, and TLR was not statistically different.
RESET[429]	All comers	3197	1 yr	Compared with the SES, the CoCr-EES had nonsignificantly different rates of TLR at 1 year (4.3% vs. 5.0%, $P_{NI} = .0001$). Definite ST was similar between the two groups (0.32% vs. 0.38%, $P = .77$).
SEA-SIDE[96]	Bifurcations	150	18 mo	Compared with the SES, the CoCr-EES showed similar procedural results in the main vessel and better results in the side branch. At 18 months the incidence of MACEs (death, MI, TVR) was 12% with CoCr-EES and 9% with SES use ($P = .60$).

TABLE 16-7 Randomized Controlled Trials With Food and Drug Administration–Approved Second-Generation Drug-Eluting Stents—cont'd

Study	Study Cohort	Number of Randomized Patients	Latest Follow-Up to Date	Principal Findings
SORT OUT IV[99,125]	All comers	2774	5 yr	CoCr-EES use resulted in nonsignificantly different 9-month MACE rates (cardiac death, MI, definite ST, or TVR) compared with SES (4.9% vs. 5.2%, $P = .71$). At 5 years, MACE rates were 14.1% with CoCr-EES versus 17.4% with SES ($P = .02$). Definite ST was 0.4% with CoCr-EES versus 2.0% with SES ($P = .0004$).
XAMI[98]	STEMI	625	1 yr	Compared with SES, the CoCr-EES had significantly lower 1-year rates of the primary composite end point of cardiac death, MI, or TVR (4.0% vs. 7.7%, $P = .048$), and the 1-year incidence of definite/probable ST was 1.2% for the CoCr-EES versus 2.7% for the SES ($P = .21$).
CoCr-EES Versus Re-ZES				
RESOLUTE[107,159]	All comers	2292	4 yr	CoCr-EES versus Re-ZES use resulted in comparable 1-year rates of TLF (8.3% vs. 8.2%, $P = .92$) and TLR (3.4% vs. 3.9%, $P = .50$), although less definite ST (0.3% vs. 1.2%, $P = .01$) and definite/probable ST was reported (0.7% vs. 1.6%, $P = .05$). At 4 years, TLF and TLR were similar between the two groups. Definite ST was 0.7% with the CoCr-EES versus 1.5% with the Re-ZES ($P = .07$).
TWENTE[108,160]	All comers with the exception of patients with STEMI	1391	2 yr	CoCr-EES versus Re-ZES use resulted in comparable 1-year rates of TVF (8.1% vs. 8.2%, $P_{NI} < .001$). Definite ST was 0.0% with CoCr-EES and 0.58% with Re-ZES ($P = .12$). Similar results were apparent at 2 years.
ISAR–LEFT MAIN[106]	Left main	750	1 yr	CoCr-EES versus Re-ZES use was noninferior for the composite end point of death, MI, and TLR (14.3% vs. 17.5%, $P = .25$). Definite/probable ST was 0.6% with the CoCr-EES versus 0.9% with the Re-ZES ($P = .99$).
CoCr-EES Versus BMS				
PRODIGY[430]	All comers	1003	2 yr	At 2-year follow-up, the CoCr-EES was associated with significantly lower rates of ST compared with the BMS (1.00% vs. 4.6%, $P = .0001$).
BASKET-PROVE[100†]	All comers with lesions in coronary arteries with diameter ≥3 mm	2314	2 yr	At 2-year follow-up, the CoCr-EES had similar rates of cardiac death and MI compared with the SES or the BMS (3.2% vs. 2.6% vs. 4.8%; P = NS for all comparisons). Rates of TVR were 3.1% with the CoCr-EES, 3.7% with the SES, and 8.9% with the BMS. Rates of definite ST were 0.6% with the CoCr-EES, 0.8% with the SES, and 1.2% with the BMS.
EXAMINATION[112,205]	STEMI	1498	2 yr	For the primary end point of death, MI, and any revascularization, no significant difference was apparent between the CoCr-EES and the BMS at 1 year. The CoCr EES was associated with significantly lower 1-year rates of definite ST compared with the BMS (0.5% vs. 1.9%, respectively, $P = .018$). Similar results were apparent at 2 years.
XIMA[111]	Elderly patients	800	1 yr	For the primary end point of death, MI, CVA, TVR, or major hemorrhage, no significant difference was apparent between the CoCr-EES and the BMS at 1 year (14.3% vs. 18.7%, respectively, $P = .09$). CoCr-EES use was associated with significantly lower 1-year rates of TVR (2.0% vs. 7.0%, $P = .001$) and MI (4.3% vs. 8.7%, $P = .01$) compared with the BMS.
SPIRIT FIRST[113,431]	Noncomplex CAD	60	5 ys	The primary end point of in-stent late loss at 6 months was significantly lower with the CoCr-EES compared with the BMS (0.10 ± 0.21 mm vs. 0.87 ± 0.37 mm, $P < .001$). No significant difference was apparent in MACE rates at 5 years.
CoCr-EES Versus PtCr-EES				
PLATINUM[110,139]	Noncomplex CAD; up to two lesions	1530	3 yr	For the primary end point of TLF, the PtCr-EES was noninferior to the CoCr-EES at 1 year (3.4% for PtCr-EES vs. 2.9% for CoCr-EES, $P_{NI} = .001$). Similar results were apparent at 3 years with no significant difference in death, MI, or ischemia-driven TLR between the two stents.
PLATINUM+[109]	All comers	2980	1 yr	For the primary end point of TVF, the PtCr-EES was noninferior to the CoCr-EES at 1 year (4.6% for PtCr-EES vs. 3.2% for CoCr-EES, $P_{NI} = .01$).

Continued

TABLE 16-7 Randomized Controlled Trials With Food and Drug Administration–Approved Second-Generation Drug-Eluting Stents—cont'd

Study	Study Cohort	Number of Randomized Patients	Latest Follow-Up to Date	Principal Findings
Re-ZES Versus PtCr-EES				
DUTCH PEERS[138]	All comers	1811	1 yr	For the primary end point of TVF, PtCr-EES was noninferior to Re-ZES at 1 year (5.0% for PtCr-EES vs. 6.0% for Re-ZES, P_{NI} = .006).
HOST-ASSURE[161]	All comers	3750	1 yr	For the primary end point of TLF, PtCr-EES was noninferior to Re-ZES at 1 year (2.9% for both PtCr-EES and Re-ZES, P_{NI} = .02).
Re-ZES Versus SES				
ESSENCE DIABETES II[432]	Diabetes mellitus	256	9 mo	Re-ZES was noninferior to SES for the primary end point of 9-month late loss (0.34 ± 0.30 mm vs. 0.39 ± 0.43 mm. P_{NI} < .001). The trial was prematurely stopped because of discontinuation of SES manufacturing.

†CoCr-EES was compared with BMS and SES.

BMS, Bare-metal stent stent; *CAD,* coronary artery disease; *CoCr-EES,* cobalt-chromium everolimus-eluting stent; *CVA,* cerebrovascular accident; *MACE,* major adverse cardiac events (cardiac death, MI, or TLR); *MI,* myocardial infarction; *MVD,* multivessel disease; *NS,* nonsignificant; *PES,* paclitaxel-eluting stents; P_{NI}, *P* value for noninferiority; P_{SUP}, *P* value for superiority; *PtCr-EES,* platinum-chromium everolimus-eluting stents; *Re-ZES,* Resolute zotarolimus-eluting stents; *TLF,* target-lesion failure (cardiac death, target-lesion MI or TLR); *TLR,* target-lesion revascularization; *TVF,* target-vessel failure (cardiac death, target vessel MI or TVR); *TVR,* target-vessel revascularization; *SES,* sirolimus-eluting stents; *ST,* stent thrombosis; *STEMI,* ST-segment elevation myocardial infarction.

The XIMA trial was a prospective RCT that compared the CoCr-EES with the BMS in 800 patients aged 80 years and older.[111] The primary end point—a composite of death, MI, cerebrovascular accident (CVA), TVR, or major hemorrhage—occurred in 18.7% of patients treated with a BMS versus 14.3% of patients treated with a CoCr-EES (*P* = .09). No difference was found in the risk of death (7.2% vs. 8.5%, respectively; *P* = .50), major hemorrhage (1.7% vs. 2.3%; *P* = .61), or CVA (1.2% vs. 1.5%; *P* = .77). In contrast, MI (8.7% vs. 4.3%; *P* = .01) and TVR (7.0% vs. 2.0%; *P* = .001) occurred more often in patients in the BMS group compared with those in the CoCr-EES group. Finally, the EXAMINATION trial was a prospective, multicenter trial that randomly assigned 1498 patients with STEMI to either a CoCr-EES or a BMS.[112] Details of this study will be discussed later (see Acute ST-Segment Elevation Myocardial Infarction). These five trials have been recently pooled in an individual patient-level meta-analysis that included 4896 randomized patients.[132] Compared with the BMS, after a median follow-up of 2 years, the CoCr-EES was associated with significantly lower rates of cardiac mortality (hazard ratio [HR] 0.67; 95% confidence interval [CI], 0.49 to 0.91), MI (HR 0.71; 95% CI, 0.55 to 0.92), definite/probable ST (HR 0.48; 95% CI, 0.31 to 0.73), and TVR (HR 0.29; 95% CI, 0.20 to 0.41), demonstrating that best-in-class second-generation DES has improved safety, including survival, compared with BMS.

Cobalt-Chromium Everolimus-Eluting Stents Versus Second-Generation Drug-Eluting Stents

At least 12 randomized trials have compared the CoCr-EES with other second-generation DESs.* The details of these trials are included under the following subsections that describe each of these second-generation devices.

Platinum-Chromium Everolimus-Eluting Stent (Promus Element/Premier)

The platinum-chromium everolimus-eluting stent (PtCr-EES) is made of a platinum-chromium alloy with an 81-μm strut thickness, high radial strength, and moderate radiopacity somewhat greater than that of the CoCr-EES. The PtCr-EES uses the same durable, biocompatible, inert fluorocopolymer (~7 μm thick) and antiproliferative agent (everolimus at 100 μg/cm^2 concentration) as the CoCr-EES but with a modified scaffold design that aims to provide improved deliverability, vessel conformability, side-branch access, radial strength, and fracture resistance. The PtCr-EES provides comparable everolimus release kinetics, arterial tissue levels, and vascular responses as the CoCr-EES in a nondiseased porcine coronary artery model.[135]

The vascular response to the PtCr-EES was assessed in a small clinical study that recruited 73 patients with a single coronary lesion with an RVD of 2.5 mm or greater and a lesion length of 24 mm or less.[136] Surveillance coronary angiography performed at 9 months after PCI showed an in-stent late loss of 0.17 mm (± 0.25), which was comparable with that of the CoCr-EES reported in the SPIRIT trials (0.10 ± 0.21 mm at 6 mo in SPIRIT FIRST,[113] 0.11 ± 0.27 mm at 6 mo in SPIRIT II,[137] and 0.16 ± 0.41 mm at 8 mo in SPIRIT III[96]). The percentage of volume obstruction determined by IVUS with a PtCr-EES at 9-month follow-up was 7.2% (± 6.2), also comparable to that reported with the CoCr-EES (8.0 ± 10.4% at 6 mo in SPIRIT FIRST,[113] 2.5 ± 4.7% at 6 mo in SPIRIT II,[94] and 6.9 ± 6.4% at 8 mo in SPIRIT III[95]).

The safety and efficacy of the PtCr-EES was assessed in four RCTs, which compared it with either the CoCr-EES—in a Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System for the Treatment of Up to Two de Novo Coronary Artery Lesions (PLATINUM)[110] and a Trial to Assess the Everolimus-Eluting Coronary Stent System (Promus Element) for Coronary Revascularization (PLATINUM Plus)[109]—or the Re-ZES in the Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis–Safety and Effectiveness of Drug-Eluting Stents and Antiplatelet Regimen (HOST-ASSURE)[137] and the Third-Generation Zotarolimus-Eluting and Everolimus-Eluting Stents in All-Comer Patients Requiring a Percutaneous Coronary Intervention (DUTCH PEERS),[138] which will be discussed later. PLATINUM was a large-scale international, multicenter, prospective, single-blind randomized trial in which 1530 patients with up to two de novo coronary lesions were randomized to either a PtCr-EES or a CoCr-EES.[110] At the 1-year follow-up, rates of TLF (target vessel–related cardiac death, target vessel–related MI, or ischemia-driven TLR) were 2.9% in patients assigned to a CoCr-EES versus 3.4% in those assigned to a PtCr-EES (*P* for noniferiority [P_{NI}] = .001). In addition, no significant differences were observed between the CoCr-EES and the PtCr-EES in cardiac death or MI (2.5% vs. 2.0%, respectively, *P* = .56), TLR (1.9% vs. 1.9%, *P* = .99), or definite/probable ST (0.4% vs. 0.4%, *P* = 1). Similar results were apparent when follow-up was extended up to 3 years, with no significant differences between a CoCr-EES and a PtCr-EES in the risk of mortality (4.3% vs. 3.7%, respectively, *P* = .62), cardiac mortality (1.9% vs. 1.2%, *P* = .27), MI

*References 97, 106-110, 116, 118, 119, 121, 133, 134.

(2.5% vs. 2.3%, $P = .81$), ischemia-driven TLR (4.9% vs. 3.5%, $P = .21$), or definite/probable ST (0.5% vs. 0.7%, $P = .76$).[139]

PLATINUM Plus was a prospective, multicenter, noninferiority trial that enrolled 2980 all-comer patients to either a PtCr-EES or a CoCr-EES.[109] At 1-year follow-up, the primary end point of target-vessel failure (TVF)—a composite of cardiac death, target-vessel MI, or TVR—occurred in 4.6% of patients in the PtCr-EES group compared with 3.2% of patients in the CoCr-EES group ($P_{NI} = .01$), with similar rates of the individual components of the primary end point in both groups. Definite/probable ST was 0.8% in the PtCr-EES group and 0.5% in the CoCr-EES group ($P = .44$).

Several reports have suggested that the Promus Element stent platform is particularly susceptible to longitudinal stent deformation,[22] an infrequent complication after stent placement that appears as a reduction or increase in stent length with strut overlap, separation, malapposition, and/or luminal obstruction.[21] When longitudinal stent deformation occurs, it can predispose to ST or restenosis and may obstruct passage of devices.[22] Stent distortion may occur after stent deployment or during positioning of a postdilation balloon, thrombectomy device, or IVUS catheter, or it may be due to guide catheter compression when the stent is deployed in an ostial or proximal location. Stent deformation may be more frequent with the Promus Element than with other second-generation DESs because the Promus Element has fewer connectors between hoops, a design intended to confer great longitudinal flexibility and deliverability.[140] Bench testing has demonstrated that the Promus Element platform (Omega) has less longitudinal strength compared with the platforms of the SES, PES, or CoCr-EES.[21] Subsequently, the design of the Promus Element was modified by the addition of connectors between the hoops in the proximal segment of the stent (the most common site of longitudinal deformation), leading to a new PtCr-EES design, the Promus Premier. In bench testing, deformation with the Promus Premier was significantly less than with the Promus Element and was similar to other stent platforms,[141] and in practice, longitudinal stent deformation has infrequently been reported with this device.

Phosphorylcholine Zotarolimus-Eluting Stent (Endeavor)

The PC-ZES elutes zotarolimus (10 μg/mm stent length) from a thin layer (5.3 μm) of the biocompatible polymer phosphorylcholine from a flexible, low-profile (91 μm strut thickness) cobalt-chromium stent. Phosphorylcholine is a naturally occurring phospholipid found in the membranes of red blood cells, and it is resistant to platelet adhesion.[142] The potencies of zotarolimus, everolimus, and sirolimus are roughly comparable, and zotarolimus is somewhat more lipophilic. However, the release rate of zotarolimus from the Endeavor (~90% within 7 days, 100% within 30 days) is significantly faster than everolimus and sirolimus released from the Xience V and Cypher stents, respectively.

In the First-in-Human Study of the Endeavor ABT-578-Eluting Phosphorylcholine-Encapsulated Stent System in De Novo Native Coronary Artery Lesions (ENDEAVOR I) FIM study,[143] the PC-ZES was implanted in 100 patients with noncomplex coronary lesions. Although TLR was required in only 1% of patients at 1 year, mean in-stent late lumen loss was 0.33 mm at 4 months and 0.61 mm at 12 months. Although significantly less than the 0.8 to 1.0 mm mean in-stent late loss typically experienced with the BMS, this degree of late loss would be expected to result in greater rates of binary restenosis and TLR compared with greater potency DESs such as the SES, CoCr-EES, and Re-ZES, which achieve greater suppression of neointimal hyperplasia.[144,145] The PC-ZES was subsequently compared with an otherwise identical BMS in the Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesions (ENDEAVOR II) trial[146,147] in 1197 randomized patients with noncomplex CAD. As described in Table 16-8, compared with the BMS, the PC-ZES resulted in significantly reduced rates of TVF and TLR at 9 months, results that were sustained for 5 years.[148] Although the 9-month rate of angiographic in-stent late loss was 0.61 mm (±0.46), this was sufficient to reduce in-segment binary restenosis to 13.2% from 35.0% with a BMS ($P < .0001$).

To assess whether this degree of late loss suppression was sufficient to prevent clinical restenosis, a series of trials were performed in which

TABLE 16-8 Randomized Controlled Trials of Endeavor Zotarolimus-Eluting Stents

Trial	Study Cohort	PC-ZES Versus	Number Randomized (Planned Angiographic Follow-Up)	Latest Follow-Up to Date	Principal Findings
CATOS[433]	CTO	SES	160 (all)	9 mo	The PC-ZES was noninferior to the SES with respect to the primary end point of in-segment binary restenosis (14.1% vs. 13.7%, $P_{NI} < .001$). No significant between-group differences were found in TVF (10.0% vs. 17.5%; $P = .17$) or in-stent thrombosis rates (0.0% vs. 1.3%; $P = .32$).
DiabeDES III[434]	Diabetes mellitus	SES	127 (105)	10 mo	The PC-ZES was associated with significantly higher 10-month late loss compared with the SES (0.74 ± 0.45 mm vs. 0.14 ± 0.37 mm, $P < .001$). Neointimal hyperplasia determined by IVUS was significantly greater with the PC-ZES compared with the SES (0.0 vs. 16.5 mm^2, $P < .001$).
ENDEAVOR II[148,214]	Noncomplex CAD	BMS	1197 (600)	5 yr	Compared with BMS use, the PC-ZES reduced the 9-month rates of TVF (the primary end point; 15.1% vs. 7.9%, $P < .0001$), TLR (11.8% vs. 4.6%, $P < .0001$), in-stent late loss (1.03 ± 0.58 to 0.61 ± 0.46 mm, $P < .001$), and in-segment binary restenosis (35.0% vs. 13.2%, $P < .0001$). The rate of ST was 0.5% with the PC-ZES versus 1.2% with the BMS ($P = .22$). At 5 years, TLR was reduced with the PC-ZES (16.5% vs. 7.4%, $P < .0001$).
ENDEAVOR III[149,435]	Noncomplex CAD	SES	436 (all)	5 yr	Compared with the SES, the PC-ZES had higher 8-month rates of in-stent late loss (0.60 ± 0.48 mm vs. 0.15 ± 0.34 mm, $P < .001$) and in-segment binary restenosis (11.7% vs. 4.3%, $P = .04$). At 5 years, MACE rates were 14.0% with the PC-ZES versus 22.2% with the BMS ($P = .05$).

Continued

TABLE 16-8 Randomized Controlled Trials of Endeavor Zotarolimus-Eluting Stents—cont'd

Trial	Study Cohort	PC-ZES Versus	Number Randomized (Planned Angiographic Follow-Up)	Latest Follow-Up to Date	Principal Findings
ENDEAVOR IV[436,437]	Noncomplex CAD	PES	1548 (328)	5 yr	Compared with the PES, the PC-ZES was noninferior for the primary end point of TVF at 9 months (6.6% vs. 7.1%, respectively; $P_{NI} < .0001$, $P_{SUP} = .69$). The PC-ZES compared with the PES resulted in higher rates of angiographic in-stent late loss (0.67 ± 0.49 mm vs. 0.42 ± 0.50 mm, $P < .001$) and a trend toward greater in-segment restenosis (15.3% vs. 10.4%; $P = .28$) at 8 months but comparable rates of TLR at 1 year (4.5% vs. 3.2%; $P = .23$) and 5 years (7.7% vs. 8.6%, $P = .70$). The rates of cardiac death or MI in PC-ZES versus PES patients was 2.1% versus 3.1%, respectively, at 1 year ($P = .20$) and was 6.4% versus 9.2%, respectively, at 5 years ($P = .049$). Definite probable ST after 5 years occurred in 1.4% of PC-ZES patients versus 1.9% of PES patients ($P = .42$).
EXCELLA II[438]	Noncomplex CAD	NES	210 (All)	9 mo	PC-ZES resulted in significantly higher rates of in-stent late lumen loss compared with NES (0.63 ± 0.42 mm vs. 0.11 ± 0.32 mm, $P < .0001$). No significant difference was found between stent groups in the device-orientated composite end point of cardiac death, MI, and clinically indicated TLR (5.6% vs 2.8%, $P = .45$).
KOMER[151]	STEMI	SES and PES	611 (348)	1 yr	For the primary composite end point of cardiac death, MI, and ischemia-driven TLR, no significant difference was apparent between PC-ZES, SES, and PES at 1 year (5.9% vs. 3.4% vs. 5.7%, respectively; $P = .46$). A trend was seen toward lower 1-year rates of ischemia-driven TLR in the SES group (0.0%) compared with the PC-ZES (2.5%) and PES (1.5%) groups ($P = .09$).
ISAR-TEST-2[150,342]	Simple and complex CAD	SES	674 (all)	2 yr	PC-ZES versus SES use resulted in higher 6- to 8-month rates of late loss (0.58 ± 0.55 mm vs. 0.24 ± 0.51 mm, $P < .001$) and binary restenosis (19.3% vs. 12.0%, $P < .01$) and higher 1-year rates of TLR (19.3% vs. 7.2%, $P < .01$). At 2 years, late loss was greater with the SES compared with the PC-ZES such that the differences in binary restenosis (20.9% vs. 18.6%) and TLR (14.3% vs. 10.7%) were not as pronounced as in the first year. The rates of death, MI, and ST were not significantly different between the two stents at 9 months or 2 years.
NAPLES[152]	Diabetes mellitus	SES and PES	226 (none)	3 yr	At 3 years, PC-ZES use was associated with significantly higher rates of death, MI, or clinically driven TVR compared with both the SES and PES (35.6% with PC-ZES, 13.2% with SES, 17.5% with PES, $P = .006$). No significant difference was apparent between the SES and the PES in any clinical end point.
PROTECT[156,157]	All comers with no more than four lesions	SES	8800 (none)	5 yr	For the primary end point of definite/probable ST, no evidence of superiority of the PC-ZES versus the SES was apparent at 3 years (1.4% with PC-ZES vs. 1.8% with SES, $P = .22$). However, the PC-ZES was associated with significantly lower rates of definite probable ST compared with the SES when follow-up was extended at 5 years (1.67% vs. 2.83%, $P = .0007$).
SORT OUT III[154,155]	All comers	SES	2333 (none)	5 yr	The PC-ZES versus the SES resulted in higher 9-month and 18-month rates of cardiac death, MI, or TVR (6% vs. 3%, $P = .0002$, and 10% vs. 5%, $P < .0001$), MI (2% vs. < 1%, $P = .006$, and 2% vs. 1%, $P = .03$), ST (1% vs. <1%, $P = .048$, and 1% vs. 1%, $P = .13$), and TLR (4% vs. 1%, $P < .0001$, and 6% vs. 1%, $P < .0001$). Mortality was higher at 18 months after PC-ZES (4% vs. 3%, $P = .035$). However, between 1 and 5 years, MACE (9.0% vs, 11.6, $P = .07$) and ST (0.1% vs. 1.8%, $P = .003$) rates were lower with the PC-ZES than with the SES, such that at 5 years, no significant difference in clinical events was apparent between the two devices.

TABLE 16-8 Randomized Controlled Trials of Endeavor Zotarolimus-Eluting Stents—cont'd

Trial	Study Cohort	PC-ZES Versus	Number Randomized (Planned Angiographic Follow-Up)	Latest Follow-Up to Date	Principal Findings
ZEST[439,440]	Simple and complex CAD	SES and PES	2645 (all)	2 yr	For the primary end point of TVF at 12 months, the PC-ZES was noninferior to the SES (10.2% vs. 8.3%, $P_{NI} = .01$, $P_{SUP} = .17$) and was superior to the PES (10.2% vs. 14.1%, $P = .01$). In-segment binary restenosis at 9 months occurred in 12.1%, 2.4%, and 12.4% of PC-ZES, SES, and PES patients ($P < .001$). At 24 months, the rates of TVF with the PES, PC-ZES, and SES were 15.3%, 11.2%, and 9.9% ($P = .43$ and .01 for PC-ZES vs. SES and PES, respectively). No significant differences were found in the rates of death, MI, or ST at 2 years between the three stents, although there was a significant difference in TVR (8.6% vs. 6.0% vs. 3.1%, $P = .03$ and .01 for PC-ZES vs. SES and PES, respectively).
ZEST-AMI[153]	STEMI	SES and PES	328 (all)	1 yr	For the primary composite end point of death, MI, and ischemia-driven TVR, no significant difference was apparent between the PC-ZES, SES, and PES at 1 year (11.3% vs. 8.2% vs. 8.2%, respectively, $P = .83$). In-segment late loss was 0.28 ± 0.42 mm with the SES versus 0.46 ± 0.48 mm with the PC-ZES versus 0.47 ± 0.50 mm with the PES (P = .029). At 8-month follow-up, restenosis rates were 2.7% with the SES versus 15.9% with the PC-ZES versus 12.3% with the PES ($P = .027$).

BMS, Bare-metal stent; *CAD,* coronary artery disease; *CTO,* chronic total obstruction; *IVUS,* intravascular ultrasound; *MACE,* major adverse cardiovascular event; *MI,* myocardial infarction; *NES,* novolimus-eluting stent; *PC-ZES,* zotarolimus-eluting stent (Endeavor platform); *PES,* paclitaxel-eluting stent; *SES,* sirolimus-eluting stent; P_{NI}, *P* value for noninferiority; P_{SUP}, *P* value for superiority; *TLR,* target-lesion revascularization; *TVF,* target-vessel failure (death, MI, or TVR); *TVR,* target-vessel revascularization; *ST,* stent thrombosis; *STEMI,* ST-segment elevation myocardial infarction.

the PC-ZES was compared with other DESs (see Table 16-8). In the Medtronic Endeavor III Drug-Eluting Coronary Stent System Clinical Trial (ENDEAVOR III),[149] the rates of late loss and restenosis were significantly greater with the PC-ZES than with the SES; indeed, in this trial, the PC-ZES failed to meet its primary end point. However, at 5-year follow-up, the PC-ZES was associated with lower rates of all-cause death (a trend was apparent for cardiac death) and significantly lower rates of MI compared with SES. In contrast, no significant difference was apparent between the PC-ZES and the SES in the rates of TVR and definite ST. These findings were corroborated in the Efficacy of Three Different Limus Agent–Eluting Stents to Prevent Restenosis (ISAR-TEST-2) trial,[150] which found no significant difference between the SES and the PC-ZES in the rates of death, MI, or definite ST. The Randomized Comparison of Zotarolimus- and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease (ENDEAVOR IV) trial[40] randomized 1548 patients to either a PC-ZES or a PES. In this trial, the PC-ZES was associated with a greater late loss and angiographic restenosis compared with the PES, although 9-month rates of TVF were comparable between the two devices. However, similar to the ENDEAVOR III experience, at 5-year follow-up, the PC-ZES was associated with similar rates of TLR and significantly lower rates of cardiac death or MI compared with the PES.

Whereas the results of these trials ultimately led to device approval for the PC-ZES, these studies were insufficiently powered to detect differences in hard clinical end points, and several other trials have been conducted with mixed results, specifically regarding the safety of the PC-ZES. No significant differences in cardiac mortality, MI, TVR, and ST were apparent between the SES, PES, and PC-ZES in the Korean Multicenter Endeavor (KOMER) trial,[151] whereas significantly higher rates of MACE and definite ST were apparent with the PC-ZES compared with the SES in the Novel Approaches for Preventing or Limiting Events in Diabetic Patients (NAPLES-DIABETES) trial[152] and in the Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent With Sirolimus-Eluting and Paclitaxel-Eluting Stent for Coronary Lesions (ZEST) trial,[153] respectively (see Table 16-8). Although these trials led to potential concerns regarding the overall performance of the PC-ZES, two larger trials have examined these issues in more detail. The 2332-patient Randomized Clinical Comparison of the Endeavor and the Cypher Coronary Stents in Nonselected Angina Pectoris Patients (SORT OUT III) trial[154] reported significantly lower rates of all-cause mortality, MI, and definite ST with the SES compared with the PC-ZES at shorter-term follow-up (1 year). However, at 5-year follow-up, MACE rates were similar between the two devices (17% with the PC-ZES vs. 15.6% with the SES, $P = .40$) because of time-related differences in clinical outcomes that favored the SES during the first year of follow-up (8.0% with the PC-ZES vs. 3.9% with the SES, $P < .0001$) but favored the PC-ZES between 1 and 5 years (9.0% vs. 11.6%, $P = .07$).[155] As shown in Figure 16-6, definite ST was more frequent with the PC-ZES than with the SES at the 1-year follow-up (1.1% vs. 0.3%, $P = .036$), whereas the opposite result was apparent in the period between 1 and 5 years (0.1% with the PC-ZES vs. 1.8% with the SES, $P = .03$).

Considered collectively, these trials demonstrate that despite greater late loss in the period of angiographic surveillance, the PC-ZES is safe and effective over long-term follow-up, compared with the first-generation DES, and is more effective than the BMS. In this regard, early angiographic measures might be less predictive of late-term outcomes, as suggested by several studies that have shown a better safety and efficacy profile with the PC-ZES compared with the first-generation DES after the first year of follow-up. With this background, the large multicenter Patient-Related Outcomes With Endeavor Versus Cypher Stenting Trial (PROTECT) was recently reported in which 8791 patients with CAD were randomized to either a PC-ZES or an SES, representing the only comparative DES trial prospectively powered to show differences in ST.[156] At a 3-year follow-up, no significant difference was apparent between the two devices with regard to the primary end point of definite/probable ST (1.4% for the PC-ZES vs. 1.8% for the SES, $P = .22$). No significant differences were reported between

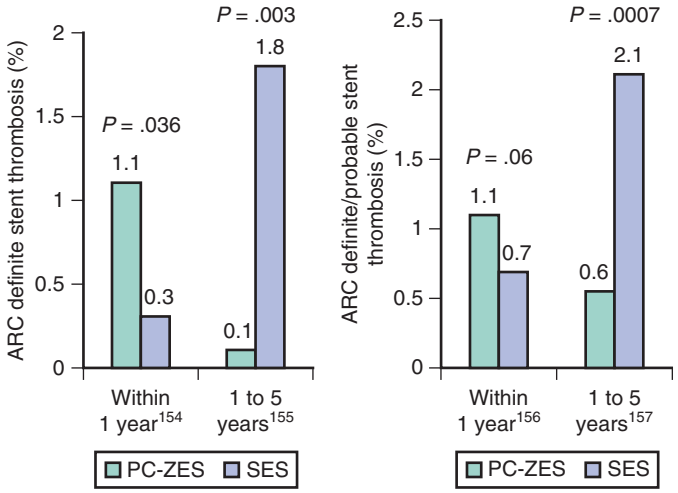

FIGURE 16-6 Stent thrombosis rates before and after 1 year in the SORT OUT III trial (*left panel*) and in the PROTECT trial (*right panel*). *ARC,* Academic Research Consortium; *SES,* sirolimus-eluting stent; *ZES,* zotarolimus-eluting stent (Endeavor platform).

the two devices in the 3-year rates of death or MI, but a significant difference in the risk of TLR favored the SES (3.5% with the SES vs. 5.6% with the PC-ZES, $P < .0001$). However, at a 5-year follow-up, definite/probable ST continued to accrue in the SES arm, such that the PC-ZES was associated with significantly lower 5-year rates of definite/probable ST compared with the SES (1.7% vs. 2.8%, respectively, $P = .0007$).[157] As shown in Figure 16-6, landmark analyses suggested time-related differences in ST between the two devices such that the PC-ZES was associated with slightly greater rates of definite/probable ST during the first year (1.1% with the PC-ZES vs. 0.7% with the SES, $P = .056$) but with significantly lower rates of definite/probable ST in the period between 1 and 5 years (0.6% with the PC-ZES vs. 2.1% with the SES, $P < .001$). In addition, the PC-ZES was associated with significantly lower 5-year rates of overall MI (5.0% vs. 6.6%, $P = .002$) and target-vessel MI (4.2% vs. 5.5%, $P = .027$) compared with the SES.

Re-ZES (Resolute)

In the Re-ZES, zotarolimus is eluted from the thin-strut cobalt-alloy BMS platform, which has undergone several iterations to increase deliverability and flexibility. Instead of the phosphorylcholine coating of the Endeavor stent, the Resolute stent uses a proprietary BioLinx tripolymer coating (4.1-µm thickness) that consists of a hydrophilic endoluminal component and a hydrophobic component adjacent to the metal stent surface. This polymer serves to slow the elution of zotarolimus relative to the Endeavor PC polymer, such that 60% of the drug is eluted by 30 days and 100% is eluted by 180 days, making this the slowest rapamycin analogue–eluting DES.

In the Clinical Evaluation of the Resolute Zotarolimus-Eluting Coronary Stent System in the Treatment of De Novo Lesions in Native Coronary Arteries (RESOLUTE)[158] trial, the Re-ZES stent was implanted in 139 patients with noncomplex CAD. The primary end point of in-stent late lumen loss at 9 months was 0.22 mm (± 0.27), and the in-segment binary restenosis rate was 2.1%, both significantly less than that seen with its bare-metal comparator platform. MACE, TLR, and Academic Research Consortium (ARC) definite/probable ST at 12 months occurred in 8.7%, 0.7%, and 0% of patients, respectively. Following these favorable results, the efficacy and safety of the Re-ZES were investigated in five RCTs that compared this device either with the CoCr-EES—in the RESOLUTE all-comers trial, The Real-Word Endeavor Resolute Versus Xience V Drug-Eluting Stent Study in Twente (TWENTE),[108] and the Intracoronary Stenting and Antithrombotic Regimen: Drug-Eluting Stents for Unprotected Left Main Stem Disease (ISAR–LEFT MAIN)[106-108]—or the PtCr-EES in the DUTCH PEERS[138] and HOST-ASSURE trials.[137]

In the RESOLUTE[107] all-comers trial, 2292 unselected patients were randomized to the Re-ZES versus the CoCr-EES (see Table 16-7). Angiographic follow-up was planned in a subset of 460 patients at 13 months, after the 12-month assessment of the major clinical end points. Compared with the CoCr-EES, the Re-ZES was noninferior for the primary 1-year end point of TLF (8.2% vs. 8.3%, $P_{NI} < .001$). No significant differences were reported between the two devices in the 1-year rates of death, cardiac death, MI, or TLR. However, the CoCr-EES did result in significantly lower 1-year rates of definite ST (0.3% with the CoCr-EES vs. 1.2% with the Re-ZES, $P = .01$) and definite or probable ST (0.7% with the CoCr-EES vs. 1.6% with the Re-ZES, $P = .05$; see Table 16-7). At 13 months, restenosis occurred infrequently with both stents, although in-segment late loss was slightly greater with the Re-ZES compared with the CoCr-EES (0.15 ± 0.43 mm vs. 0.06 ± 0.40 mm, $P = .04$). When clinical follow-up was extended to 4 years, the results between the two stents were similar.[159] Specifically, the rates of TLF (15.2% with the Re-ZES vs. 14.6% with the CoCr-EES, $P = .68$), cardiac death (5.4% vs. 4.7%, $P = .44$), target-vessel MI (5.3% vs. 5.4%, $P = 1.00$), and clinically indicated TLR (7.0% vs. 6.5%, $P = .62$) were similar between the Re-ZES and the CoCr-EES. In addition, the difference in definite ST, which was apparent at 1 year, was no longer statistically significant, although a trend was still maintained (0.7% with the CoCr-EES vs. 1.4% with the Re-ZES, $P = .07$).

In the TWENTE trial, 1391 patients were randomly assigned to receive either a CoCr-EES or an Re-ZES.[108] At a 1-year follow-up, rates of TVF—cardiac death, MI, or clinically driven TVR, the primary end point of the study—were 8.1% in the CoCr-EES group and 8.2% in the Re-ZES group ($P_{NI} = .001$). No significant difference was found in the rate of TVF components between the two devices. Definite/probable ST rates were relatively low and were similar for the Re-ZES and CoCr-EES (0.9% and 1.2%, respectively, $P = .59$). Definite ST rates were also low in both stent groups (0.58% with the Re-ZES and 0% with the CoCr-EES, $P = .12$). At a 2-year follow-up, no significant difference was apparent between the two stent groups with respect to the primary end point of TVF (10.8% for the Re-ZES vs. 11.6% for the CoCr-EES, $P = .65$) despite fewer TLRs in patients treated with the CoCr-EES (4.9% vs. 2.6%, $P = .03$).[160] Similar results were apparent in the Prospective Randomized Trial of Everolimus- and Zotarolimus-Eluting Stents for Treatment of Unprotected Left Main Coronary Artery Disease (ISAR–LEFT MAIN-2) trial,[106] discussed further in the subsection on left main and multivessel disease. (See Chapter 23, Percutaneous Coronary Intervention for Unprotected Left Main Coronary Artery Stenosis, and Chapter 24, Complex and Multivessel Percutaneous Coronary Intervention.)

Two RCTs have compared the Re-ZES with the PtCr-EES. In the 1811-patient DUTCH PEERS trial,[138] the primary end point of TVF (cardiac death, target-vessel MI, or TVR) at 1 year was 6% in the Re-ZES group and 5% in the PtCr-EES group, thus meeting the established criteria of noninferiority of the Re-ZES versus the PtCr-EES ($P_{NI} = .006$). No significant difference was apparent in individual components of the primary end point or in the rate of definite ST (0.3% vs. 0.7%, $P = .34$, respectively). In the HOST-ASSURE trial,[161] 3750 all-comer patients were randomized to either the Re-ZES or the PtCr-EES. At 1-year follow-up, the Re-ZES was noninferior to the PtCr-EES for the primary end point of TLF (cardiac death, target-vessel MI, and ischemia-driven TLR), which was 2.9% for both the Re-ZES and the PtCr-EES ($P_{NI} = .02$). No significant difference was apparent in individual components of the primary end point, and definite ST rates were similar (0.3% vs. 0.2%, $P = .34$).

In summary, these trials have collectively established the overall similar efficacy and safety profiles of the Re-ZES, CoCr-EES, and PtCr-EES. All of these trials, however, have been insufficiently powered to detect small differences in low-frequency end points such as ST. In addition, four out of the five randomized trials that compared the

Re-ZES with the other second-generation DESs—ISAR–LEFT MAIN-2, TWENTE, DUTCH PEERS, and HOST-ASSURE—turned out to be insufficiently powered also in relation to their respective primary study end points because of observed event rates that were lower than expected. Nonetheless, the current amalgamation of data regarding the Re-ZES supports its use as a consistently high-performing second-generation durable-polymer DES platform.

Bioabsorbable Polymer–Based Second-Generation Drug-Eluting Stents

Through drug elution and complete bioabsorption of the polymer, bioabsorbable polymer–based drug-eluting stents (BP-DESs) offer the potential to couple DES efficacy with the late safety profile of the BMS. In most BP-DESs, the polymer is coreleased with the drug and leaves behind a bare platform, or only a basecoat, that is potentially free of inflammatory stimuli triggered by the permanent polymers that coated first-generation DESs. Most BP coatings are composed of poly-L-lactic acid (PLLA) or polyglycolic acid (PLGA), which are absorbed over a variable amount of time. A variety of BP-DES has been recently developed, which differs by the stent platform, the composition and structure of the polymer and the kinetics of polymer bioabsorption, and the eluted drug (Fig. 16-7). Among these devices, the one that has received the most extensive investigation so far is the bioabsorbable polymer biolimus-eluting stent (BP-BES).

Bioabsorbable Polymer Biolimus-Eluting Stent (BioMatrix/Nobori) and Comparisons With First-Generation Drug-Eluting Stents

The BP-BES, which is manufactured as either BioMatrix (Biosensors, Newport Beach CA) or Nobori (Terumo Clinical Supply, Kakamigahara, Japan), elutes biolimus A9 (15.6 μg/mm), a semisynthetic rapamycin analogue with similar potency but greater lipophilicity than sirolimus, from the stainless steel S-stent platform (120- to 125-μm strut thickness). BioMatrix and Nobori use similar stent platforms, polymers, and drugs with only slight differences in the delivery system, delivery balloon, and stent-coating process. The delivery polymer is made of PLLA, which is applied solely to the abluminal stent surface (11 to 20 μm thick) and is metabolized via the Krebs cycle into carbon dioxide and water after a 6- to 9-month period. Conceptually, such a stent might not be prone to late inflammatory reactions, as are occasionally seen with durable polymers, and thus results in improved outcomes after 1 year.

As shown in Table 16-9, the BioMatrix BP-BES was investigated in the Limus Eluted From a Durable Versus Erodable Stent Coating Study (LEADERS)[162] and in the Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare-Metal Stents in Acute ST-Elevation Myocardial Infarction (COMFORTABLE-AMI) trial,[163] with a total of 2868 randomized patients. In the LEADERS trial, 1707 all-comer patients—55% of whom had ACSs—were randomized to a BP-BES versus an SES.[162] The BP-BES was noninferior to the SES for the primary 9-month composite end point of cardiac death, MI, or TVR and demonstrated similar rates of TLR and ST. A total of 427 patients were allocated to angiographic follow-up at 9 months, which demonstrated that the BP-BES was noninferior to the SES for the primary angiographic end point of in-stent diameter stenosis (mean 20.9% vs. 23.3%, $P_{NI} = .001$, $P_{SUP} = .26$). At 4-year follow-up, not only did the BP-BES maintain noninferiority compared with the SES, but it was also associated with significantly lower rates of very late definite ST with a positive interaction between the risk of ST and the time of its occurrence.[164] These findings were confirmed in a meta-analysis[165] of patient-level data from the LEADERS,[162] Rapamycin-Eluting Stents With Different Polymer Coating to Reduce Restenosis (ISAR-TEST-3),[166] and Intracoronary Stenting and Angiographic Results: Test Efficacy of Three Limus-Eluting Stents (ISAR-TEST-4) trials[97] to compare different types of BP-DES—namely, the BP-BES and the Yukon Choice PC-SES (Translumina, Germany)—with a first-generation SES. At 4-year follow-up, the risks of TLR and definite ST were significantly lower with the BP-DES compared with the SES. Of note, the BP-DES was associated with a significant reduction of very late ST compared with the SES, with a significant reduction also in the risk of late MI. Overall, these findings are consistent with the notion that bioabsorption of the polymer after elution of the antiproliferative drug may minimize the risk of late adverse events. BP-BESs were also studied in the COMFORTABLE-AMI trial,[163] a prospective multicenter trial that randomly assigned 1161 patients with ST-segment elevation MI to either a BP-BES or a BMS. The results of this trial are discussed later.

The Nobori BP-BES has been investigated in six randomized trials—Nobori I phase I,[167] Nobori I phase II,[168] Nobori Japan,[102] SORT OUT V,[169] COMPARE II,[116] and NEXT[134]—with 9099 randomized patients. In the small Randomized Comparison of Nobori, Biolimus A9-Eluting Coronary Stent with a Taxus Paclitaxel-Eluting Coronary Stent in Patients With Stenosis in Native Coronary Arteries (Nobori I) phase I[167] ($N = 120$) and phase II trials[168] ($N = 243$), the BP-BES was shown to be noninferior compared with the PES for the primary end point of 9-month late lumen loss, with demonstration of superiority in Nobori I phase II. Similarly, in the somewhat larger Nobori Japan trial (Randomized Comparison of the Nobori Biolimus A9-Eluting Stent With the Sirolimus-Eluting Stent in Patients With Stenosis in Native Coronary Arteries; $N = 326$), the Nobori was shown to be noninferior compared with the SES for the composite primary end point of cardiac death, MI, or TVR at 9-month follow-up.[102] However, in the SORT OUT V trial, a large-scale prospective randomized trial that compared the Nobori ($n = 1229$) with the Cypher ($n = 1239$),[169] the Nobori failed to reach the primary hypothesis of noninferiority for the primary end point of cardiac death, MI, definite ST, or TVR at 9 months (4.1% with the BP-BES vs. 3.1% with the SES, $P_{NI} = .06$). In addition, a significant difference in the risk of ST in favor of the SES was apparent at 1 year (0.7% with the BP-BES vs. 0.2% with the SES, $P = .03$). These early differences were mitigated at 3-year follow-up with no significant differences in MACE rates (10.1% with the Nobori vs. 11.2% with the Cypher, $P = .41$) or ST (1.4% with the Nobori vs. 1.0% with the Cypher, $P = .45$).[170] Of note, six episodes of definite ST occurred between 2 and 3 years with the Cypher, whereas only one occurred with the Nobori.

In summary the Nobori and the BioMatrix have been compared with first-generation DESs in a total of five RCTs, and although some of them have shown improved safety with similar efficacy of the BP-BES compared with either the PES or SES, others have not confirmed this association.

Bioabsorbable Polymer Biolimus-Eluting Stents (BioMatrix/Nobori) and Comparisons With Second-Generation Drug-Eluting Stents

Among the second-generation durable polymer–based DESs, the CoCr-EES is the only one that has been compared with the BES in three RCTs: COMPARE II,[116] NEXT,[134] and BASKET-PROVE II.[114] Abluminal Biodegradable Polymer Biolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent (COMPARE II)[116] was a prospective, multicenter, controlled, randomized trial that compared the BP-BES with the CoCr-EES in 2707 all-comer patients. At 1-year follow-up, the BP-BES was shown to be noninferior to the CoCr-EES for the primary end point of cardiac death, MI, or TVR (5.2% with the BP-BES vs. 4.8% with the CoCr-EES, $P_{NI} < .0001$). No significant difference was found between the two devices in the rates of the individual components of the primary end point, and rates of ST were similar (0.4% vs. 0.7%, respectively; $P = .37$). Similar results were apparent at the 3-year follow-up.[171] The Nobori Biolimus-Eluting Versus Xience/Promus Everolimus-Eluting Stent Trial (NEXT)[134] was a controlled, multicenter noninferiority trial that randomly assigned 3235 patients to either the BP-BES or the CoCr-EES. At 1-year follow-up, the BP-BES was noninferior compared with the CoCr-EES for the primary end point of TLR (4.2% with the BES vs. 4.2% with the CoCr-EES, $P_{NI} < .0001$). Episodes of ST were rare in both groups, but they were numerically higher with the BP-BES than with the CoCr-EES (0.25% with the BES vs. 0.06% with the CoCr-EES, $P = .18$). The BP-BES was also noninferior to the CoCr-EES for the primary angiographic end point of in-segment late loss (0.03 ± 0.39 mm vs. 0.06 ± 0.45 mm, respectively, $P_{NI} < .0001$). These results were sustained at 2 years.[115] Finally,

Stent	Orsiro	Inspiron	Elixir DESyne	Elixir Myolimus	Infinnium	Supralimus	Firehawk	Biomatrix	Nobori	Excel stent	Axxess
Company	Biotronik	Scitech	Elixir Medical Corp	Elixir Medical Corp	Sahajanand Medical Technologies	Sahajanand Medical Technologies	MicroPort Medical	Biosensors	Terumo	JW Medical Systems	Devax Inc
Eluted drug	Sirolimus	Sirolimus	Novolimus	Novolimus	Paclitaxel	Sirolimus	Paclitaxel	Biolimus A9	Biolimus A9	Sirolimus	Biolimus A9
Stent platform	CoCr	CoCr	CoCr	CoCr	SS	SS	CoCr	SS	SS	SS	Nitinol
Strut thickness (μm)	60	75	80	80	80	80	86	112	112	119	152
Polymer	PLLA	PLA, PLGA	Abluminal PLA	Abluminal PLA	PLLA, PLGA, PCL, PVP	PLLA, PLGA, PVP	PLA	Abluminal PLA	Abluminal PLA	PLA	Abluminal PLA
Time of polymer degradation (months)	7	6–9	6–9	6–9	7	7	6–9	6–9	6–9	6–9	6–9

A

Stent	MiStent	Sparrow limus-eluting stent	Synergy	Ultimaster DES	Noya	Eucatax	Yukon Choicè PC	Combo	Jactax	Coracto
Company	Micell Technologies	Cardiomind	Boston Scientific	Terumo	Medfavour Medical	Eucatech Medical	Translumina	Orbusneich Medical	Boston Scientific	Alvimedica
Eluted drug	Sirolimus	Sirolimus	Everolimus	Sirolimus	Sirolimus	Paclitaxel	Sirolimus	Sirolimus	Paclitaxel	Sirolimus
Stent platform	CoCr	Nitinol	PtCr	CoCr	CoCr	SS	SS	SS	SS	SS
Strut thickness (μm)	64	67	74	80	81	85	87	90	97	100
Polymer	PLGA	Dl-lactide, glycolide, ε-caprolactone and polyethylene-glicol copolymer	PLGA rollcoat abluminal	PDLLA-PCL copolymer	PDLLA	PLGA	PLA and shellac	Abluminal Dl-lactide, glycolide, ε-caprolactone and polyethylene-glycol with CD34 antibody layer	Abluminal (PLA)	PLGA
Time of polymer degradation (months)	2	6	3–4	3–4	4	2	2	3	4	2

B

FIGURE 16-7 Main characteristics of drug-eluting stents coated with bioabsorbable polymers with a kinetics of bioabsorption longer (**A**) or shorter (**B**) than 6 months. *CoCr,* Chromium cobalt; *PCL,* poli (ε-caprolactone); *PDLLA,* poly-D,L-lactic acid; *PLA,* polylactic acid; *PLGA,* polyglycolic acid; *PLLA,* poly-L-lactic acid; *PtCr,* platinum chromium; *PVP,* poly(N-vinyl-2-pyrrolidone); *SS,* stainless steel.

in BASKET-PROVE II, 2291 patients who required coronary stents 3.0 mm or more in diameter were randomized to a biolimus-A9–eluting BP-DES, CoCr-EES, or BMS.[114] The primary composite end point of cardiac death, MI, or clinically indicated TVR within 2 years occurred in 6.8% of patients with the CoCr-EES, in 7.6% with the BP-BES, and in 12.7% with the BMS. The BP-BES was noninferior to the CoCr-EES by intention-to-treat analysis (P_{NI} = .042) but not in a per-protocol analysis (P_{NI} = .09). The three stent groups did not differ in event rates beyond 1 year.

In summary, although no major differences emerged between the BP-DES and the CoCr-EES in these three trials, no evidence suggested that the BP-DES provided any late safety advantages compared with the CoCr-EES, and larger trials are required to determine whether the BP-DES matches the safety and efficacy profile of the CoCr-EES.

TABLE 16-9 Randomized Controlled Trials of Bioabsorbable Polymer-Based Drug-Eluting Stents

Trial	Study Cohort	Stent Comparators	Number Randomized	Latest Follow-Up to Date	Brand	Results of the Primary End Point
BASKET–PROVE II[114]	All comers with lesions in coronary arteries ≥3 mm	BP-BES BMS CoCr-EES	2314	2 yr	Nobori ProKinetic Xience	The BP-BES was noninferior to the CoCr-EES with respect to the primary end point of cardiac death, MI, or clinically indicated TVR at 2 years in the intention-to-treat analysis but not in a per-protocol analysis.
BIOFLOW II[121]	Noncomplex CAD	BP-SES CoCr-EES	452	9 mo	Orsiro Xience	The BP-SES was noninferior to the CoCr-EES with respect to the primary end point of in-stent late lumen loss (0.10 ± 0.32 mm vs. 0.11 ± 0.29 mm, respectively, $P_{NI} < .0001$). No significant between-group differences were found in the rate of TLF (6.5% vs. 8.0%, $P = .58$). No episodes of ST were reported in either group.
BIOSCIENCE[119]	Minimum exclusion criteria	BP-SES CoCr-EES	2119	12 mo	Orsiro Xience	The BP-SES was noninferior to the CoCr-EES with respect to the primary end point of TLF (6.5% vs. 6.6%, respectively; $P_{NI} < .0004$).
CARE II[441]	Noncomplex CAD	BP-Sparrow SES Sparrow-BMS Driver	138	9 mo	Sparrow limus Sparrow BMS Driver	The Sparrow SES was superior to both the Sparrow-BMS and the Driver with respect to the primary end point of in-stent late lumen loss at 6 months (0.29 ± 0.45 mm with Sparrow SES vs. 0.86 ± 0.54 mm with Sparrow BMS vs. 0.94 ± 0.39 mm with Driver, $P < .0001$).
CENTURY II[120]	Noncomplex CAD	BP-SES CoCr-EES	1123	9 mo	Ultimaster Xience	The Ultimaster was noninferior to the CoCr-EES for the primary end point of TLF (4.1% with BP-SES vs. 5.4% with CoCr-EES, $P_{NI} < .0001$).
COMFORTABLE-AMI[163]	STEMI	BP-BES BMS	1161	1 yr	BioMatrix Gazelle	The BP-BES was superior to the BMS with respect to the primary end point of cardiac death, target-vessel MI, or ischemia-driven TLR at 1 year (4.3% with BP-BES vs. 8.7% with BMS, $P = .004$). Rates of cardiac death were not significantly different between the two devices, whereas BP-BES use was associated with significantly lower rates of target-vessel MI and ischemia-driven TLR.
COMPARE II[116,171]	All comers	CoCr-EES BP-BES	2707	3 years	Nobori Xience	The BP-BES was noninferior to the CoCr-EES for the primary end point of cardiac death, MI, or TVR at 1 year (5.2% with BP-PES vs. 4.8% with CoCr-EES, $P_{NI} < .0001$). No significant difference was apparent in the individual components of the primary end point. Similar results were apparent at 3 years.
CORACTO[442]	CTO	BP-SES BMS	95	2 years	Coracto Constant	The BP-SES was superior to the BMS for the primary end point of in-stent LLL at 6 months (0.77 ± 0.63 mm with BP-SES vs. 1.82 ± 0.82 mm with BMS, $P < .0001$). In segment restenosis was 17.4% with the the BP-SES versus 60.0% with the BMS ($P < .0001$). No significant difference was found in the risk of death or MI between the two stents.
DESSOLVE II[174,443]	Noncomplex CAD	BP-SES PC-ZES	184	2 yr	MiStent Endeavor	The BP-SES was superior to the PC-ZES for the primary end point of in-stent LLL at 9 months (0.27 ± 0.46 mm vs. 0.58 ± 0.41 mm, $P < .001$). No significant difference was found in the risk of death, MI, or TVR between the two stents at 2 years.

Continued

TABLE 16-9 Randomized Controlled Trials of Bioabsorbable Polymer-Based Drug-Eluting Stents—cont'd

Trial	Study Cohort	Stent Comparators	Number Randomized	Latest Follow-Up to Date	Brand	Results of the Primary End Point
EUCATAX[444,445]	Noncomplex CAD	BP-PES BMS	422	2 yr	Eucatax Equivalent BMS	The BP-PES was superior to the BMS for the primary end point of cardiac death, MI, or TVR at 1 year (9.5% with BP-PES vs. 17.1% with BMS, $P = .02$).
EVOLUTION[446,447]	Noncomplex CAD	BP-SES SES	1923	2 yr	Excel Cypher	The BP-SES was noninferior to the SES for the primary end point of cardiac death, MI, or ischemia-driven TVR at 1 year (0.89% with BP-SES vs. 1.34% with SES, $P = .25$). No significant difference was apparent in the rates of the individual components of the primary end point.
EVOLVE I[133]	Noncomplex CAD	HD BP-EES LD BP-EES PtCr-EES	291	6 mo	Synergy HD Synergy LD Promus Element	The BP-EES was noninferior to the PtCr-EES for the primary end point of cardiac death, target-vessel MI, or TVR at 30 days (0.0% with PtCr-EES, 1.1% with Synergy HD, and 3.1% with Synergy LD, $P_{NI} < .0001$). At 6 months, in-stent LLL was 0.15 ± 0.34 mm for the PtCr-EES, 0.10 ± 0.25 mm for the Synergy HD, and 0.13 ± 0.26 mm for the Synergy LD ($P < 0.01$).
EVOLVE II[175]	Noncomplex CAD	BP-EES PtCr-EES	1684	12 mo	Synergy Promus Element	The BP-EES was noninferior to the PtCr-EES for the primary end point of TLF (6.7% with BP-EES vs. 6.2% with PtCr-EES; $P_{NI} = .0003$).
EXCELLA II[438]	Noncomplex CAD	BP-NES PC-ZES	146	6 mo	Elixir DESyne Endeavor	The BP-NES was superior to the PC-ZES for the primary end point of in-stent LLL at 9 months (0.11 ± 0.32 mm with BP-NES vs. 0.63 ± 0.42 mm with PC-ZES, $P < .0001$). No significant difference was found in the risk of death, MI, or TVR between the two devices.
INSPIRON-I[448]	Noncomplex CAD	BP-SES BMS	58	2 yr	Inspiron Cronus[449]	The Inspiron was superior to the Cronus for the primary end point of in-stent LLL at 6 months (0.22 mm with Inspiron vs. 0.84 mm with Cronus, $P < .001$). At 2 years, the Inspiron was associated with lower rates of TLR compared with the Cronus (0.0% vs. 21.1%, $P = .02$).
ISAR-TEST-3[117,166]	Noncomplex CAD	BP-SES SES PF-SES	404	2 yr	Yukon C Cypher Yukon[117]	The BP-SES was noninferior to the SES for the primary end point of in-stent LLL at 8 months (0.17 ± 0.45 mm with BP-SES vs. 0.23 ± 0.46 mm with SES, $P_{NI} < .001$). The PF-SES did not meet the prespecified criteria for noninferiority (in-stent LLL = 0.47 ± 0.56 mm, $P_{NI} = .94$).
ISAR-TEST-4[97,428]	Noncomplex CAD	BP-SES CoCr-EES SES	2603	3 yr	Yukon C Xience Cypher	The BP-SES was noninferior to pooled CoCr-EES and SES data for the primary end point of cardiac death, MI, or TLR at 1 year (13.8% vs. 14.4%, respectively, $P = .005$). Rates of cardiac death, MI, TLR, and ST were similar among the three stent groups.
LEADERS[162,164]	All comers	BP-BES SES	1707	4 yr	BioMatrix Cypher	The BP-BES was noninferior to the SES for the primary end point of cardiac death, MI, or clinically indicated TVR at 9 months (9% with BP-BES vs. 11% with SES, $P_{NI} = .003$). Noninferiority was sustained at 4 years, with significantly lower rates of very late ST with the BP-BES compared with the SES (0.4% vs. 2.0%, $P = .004$).

TABLE 16-9 Randomized Controlled Trials of Bioabsorbable Polymer-Based Drug-Eluting Stents—cont'd

Trial	Study Cohort	Stent Comparators	Number Randomized	Latest Follow-Up to Date	Brand	Results of the Primary End Point
NEXT[115,134]	All comers	BP-BES CoCr-EES	3235	2 yr	Nobori Xience	The BP-BES was noninferior to the CoCr-EES for the primary end point of TLR at 1 year (4.2% in both groups, P_{NI} < .0001). Rates of cardiac death, MI, and ST were similar between the two stent groups. Noninferiority was sustained at 2-year follow-up.
NOBORI I phase I[167,450]	Noncomplex CAD	BP-BES PES	120	5 yr	Nobori Taxus	The BP-BES was noninferior to the PES for the primary end point of in-stent LLL at 6 months (0.15 ± 0.27 mm vs. 0.32 ± 0.33 mm, respectively, P = .06). No significant difference was apparent between the two stents in the risk of death, MI, or TVR up to the 5-year follow-up.
NOBORI I phase II[168,451]	Noncomplex CAD	BP-BES PES	243	3 yr	Nobori Taxus	The BP-BES was superior to the PES for the primary end point of in-stent LLL at 9 months (0.11 ± 0.30 mm vs. 0.32 ± 0.50 mm, respectively, P = .001). No significant difference was found in the risk of death, MI, TLR, or ST between the two devices up to the 3-year follow-up.
NOBORI JAPAN[102,429]	Noncomplex CAD	BP-BES SES	326	3 yr	Nobori Cypher	The BP-BES was noninferior to the SES for the primary end point of cardiac death, MI, or TVR at 9 months (7.4% vs. 6.3%, respectively, P_{NI} < .001). Similar results were apparent at 3 years.
NOYA I[452,453]	Noncomplex CAD	BP-SES SES	300	2 yr	Noya Firebird 2	The BP-SES was noninferior to the SES for the primary end point of in-stent LLL at 9 months (0.11 ± 0.18 mm vs. 0.14 ± 0.23 mm, respectively, P_{NI} < .001). No significant difference was apparent in the risk of cardiac death, MI, TLR, or ST between the two devices at 2 years.
OCTDESI[454]	Noncomplex CAD	BP-PES PES	60	6 mo	HD Jacktax LD Jacktax Taxus Liberté	The Jactax (both HD and LD) resulted in similar strut coverage as the Taxus Liberté at 6 months (7.0 ± 12.2% for Jactax HD, 4.6 ± 7.3% for Jactax LD, and 5.3 ± 14.7% for Taxus Liberté, P = 0.81). No deaths, MI, or ST were reported through 1 year in either stent group.
PAINT[455]	Noncomplex CAD	BP-PES BP-SES BMS	274	1 yr	Infinnium Supralimus Milennium Matrix	The BP-PES and BP-SES were superior to the BMS for the primary end point of in-stent LLL (0.54 ± 0.44 mm with BP-PES vs. 0.32 ± 0.43 mm with BP-SES vs. 0.90 ± 0.45 mm with BMS, P < .001). No significant difference was found in the risk of death or MI between the three stents, whereas TVR was significantly lower with the BP-BES and BP-SES than with the BMS (5.6% with BP-PES, 5.8% with BP-SES, and 17.6% with BMS, P < .01).
REMEDEE[173]	Noncomplex CAD	BP-SES-CD34 ab PES	183	9 mo	Combo Taxus Liberté	The BP-SES-CD34 ab was noninferior to the SES for the primary end point of in-stent LLL (0.39 ± 0.45 mm vs. 0.44 ± 0.56 mm, respectively, P_{NI} = .001). At 1 year, no significant difference was found in the risk of death, MI, TLR, or ST between the two devices.

Continued

TABLE 16-9 Randomized Controlled Trials of Bioabsorbable Polymer-Based Drug-Eluting Stents—cont'd

Trial	Study Cohort	Stent Comparators	Number Randomized	Latest Follow-Up to Date	Brand	Results of the Primary End Point
SORT OUT V[169,170]	All comers	BP-BES SES	2468	3 years	Nobori Cypher	The BP-BES failed to achieve noninferiority compared with the SES for the primary end point of cardiac death, MI, definite ST, or TVR at 9 months (4.1% with BP-BES vs. 3.1% with SES, $P_{NI} = .06$). In addition, the BP-BES was associated with significantly higher 1-year rates of definite ST than the SES (0.7% vs. 0.2%, respectively, $P = .03$). However, no significant differences were apparent in MACE and ST between the two devices at the 3-year follow-up.
TARGET I[118,456]	Noncomplex CAD	BP-SES CoCr-EES	460	2 years	FireHawk Xience	The BP-SES was noninferior to the CoCr-EES for the primary end point of in-stent LLL at 9 months (0.13 ± 0.24 mm vs. 0.13 ± 0.18 mm, respectively, $P_{NI} < .0001$). No significant difference was found in the rates of TLF between the two devices up to 2 years.

ab, Antibody; *BES,* biolimus-eluting stents; *BMS,* bare-metal stent stents; *BP,* bioabsorbable polymer; *CAD,* coronary artery disease; *CoCr-EES,* cobalt-chromium everolimus-eluting stent; *CTO,* chronic total obstruction; *EES,* everolimus-eluting stent; *HD,* high dose; *LD,* low dose; *LLL,* late lumen loss; *MACE,* major adverse cardiovascular events (death, MI, TVR); *MI,* myocardial infarction; *NES,* novolimus-eluting stent; *PC-ZES,* zotarolimus-eluting stent (Endeavor platform); *PES,* paclitaxel-eluting stent; *PF,* polymer free; P_{NI}, *P* value for noninferiority; *PtCr,* platinum chromium; *SES,* sirolimus-eluting stent; *ST,* stent thrombosis; *TLR,* target-lesion revascularization; *TLF,* target-lesion failure (cardiac death, target lesion MI, or TLR); *TVR,* target-vessel revascularization.

Other Bioabsorbable Polymer–Based Drug-Eluting Stents

A variety of other BP-DESs have been designed and studied to varying degrees (see Fig. 16-7). Some BP-DESs are no longer manufactured (CoStar, Xtent, Nevo) either because of disappointing clinical results[172] or for commercial reasons. As shown in Table 16-9, most of these devices have undergone small-sized RCTs powered for angiographic end points. With respect to the sirolimus-based BP-DES, the Combo (OrbusNeich, Hong Kong) and MiStent (Micell Technologies, Durham, NC) SESs have shown promising angiographic outcomes.[173,174] The Yukon Choice PC SES was studied in the ISAR-TEST-3 and -4 trials and has been demonstrated to be noninferior to both the CoCr-EES and the SES for the composite end point of cardiac death, target-vessel MI, or TLR (see "Bioabsorbable Polymer Biolimus-Eluting Stent [BioMatrix/Nobori] and Comparisons With First-Generation Drug-Eluting Stents" section).[97,166] Additionally, the Orsiro (Biotronik AG, Germany) BP-SES has been shown to be noninferior to the CoCr-EES for in-stent late lumen loss at 9 months.[121] More recently, in the large-scale Randomized Comparison of a Sirolimus-Eluting Stent With Biodegradable Polymer Versus an Everolimus-Eluting Stent With a Durable Polymer for Percutaneous Coronary Revascularization (BIO-SCIENCE) trial,[119] 2119 patients with few exclusion criteria were randomly allocated to receive either the Orsiro or a CoCr-EES. At 1-year follow-up, TLF was 6.5% with the Orsiro and 6.6% with the CoCr-EES ($P_{NI} < .0004$) with ST rates of 0.9% versus 0.4% ($P = .16$). In a prespecified analysis of the primary end point, the Orsiro was associated with significantly lower rates of TLF compared with the CoCr-EES in patients who presented with STEMI. Finally, in the recently reported Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients With Coronary Artery Disease (CENTURY II) trial,[120] 1123 patients were randomly allocated to either a CoCr-EES or the Ultimaster (Terumo Clinical Supply, Kakamigahara, Japan) stent, a BP-based SES. At 9 months, the primary end point—a composite of cardiac death, target-vessel MI, and TLR—did not significantly differ between the two stents (4.14% with the BP-SES vs. 5.38% with the CoCr-EES, $P = .66$).

The platinum-chromium PLGA-based everolimus-eluting Synergy stent (Boston Scientific) is characterized by very thin struts (74 μm) and a 4-μm thick abluminal coating of PLGA polymer, which is completely absorbed within 4 months. In the Prospective Randomized Multicenter Single-Blind Noninferiority Trial to Assess the Safety and Performance of the Evolution Everolimus-Eluting Monorail Coronary Stent System for the Treatment of a De Novo Atherosclerotic Lesion (EVOLVE) trial,[133] in which 291 patients were randomized, this stent—at both full and half concentration doses of everolimus—was shown to be noninferior to the durable polymer PtCr-EES for the primary end point of angiographic late lumen loss (mean 0.10, 0.13, and 0.15 mm, respectively). In addition, at 6-month follow-up, clinical event rates were comparable among the three stent groups. The Prospective Multicenter Trial to Assess the Safety and Effectiveness of the Synergy Everolimus-Eluting Platinum Chromium Coronary Stent System for the Treatment of Atherosclerotic Lesions (EVOLVE II)[175] was a 1684-patient multicenter randomized trial in which the Synergy stent (100 μg everolimus/cm^2) was compared with the durable polymer PtCr-EES (Promus Element). At 1 year, the Synergy and Promus Element demonstrated similar rates of TLF (6.5% vs. 6.7% respectively, $P_{NI} = .0005$), with similar rates of the individual components of this end point. ST rates were similarly low with both stents, and no stent thromboses were observed with the Synergy stent beyond 30 days. Longer-term follow-up from this trial and additional studies in higher-risk patients than those enrolled in EVOLVE II will allow a more complete assessment of the safety and efficacy profile with this stent compared with a durable polymer EES.

Safety and Efficacy of Drug-Eluting and Bare-Metal Stents: Synthesizing the Data Through Meta-Analyses

DESs are among the most-studied devices used in medicine today, and abundant assessments of comparative device efficacy have been performed through a multitude of randomized trials adequately powered for both surrogate and clinical end points. However, with the one exception of the PROTECT trial,[156] these trials have been insufficiently powered to detect differences in infrequent safety end points such as death, MI, or ST. In addition, several large head-to-head trials of DESs have had lower than expected clinical event rates, which further limits their ability to reliably discriminate differences between stent types.[106,108,109,116,134,137,138] Furthermore, few studies have directly compared second-generation DESs with each other or with BMSs. In recognition of these issues, network meta-analyses have been performed

to investigate relative differences in safety and efficacy among the various devices. Network meta-analysis and mixed treated comparisons are novel research methods capable of comparing different therapies using a common reference treatment.[176]

In an analysis of 49 RCTs in which 50,844 patients were enrolled and assigned to receive FDA-approved stents, Palmerini and colleagues[177] reported that (1) at 1- and 2-year follow-up, the risk of definite ST was significantly lower with a CoCr-EES than with a BMS, a result not apparent with other DESs; (2) the reduction in ST with a CoCr-EES compared with a BMS was apparent both at 30 days and between 31 days and 1 year; and (3) the CoCr-EES was also associated with significantly lower 1-year rates of definite ST compared with other first- and second-generation DESs, including the PES, SES, PC-ZES, and Re-ZES (Fig. 16-8).

In a broader network meta-analysis that included 77 RCTs with 117,762 patient-years of follow-up, study selection was not restricted to FDA-approved devices, nor was it restricted to RCTs that reported ST using the ARC criteria. Bangalore and colleagues[178] reported comparable mortality rates with first-generation DESs, second-generation DESs, and BMSs. However, rates of MI were significantly lower with the SES, Re-ZES, and CoCr-EES (but not with the PES) compared with the BMS. Data on ST were consistent with the previous network meta-analysis, finding the lowest rates with the CoCr-EES. In addition, each DES reduced long-term TVR compared with BMSs, but the magnitude of the effect varied in relation to the type of DES, such that the CoCr-EES, SES, and Re-ZES had greater efficacy in reducing TVR than did the PES or PC-ZES.

Several network meta-analyses have also investigated the relative safety and efficacy of BP-based DESs versus other second-generation DESs and BMSs.[179-182] An analysis that included 89 randomized trials with 85,490 patients resulted in three major findings. First, BP-BESs were associated with significantly lower 1-year rates of cardiac death or MI, MI, and TVR compared with BMSs; lower 1-year rates of TVR were seen compared with PC-ZESs; and long-term outcomes were improved compared with BMSs and PESs. Second, BP-BESs were associated with higher rates of 1-year and long-term definite ST compared with CoCr-EESs, with a trend that suggested lower rates of MI with CoCr-EESs compared with BP-BESs. Third, significant time-related differences in ST were apparent among different stent types; the CoCr-EES was associated with the lowest rates of ST in the early and late periods, and the PES and SES had the highest risks of very late ST (Fig. 16-9).[182] In another network meta-analysis that included 126 randomized trials with 258,544 patient-years of follow-up, pooled BP-DES data showed similar efficacy as second-generation DESs in reducing TVR but had higher rates of ST than CoCr-EESs.[179] Similar findings have been observed in two other network meta-analyses.[180,181]

In summary, whereas most individual studies have not been adequately powered to assess overall DES safety, network meta-analyses have confirmed that second-generation durable polymer–based DESs are both highly efficacious and have demonstrable safety advantages over first-generation DES platforms and even over BMSs. Meta-analyses to date have not demonstrated a safety advantage of BP-based DESs over second-generation durable polymer-based DESs. Longer-term follow-up from other studies (e.g., EVOLVE II) will provide important additional data in this regard.

Polymer-Free Drug-Eluting Stents

Polymer-free DESs feature the attractive combination of antiproliferative drug elution without a polymer coating. Polymer-free elution mechanisms include use of a nonpolymeric coating intermediate; surface modification techniques to adhere the drug onto the stent, with or without covalent bonding or chemical precipitation; use of reservoirs (grooves or wells) within the stent struts; and filling the inside of a hollow stent with drug that can diffuse out through holes drilled in the struts. As shown in Figure 16-10, several polymer-free DESs have been developed with different characteristics and novel mechanisms to control drug elution. However, clinical studies with these devices have been of limited size, were underpowered for clinical end points, and reported conflicting results (Table 16-10). In view of these limitations, a meta-analysis that included eight RCTs with 6178 patients comparing pooled polymer-free DESs with SESs, PESs, or Re-ZESs was recently reported.[183] In that meta-analysis, the polymer-free DES appeared to be safe and effective, but it did not provide any advantages compared with the other permanent polymer-based DESs. Larger-scale studies are planned with several of these devices.

Conclusions

In summary, significant progress has been made with second-generation DESs compared with their first-generation counterparts in terms of enhanced deliverability, antirestenotic efficacy, and safety. Nonetheless, progressive iterations of stent platforms, drug delivery systems (including the absence of polymer), and drugs are being explored in an attempt to further improve clinical outcomes with these devices.

STENTS IN SPECIFIC SITUATIONS

Acute ST-Segment Elevation Myocardial Infarction

Acute ST-segment elevation myocardial infarction (STEMI) is caused in most cases by rupture of a thin-cap fibroatheroma, a lesion consisting of a lipid-rich necrotic core and an overlying thin (<65 μm), inflamed fibrous cap.[184] Tissue factor and other prothrombotic constituents are released and result in thrombotic occlusion of the coronary vessel and subsequent myocardial necrosis. Timely reperfusion with PCI results in improved myocardial salvage and reduced rates of recurrent ischemia, reinfarction, stroke, and death compared with fibrinolytic therapy.[185] As shown in Figure 16-11, compared with balloon angioplasty, implanting a BMS in STEMI further reduces TVR but not death or reinfarction.[186] Stent implantation in or adjacent to a fibroatheroma may result in delayed endothelialization,[187] and the highest rates of ST have been reported after stent implantation in STEMI, although this risk can be somewhat ameliorated with more potent antiplatelet agents.[188,189]

The safety and efficacy of DES in STEMI have been reported from at least 20 randomized trials in 11,924 patients and from at least 18 registries in 26,521 patients (Table 16-11). Considering that in five trials, three or more different DESs have been compared with each other or versus BMSs,[100,131,151,153,190] collectively, 15 RCTs have compared first-generation DESs with BMSs,[100,131,190-201] and seven have compared first-generation DESs to each other,[†] four compared second-generation DESs with BMSs,[100,112,131,163] and six compared second-generation DESs against first-generation DESs.[92,98,100,131,151,153] In general, these studies have established the efficacy and safety of the DES compared with the BMS, with lower rates of TVR and similar rates of death and MI. However, these individual studies were insufficiently powered to detect differences in safety end points across stent platforms, and therefore several meta-analyses have been performed to pool data. In the Drug-Eluting Stent in Primary Angioplasty (DESERT) cooperation,[204] individual patient data were collected from 11 randomized trials that included 6298 patients randomized to either a first-generation DES (n = 3980) or a BMS (n = 2318). Compared with the BMS, first-generation DESs were associated with similar rates of death, MI, and ST but lower rates of TVR at a mean follow-up of 1201 days. However, first-generation DESs were associated with higher rates of very late ST and reinfarction.

Given the safety concerns of the first-generation DES, particularly in the high-risk cohort of patients undergoing STEMI PCI, several studies have examined whether second-generation DESs have further improved the outcomes of patients with STEMI. In the EXAMINATION trial, 1504 patients who presented with STEMI within 48 hours from symptom onset were randomized to either a CoCr-EES (n = 751)

[†]References 73, 100, 131, 151, 153, 202, 203.

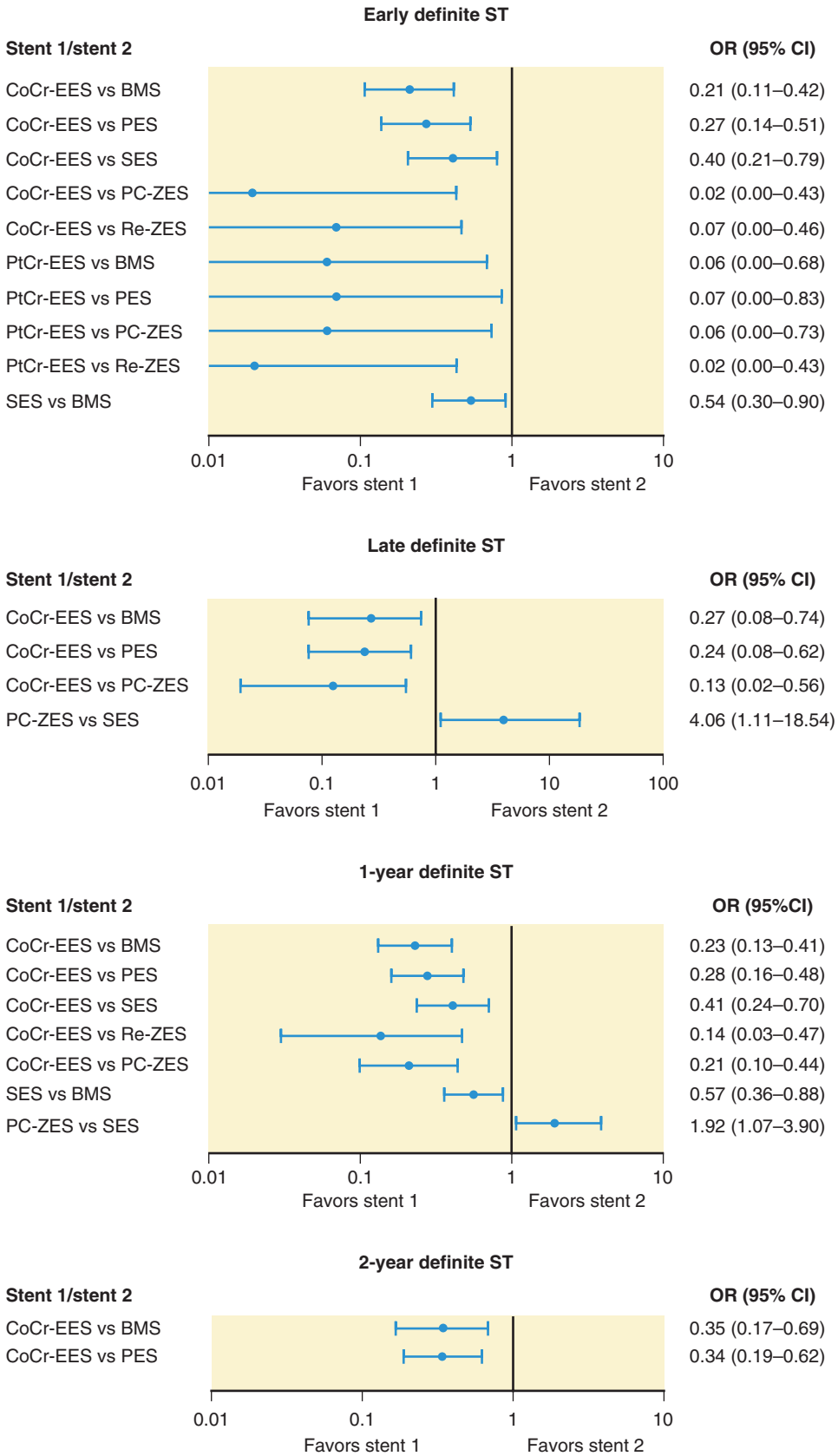

FIGURE 16-8 Network meta-analysis including 49 randomized controlled trials and 50,844 patients, which shows time-related differences between various drug-eluting and bare-metal stents (BMSs). Only statistically significant differences are shown. *CI,* Confidence interval; *CoCr-EES,* cobalt-chromium everolimus-eluting stent; *OR,* odds ratio; *PC-ZES,* phosphorylcholine polymer–based zotarolimus-eluting stents; *PES,* paclitaxel-eluting stent; *PtCr-EES,* platinum-chromium everolimus-eluting stent; *Re-ZES,* Resolute zotarolimus-eluting stent; *SES,* sirolimus-eluting stent; *ST,* stent thrombosis.

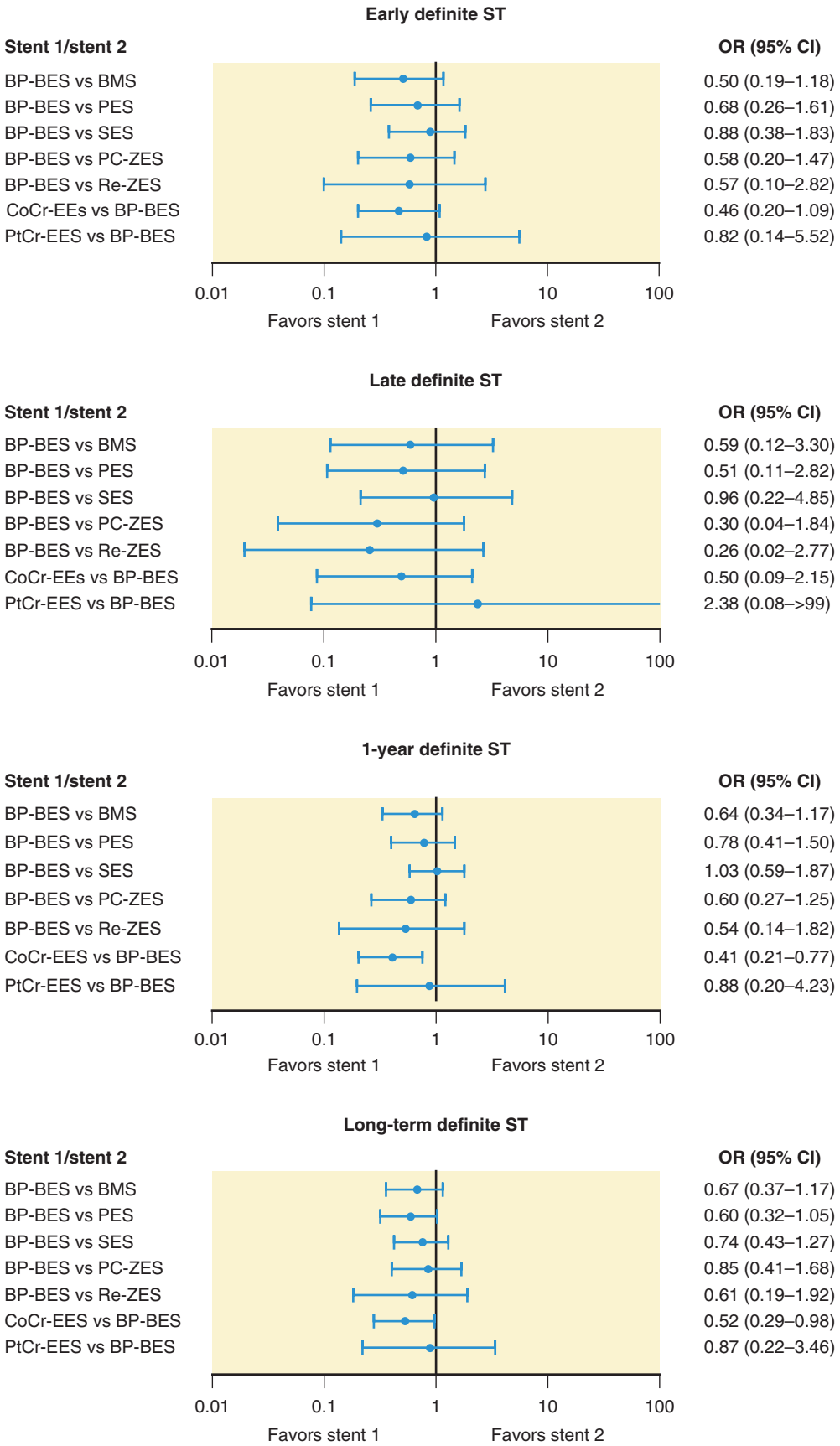

FIGURE 16-9 Network meta-analysis including 89 randomized controlled trials and 85,490 patients, which shows time-related differences between biolimus-eluting stents versus other drug-eluting stents and bare-metal stents (BMSs). *BP-BES,* Bioabsorbable polymer-based biolimus-eluting stent; *CI,* confidence interval; *CoCr-EES,* cobalt-chromium everolimus-eluting stents; *OR,* odds ratio; *PC-ZES,* phosphorylcholine polymer–based zotarolimus-eluting stents; *PES,* paclitaxel-eluting stents; *PtCr-EES,* platinum-chromium everolimus-eluting stents; *Re-ZES,* Resolute zotarolimus-eluting stents; *SES,* sirolimus-eluting stent; *ST,* stent thrombosis.

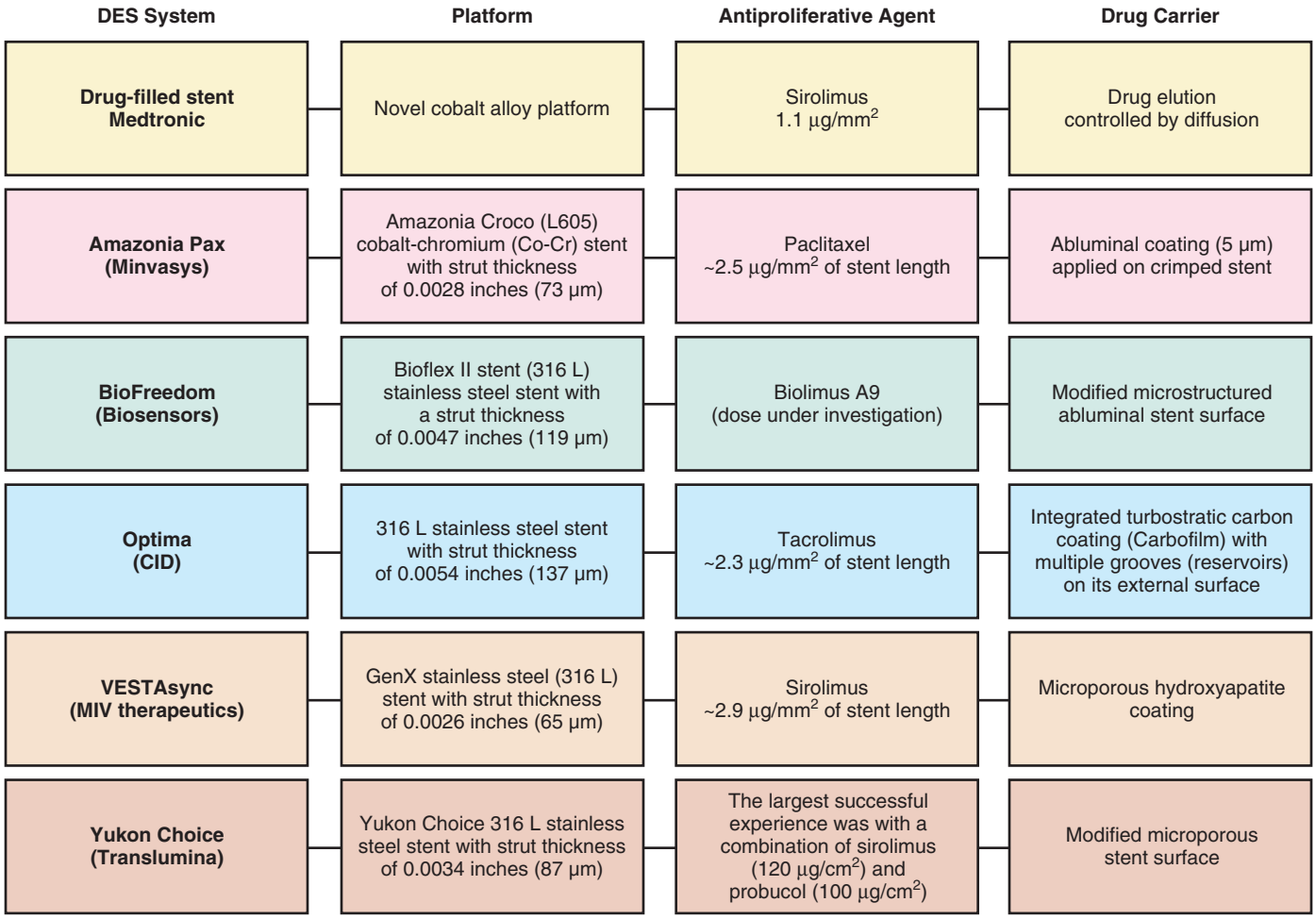

FIGURE 16-10 Main characteristics of polymer-free drug-eluting stents.

or the equivalent BMS ($n = 747$).[112] At 1-year follow-up, the primary composite end point of all-cause death, MI, or any revascularization did not differ between the two groups (11.9% in the CoCr-EES group vs. 14.2% in the BMS group, $P = .19$). However, CoCr-EES use resulted in significantly lower rates of both TVR and definite ST compared with the BMS. Similar results have been confirmed at 2-year follow-up.[205] In the Xience V Stent Versus Cypher Stent in Primary PCI for Acute Myocardial Infarction (XAMI)[98] trial, 625 patients with STEMI were randomized to either a CoCr-EES ($n = 404$) or an SES ($n = 221$). At 1 year, the CoCr-EES was found to be noninferior to the SES for the primary end point of cardiac death, MI, or any TVR with a MACE rate of 4% for the CoCr-EES versus 7.7% for the SES. The PC-ZES has been compared with both the PES and SES in the Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent Versus Sirolimus-Eluting Stent Versus Paclitaxel-Eluting Stent for Acute Myocardial Infarction Patients (ZEST-AMI)[98,153] and KOMER[151] trials. The ZEST-AMI trial included 328 patients randomly assigned to a PC-ZES ($n = 108$), SES ($n = 110$), or PES ($n = 110$).[153] At 1-year follow-up, the primary end point—a composite of cardiac death, MI, and ischemia-driven TVR—did not differ among the three groups. Similar results were apparent in the KOMER trial,[151] in which 611 patients with STEMI undergoing primary PCI were randomized to a PC-ZES ($n = 205$), SES ($n = 204$), or PES ($n = 202$). The cumulative 1-year rate of MACE was 5.9% in the PC-ZES group, 3.4% in the SES group, and 5.7% in the PES group.

Among the bioabsorbable polymer-based DESs, the BP-BES is the only one that has been extensively investigated in patients with STEMI. In the COMFORTABLE-AMI trial,[163] 1157 patients who presented with STEMI within 24 hours from symptom onset were randomized to either the BP-BES ($n = 575$) or to the equivalent BMS ($n = 582$). Compared with a BMS, the BP-BES resulted in a significantly lower 1-year rate of the primary end point, a composite of cardiac death, MI, or ischemia-driven TLR (4.3% in the BP-BES group vs. 8.7% in the BMS group, $P = .04$). The difference was largely driven by a lower risk of target-vessel reinfarction and ischemia-driven TVR, and no differences in ST were noted. These results were confirmed at 2-year follow-up.[206]

Given the availability of multiple studies to examine the performance of different DESs and BMSs in STEMI, the relative safety and efficacy of these devices has been further investigated in two network meta-analyses. In a meta-analysis that combined 22 trials and included 12,453 randomized patients treated with CoCr-EESs, PESs, SESs, and PC-ZESs, use of the CoCr-EES was associated with significantly lower rates of cardiac death or MI and ST than use of a BMS.[207] The difference in ST was apparent as early as 30 days and was maintained up to 2 years. CoCr-EESs were also associated with significantly lower rates of 1-year ST than PESs, and SESs were associated with significantly lower rates of cardiac death and MI than BMSs at 1 year but not at long-term follow-up. CoCr-EESs, PESs, and SESs had significantly lower rates of 1-year TVR than BMSs, with the SES also showing lower rates of TVR than the PES. Similar results were found in a confirmatory network meta-analysis.[208] In summary, although first-generation DESs have significantly improved the outcomes of patients with STEMI by significantly reducing the risk of TVR, they have been associated with increased rates of very late ST and reinfarction.[204] By reducing both

TABLE 16-10 Randomized Controlled Trials of Polymer-Free Drug-Eluting Stents

First Author/Trial	Study Cohort	Stent Comparators	Number Randomized	Latest Follow-Up to Date	Brand	Results of the Primary End Point
Carrié[457]	Noncomplex CAD	PF-AES PES	323	1 yr	Cre8 Taxus Liberté	The PF-AES was superior to the PES for the primary end point of in-stent LLL at 6 months (0.14 ± 0.36 mm vs. 0.34 ± 0.40 mm, respectively, $P < .0001$). At 1 year, rates of cardiac death, MI, TLR, and ST did not significantly differ between the two devices.
Dang[458]	STEMI	PF-PES SES	105	1 yr	Yinyi Partner	At 1 year, the PF-PES and the SES had similar rates of cardiac death, MI, or TLR. The two groups had also comparable angiographic outcomes and similar rates of in-stent restenosis (8.6% for PF-PES vs. 5.0% for SES).
ISAR-TEST[459,460]	Noncomplex CAD	PF-SES PES	450	5 yr	Yukon Taxus Liberté	The PF-SES was noninferior to the PES for the primary end point of in-stent LLL at 9 months (0.48 ± 0.61 mm vs. 0.48 ± 0.58 mm, respectively, $P_{NI} = .02$). At 5 years, rates of cardiac death, MI, TLR, and ST did not differ significantly between the two devices.
ISAR-TEST-2[150,342]	Noncomplex CAD	PF Dual DES* SES PC-ZES	1007	2 yr	Yukon platform Cypher Endeavor	The 6-month rates of binary restenosis in the Dual DES group were significantly lower compared with the PC-ZES group (11.0% vs. 19.3%, respectively, $P = .002$) and similar to the SES group (12.0%, $P = .68$). Also, TLR with the Dual DES was significantly lower compared with the PC-ZES and was similar to the SES. Between 1 and 2 years, Dual DES use was associated with significantly lower rates of TLR compared with the SES, but similar to PC-ZES.
ISAR-TEST-3[117,166]	Noncomplex CAD	PF-SES BP-SES SES	605	2 yr	Yukon C BP-Yukon Cypher	The PF-SES did not meet the criteria of noninferiority of LLL at 6 months compared with the SES (0.47 ± 0.56 mm vs. 0.23 ± 0.46 mm, respectively, $P_{NI} = .94$). No differences in safety outcomes were reported among the three stent groups up to 2 years.
ISAR-TEST-5[461]	Minimal exclusion criteria including patients with unprotected left main disease or cardiogenic shock	Dual DES PC-ZES	3002	1 yr	Yukon platform Endeavor	The Dual DES was noninferior to the ZES for the primary end point of cardiac death, MI, or TLR at 1 year (13.1% vs. 13.5%, respectively, $P_{NI} = .006$). Rates of in-stent binary angiographic restenosis were similar between the two stents.
LYPSIA Yukon[462,463]	Diabetes mellitus	PF-SES PES	240	5 yr	Yukon Taxus	The PF-SES did not meet the criteria of noninferiority of LLL at 9 months compared with the PES (0.63 ± 0.62 mm vs. 0.45 ± 0.60 mm, respectively). No significant differences were reported between the groups in the risk of death, MI, TLR, or ST up to 5 years.
Zhang[464]	Minimal exclusion criteria including patients with unprotected left main disease	PF-PES BP-SES SES	989	2 yr	Yinyi Excel Partner	The PF-PES and the BP-SES were noninferior to the SES for the primary end point of cardiac death, MI, or TVR at 2 years (6.2% with PF-PES vs. 6.6% with BP-SES vs. 7.2% with SES). No significant differences were reported among groups in the risk of ST.

*This stent elutes both sirolimus and probucol.

AES, Amphilimus-eluting stents; *BP,* bioabsorbable polymer; *CAD,* coronary artery disease; *DES,* drug-eluting stent; *LLL,* late lumen loss; *MI,* myocardial infarction; *PC-ZES,* phosphorylcholine polymer–based zotarolimus-eluting stent; *PES,* paclitaxel-eluting stent; *PF,* polymer free; P_{NI}, *P* value for noninferiority; *STEMI,* ST-segment elevation MI; *SES,* sirolimus-eluting stents; *ST,* stent thrombosis; *TLR,* target lesion revascularization; *TVR,* target-vessel revascularization.

	Bare-metal stents	Balloon angioplasty	RR [95% CI]	RR [95% CI]	*P* Value
30-day events					
Mortality	2.9%	3.0%		0.97 [0.74–1.27]	.83
Reinfarction	2.0%	2.2%		0.92 [0.66–1.27]	.61
TVR	3.1%	5.1%		0.60 [0.47–0.77]	.0001
6- to12-month events					
Mortality	5.1%	5.2%		0.98 [0.79–1.10]	.82
Reinfarction	3.7%	3.9%		0.94 [0.74–1.20]	.61
TVR	11.3%	18.4%		0.62 [0.55–0.69]	<.0001

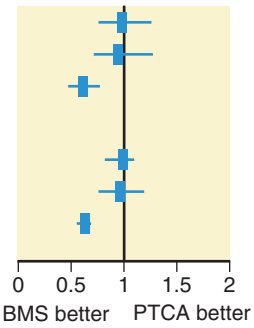

FIGURE 16-11 Meta-analysis from 13 randomized controlled trials to compare the bare-metal stent (BMS) with balloon angioplasty in acute myocardial infarction in 6922 patients. *CI,* Confidence interval; *PTCA,* percutaneous transluminal coronary angioplasty; *RR,* risk ratio; *TVR,* target-vessel revascularization.

TABLE 16-11 Comparative Randomized Trials of Drug-Eluting Stents in St-Segment Elevation Acute Myocardial Infarction

First Author/Study	Stent Comparators	Number Randomized	Latest Follow-Up	Results of the Primary End Point
Diaz de Llera[402]	SES BMS	114	1 yr	The SES was associated with a trend toward reduced 1-year rates of TVR compared with the BMS (0% SES vs. 5.7% BMS, $P = .064$).
EXAMINATION[112,205]	CoCr-EES BMS	1504	2 yr	The CoCr-EES and BMS had similar rates of the primary end point of all-cause death, MI, or any revascularization at 1 year (11.9% CoCr-EES vs. 14.2% BMS, $P = .19$). The CoCr-EES was associated with significantly lower 1-year rates of definite ST compared with the BMS (0.5% vs. 1.9%, respectively, $P = .019$). Similar results were apparent at 2 years.
GRACIA-3[200]	PES BMS	419	1 yr	No significant difference was found in the risk of in-segment binary restenosis between the PES and BMS at 1 year (10.1% vs. 11.3%; respectively; $P = .89$). In-segment LLL was significantly lower with the PES compared with the BMS (0.04 ± 0.05 mm vs. 0.27 ± 0.05 mm, $P = .003$)
HAAMU[197]	PES BMS	164	1 yr	The PES was associated with a significantly lower LLL compared with the BMS at 6 months (0.26 ± 0.45 mm vs. 0.73 ± 0.56 mm, $P < .001$).
HORIZONS-AMI[413,465]	PES BMS	3006	3 yr	The PES was associated with significantly lower 1-year rates of ischemia-driven TVR (5.8% vs. 8.7%; $P = .006$). No significant difference was found in the risk of death, reinfarction, or ST between the two devices.
Juwana[203]	PES SES	397	1 yr	SES was associated with a significantly lower LLL compared with PES at 1 year (0.01 ± 0.42 mm vs. 0.21 ± 0.50 mm, $P = .001$). No significant difference was found in the risk of death, MI, or ST between the two devices.
KOMER[151]	PES SES PC-ZES	611	18 mo	No significant difference was found in the risk of death, MI, or ST between the PES, SES, and PC-ZES (5.7% vs. 3.4% vs. 5.9%, respectively; $P = .46$). A trend toward lower rates of ischemia-driven TLR was seen with the SES compared with either the PES or the PC-ZES at 18 months (0.5% SES vs. 1.5% PES vs. 3.4% PC-ZES, $P = .09$).
MISSION![193,466]	SES BMS	310	5 yr	The SES was associated with a significantly lower LLL compared with the BMS at 9 months (0.12 ± 0.43 mm vs. 0.68 ± 0.57 mm, $P < .001$). No significant difference was found in the risk of death, MI, or ST between the two devices.
MULTISTRATEGY[191,467]	SES BMS	744	3 yr	The SES was associated with significantly lower 1-year rates of all-cause death, MI, and clinically driven TVR (7.8% vs. 14.5%, $P = .004$). No significant difference was found in the risk of ST between the two stents.
Pasceri[199]	SES BMS	65	1 yr	No significant difference was reported in the risk of death, MI, TVR, or ST between the SES and the BMS at 1 year.
PASEO[202,468]	PES SES BMS	270	4 yr	The PES and the SES were associated with significantly lower 1-year rates of TLR compared with the BMS (4.4% PES vs. 3.3% SES vs. 14.4% BMS, $P = .03$ for PES vs. BMS, and $P = .016$ for SES vs. BMS). No significant difference was found in the risk of death, MI, or ST among the three devices.
PASSION[196,469,470]	PES BMS	619	5 yr	A trend was seen toward lower rates of cardiac death, MI, or TLR with the PES compared with the BMS (8.8% vs. 12.8%; $P = .09$). No significant difference was found in the risk of ST between the two stents.
PROSIT[425,471]	PES SES	308	3 yr	A trend was seen toward lower rates of all-cause death, MI, ST, or TLR with the SES compared with the PES at 1 year (5.8% vs. 11.7%; $P = .07$). In-segment LLL was 0.09 ± 0.45 mm with the SES versus 0.33 ± 0.68 mm with the PES; ($P = .002$) on 6-month follow-up angiography. Similar results were apparent at 3 years.

TABLE 16-11 Comparative Randomized Trials of Drug-Eluting Stents in St-Segment Elevation Acute Myocardial Infarction—cont'd

First Author/Study	Stent Comparators	Number Randomized	Latest Follow-Up	Results of the Primary End Point
SELECTION[198]	PES BMS	76	7 mo	The percentage of the stent volume obstruction by neointimal hyperplasia measured by IVUS was significantly lower with the PES compared with the BMS at 7 months (4.6% vs. 20%; $P < .01$). The PES was also associated with significantly lower rates of death, MI, and TLR compared with the BMS.
SESAMI[194,472,473]	SES BMS	320	5 yr	The SES was associated with significantly lower 1-year rates of binary restenosis (9.3% vs. 21.3%, $P = .032$), and TLR (4.3% vs. 11.2%; $P = .02$) compared with the BMS. No significant difference was found in the risk of death, MI, or ST between the two devices up to 5 years.
STRATEGY[195,474]	SES BMS	175	5 yr	The SES plus a high-dose bolus of tirofiban was associated with significantly lower 1-year rates of death, MI, stroke, and binary restenosis compared with the BMS plus abciximab (19% vs. 50%, $P < .001$). Similar results were apparent at 5 years, but the difference between the two groups tended to be attenuated (29.9% SES vs. 43.2% BMS, $P = .067$).
TYPHOON[192,475]	SES BMS	712	4 yr	The rate of the primary end point—a composite of cardiac death, MI, or TVR—was significantly lower with the SES than with the BMS (7.3% vs. 14.3%, $P = .004$). No significant differences were found in the risk of death or MI between the two stent groups, but rates of TVR were lower with the SES compared with the BMS (5.6% vs. 13.4%, respectively; $P < .001$). Similar results were apparent at 4 years.
XAMI[98]	CoCr-EES SES	625	1 yr	The CoCr-EES was noninferior to the SES for the primary end point of cardiac death, MI, or TVR at 1 year (4.0% vs. 5.3%, respectively, $P_{NI} = .048$)
ZEST-AMI[153]	PES SES PC-ZES	328	1 yr	At 1 year, the incidence of the primary end point—a composite of death, MI, or TVR—was 11.3% with the PC-ZES and 8.2% both for the SES and the PES ($P = .83$). Individual components of the primary end point did not differ among the three groups.

BMS, Bare-metal stent stent; *CoCr-EES,* cobalt-chromium everolimus-eluting stent; *IVUS,* intravascular ultrasound; *LLL,* late lumen loss; *MI,* myocardial infarction; *PC-ZES,* phosphorylcholine polymer–based zotarolimus-eluting stent; *PES,* paclitaxel-eluting stent; *SES,* sirolimus-eluting stent; *ST,* stent thrombosis; *TLR,* target-lesion revascularization; *TVR,* target-vessel revascularization.

TVR and ST, second-generation DESs have further improved the outcomes of patients with STEMI, with a possible additional benefit in terms of cardiac mortality and reinfarction compared with the PES and the BMS.

Stents to Reduce Distal Embolization in ST-Elevation Myocardial Infarction

Beyond the use of DESs in STEMI, several novel STEMI-specific stent devices are currently under investigation. These devices aim to reduce the impact of distal embolization of thrombus during STEMI PCI, an event that has been associated with a higher incidence of periprocedural complications, greater infarct size, and increased mortality.[209] A novel BMS covered with a PET micronet mesh (MGuard, Inspire MD, Tel Aviv, Israel) may trap friable thrombotic and atheromatous material between the micronet and vessel wall, thereby preventing distal embolization.[210] This device was investigated in the Prospective, Randomized, Multicenter Evaluation of a Polyethylene Terephthalate Micronet Mesh-Covered Stent (MGuard) in ST-Segment Elevation Myocardial Infarction (MASTER),[211] in which 433 patients with STEMI who presented within 12 hours from symptom onset were randomized. The MGuard resulted in increased rates of post-PCI Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow and a significant improvement in the primary end point of complete ST-segment resolution compared with a commercially available BMS or DES. A larger multicenter clinical study, MGuard Prime Stent System Clinical Trial in Patients With Acute ST-Elevation Myocardial Infarction (MASTER II), was initiated to further evaluate the efficacy and safety of this device for patients undergoing PCI in STEMI, but unfortunately, it was prematurely terminated because of slow enrollment after 310 of 1114 planned patients were recruited. A drug-eluting version of this device is under development.

One other device that is actively undergoing investigation in STEMI PCI is a self-expanding BMS (Stentys; Stentys Corporation, Paris, France) that compared with balloon-expandable stents aims to reduce deployment pressure and improve acute and late stent apposition, as thrombus between the vessel wall and the stent resolves. In the 80-patient Randomized Comparison Between the Stentys Self-Expanding Coronary Stent and a Balloon-Expandable Stent in Acute Myocardial Infarction (APPOSITION II),[27] which compared the Stentys with a BMS, a lower number of malapposed stent struts was observed at three days with the self-expanding device, with a similar frequency of MACE at 6 months. Unfortunately, the larger Stentys Coronary Stent System Clinical Trial in Patients With Acute Myocardial Infarction (APPOSITION V) trial was prematurely terminated because of slow enrollment after only 300 of 880 patients were enrolled. The failure to complete recruitment in both MASTER-II and APPOSITION V reflects the increasing use of DESs and declining use of BMSs in STEMI.

Diabetes Mellitus

Patients with diabetes have higher rates of angiographic and clinical restenosis after BMS implantation than those without diabetes.[212,213] In general, the pivotal trials in which DESs were compared with BMSs revealed comparable relative safety and efficacy with DES use in patients with diabetes compared with those without diabetes although with greater absolute reductions in TLR and TVR in diabetic patients given their higher baseline risk.[214-216] Most prior studies have shown comparable rates of in-stent late loss with the PES in patients with versus those without diabetes,[217] suggesting that the multiple pathways by which paclitaxel interferes with restenosis (by affecting microtubular function) makes its action relatively independent of the diabetic state.[218] Considerable controversy surrounds whether the greater suppression of late loss from stents that elute potent rapamycin analogues, such as the SES or EES, is preserved in patients with diabetes, given that the effect of rapamycin in interfering with the cell cycle is regulated by glycosylation-dependent enzymes.[219] In this regard, several small- to moderate-sized studies have provided conflicting results. For example, among 379 patients with diabetes randomized to the SES

versus the PES in the Sirolimus Versus Paclitaxel-Eluting Stents in De Novo Coronary Artery Lesions (REALITY)[72] trial, the rates of restenosis and clinical events were comparable with both stents. In contrast, in the randomized 250-patient Paclitaxel-Eluting or Sirolimus-Eluting Stents to Prevent Restenosis in Diabetic Patients (ISAR-DIABETES) trial,[220] compared with the PES, use of the SES resulted in a greater reduction in late loss at 6 months, but rates of TLR were nonsignificantly different at 9 months.

This issue has been comprehensively addressed by a pooled patient-level analysis from the SPIRIT II through IV and COMPARE trials, in which 6789 patients were randomized to the CoCr-EES or the PES (Express or Liberté platforms). A total of 1869 patients (25%) had diabetes. In patients without diabetes, CoCr-EES use was associated with a marked reduction in the 1-year composite rate of cardiac death, MI, or ischemia-driven TLR when compared with the PES.[221] The CoCr-EES also markedly reduced the individual rates of MI, ST, and TLR compared with the PES. In contrast, among patients with diabetes, the rates of composite adverse events at 1 year and their components were almost identical between the two stent types, and a significant interaction was observed between diabetes and stent platform. In a network meta-analysis that included 42 trials with 22,844 patient-years of follow-up, all DESs (the SES, PES, CoCr-EES, and Re-ZES) significantly reduced the risk of TVR compared with the BMS in diabetic patients, but the magnitude of this effect varied with the type of stent.[222] In fact, the SES and CoCr-EES appeared more efficacious than the PES and Re-ZES in reducing the risk of TVR, with an 87% probability that the CoCr-EES was associated with the lowest rate of TVR. There was no increased risk of death or MI with any DES compared to the BMS. Finally, the CoCr-EES had a 62% probability to be the stent associated with the lowest risk of any ST.

Beyond stent selection during PCI in diabetic patients, the most critical revascularization decision in patients with diabetes mellitus is the mode of revascularization; that is, whether to perform PCI or coronary artery bypass grafting (CABG). Prior studies have demonstrated higher rates of repeat revascularization procedures among diabetic patients treated with a BMS compared with those who underwent CABG, although the rates of death, MI, and stroke have been similar.[223] The use of a DES for diabetic patients was examined in the Coronary Artery Revascularization in Diabetes (CARDia)[224] trial, which randomized 510 patients with diabetes mellitus and multivessel disease to PCI with either an SES (69%) or a BMS (31%) versus CABG. The primary end point of all-cause death, MI, or stroke at 1 year occurred in 10.5% of patients with CABG versus 13.0% with PCI ($P = .39$); among the SES subgroup, the 1-year event rates were 12.4% versus 11.6%, respectively ($P = .82$). Whereas CARDia was too underpowered to be definitive, the Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM)[225] trial enrolled 1900 patients with diabetes mellitus and multivessel CAD to CABG versus PCI with a first- generation DES (an SES or PES). As shown in Figure 16-12, the 5-year rate of the primary end point was significantly higher among PCI patients compared with CABG patients (26.6% vs. 18.7%, respectively, $P = .005$). This difference was driven by a significant reduction in the risk of all-cause death ($P = .049$) and MI ($P < .001$) with CABG compared with PCI. However, stroke rates were significantly higher in the CABG group (5.2% vs. 2.4% in the PCI group, $P = .03$), a finding consistent with other reports not restricted to a diabetic population.[226,227] The relevance of these findings is uncertain, given the improved outcomes with currently used second-generation DES platforms. Moreover, whether diabetes independently modifies the relative outcomes after revascularization with PCI, compared with CABG, is a matter of debate. In the randomized Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial to compare PES use against CABG in patients with triple-vessel disease or left main CAD, patients with diabetes were at higher risk for 4-year mortality after both PCI and CABG. However, the presence of diabetes did not discriminate between the relative benefits of CABG versus PCI after considering other clinical and anatomic features.[228]

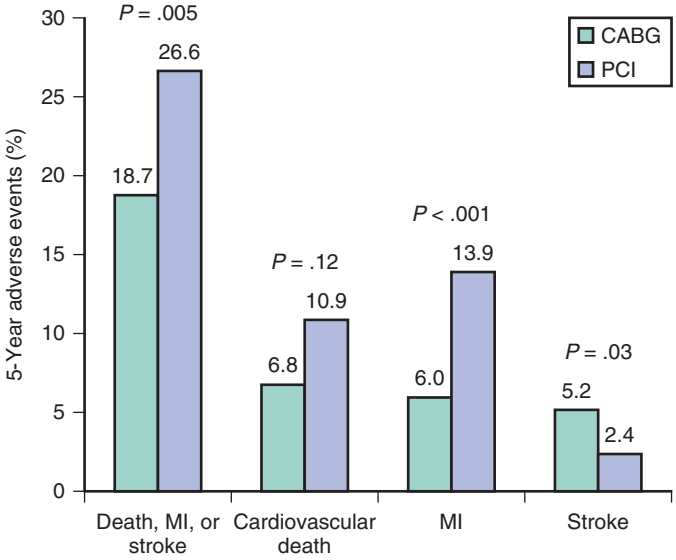

FIGURE 16-12 Five-year results from the FREEDOM trial,[226] in which 1900 patients with diabetes mellitus and multivessel coronary artery disease were randomized to percutaneous coronary intervention (PCI) versus coronary artery bypass graft surgery (CABG). *MI,* Myocardial infarction.

Left Main and Multivessel Disease

Although they are distinctly different conditions, revascularization decisions for patients with left main and multivessel disease (MVD) are often considered together because historically the default strategy has been CABG. Patients with MVD treated with PCI have higher restenosis and ST rates than those with single-vessel disease, especially when diffuse disease, small vessels, and bifurcation lesions that require treatment are present. In contrast, whereas restenosis and thrombosis are relatively rare after stenting the relatively short, large-caliber left main segment, PCI failure in the left main coronary artery jeopardizes a sufficiently large amount of myocardium such as to entail a high risk of mortality.

Prior to the introduction of DES technology, meta-analyses of trials to compare PCI with CABG in patients with MVD demonstrated similar rates of death, MI, or stroke with PCI using BMS or balloon angioplasty alone, but higher rates of repeat revascularization were reported.[229] However, BMSs were used in only four of these trials in 3051 patients,[230-233] and no study utilized DESs. In light of the demonstrable efficacy of DESs in reducing revascularization procedures compared with BMSs, the SYNTAX trial[234] was undertaken wherein 1800 patients with triple-vessel disease ($n = 1095$) and/or left main disease ($n = 705$) were randomized to either a PES or CABG using broader inclusion criteria compared with previous trials. The primary end point of the SYNTAX trial—the 1-year composite rate of all-cause mortality, stroke, MI, or unplanned repeat revascularization—occurred significantly less commonly with CABG than with PES (Fig. 16-13, *left*), largely because of greater rates of repeat revascularization with PCI compared with CABG. Conversely, the 1-year rate of stroke was lower with PCI, and the composite rates of death, MI, or stroke were similar in both arms at 1 year. However, as shown in Figure 16-13 (*right panel*), 5-year follow-up from the SYNTAX trial demonstrated a more marked advantage that favored CABG with respect to the primary composite end point (26.9% in the CABG group vs. 37.3% in the PCI group, $P < .0001$).[235] In addition, rates of MI (3.8% in the CABG group vs. 9.7% in the PCI group, $P < .0001$) and TVR (13.7% vs. 25.9%, $P < .0001$) were significantly lower with CABG compared with PCI, whereas the risk of death or stroke was not significantly different

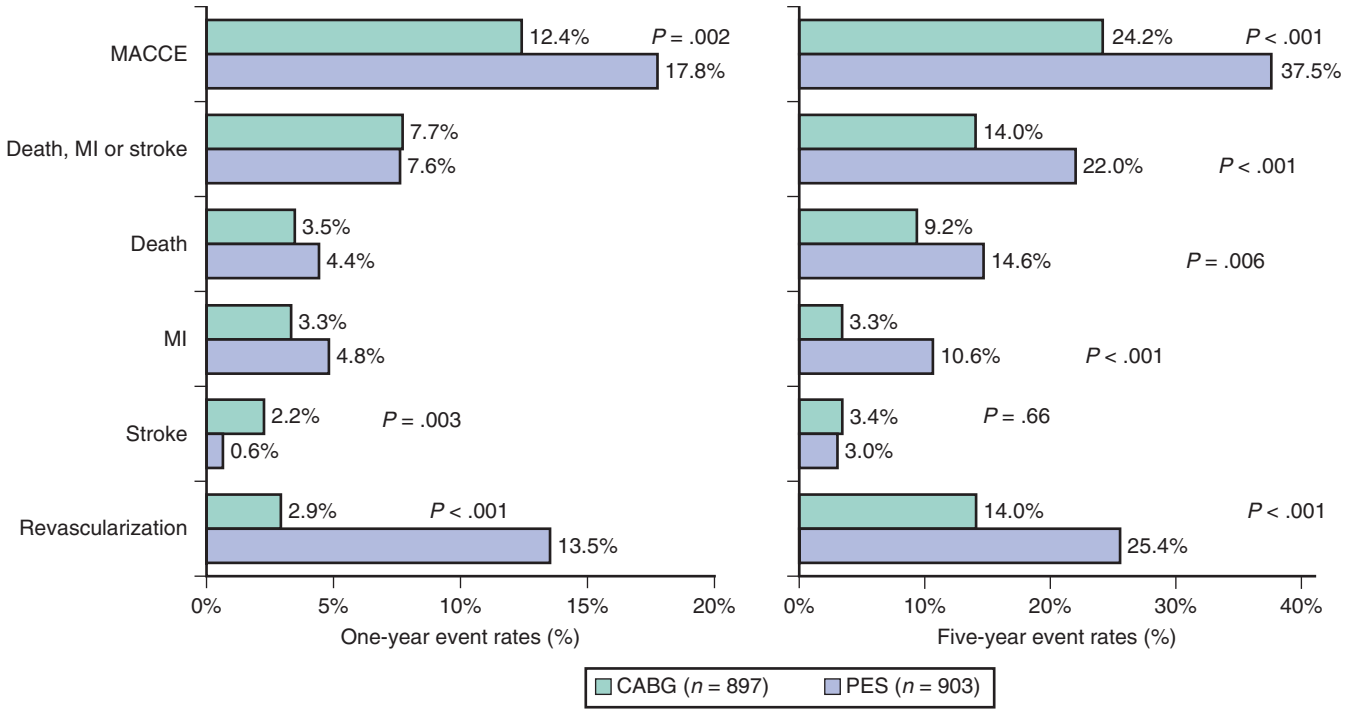

FIGURE 16-13 Results from 1 year (*left*)[234] and 5 years (*right*)[235] from the SYNTAX trial, in which 1800 patients with triple-vessel and/or left main disease were randomized to a paclitaxel-eluting stent (PES) or coronary artery bypass graft surgery (CABG). *MACCE,* Major adverse cardiovascular or cerebrovascular event (death, myocardial infarction [MI], stroke, or unplanned repeat revascularization). *P* = NS (not significant) unless otherwise noted.

TABLE 16-12 Five-Year Outcomes From the SYNTAX Trial[235] In Patients With Triple-Vessel Disease Stratified by SYNTAX Score Tertiles

	LOW SYNTAX TERTILE (≤22)			INTERMEDIATE SYNTAX TERTILE (23-32)			HIGH SYNTAX TERTILE (≥33)		
	PES (*n* = 181)	CABG (*n* = 171)	*P* value	PES (*n* = 207)	CABG (*n* = 208)	*P* value	PES (*n* = 155)	CABG (*n* = 166)	*P* value
MACCE	33.3%	26.8%	.21	37.9%	22.6%	<.001	41.9%	24.1%	<.001
• Death, MI, or stroke	17.5%	14.8%	.56	23.2%	14.7%	.035	26.2%	12.5%	.02
• Death	10.2%	9.3%	.81	16.3%	9.6%	.047	17.8%	8.8%	.015
• MI	8.8%	4.9%	.20	13.8%	3.1%	<.001	8.7%	1.9%	.008
• Stroke	1.8%	3.9%	.24	2.5%	3.6%	.53	5.1%	2.6%	.31
• Revascularization	23.1%	14.9%	.038	25.1%	11.0%	<.001	28.2%	12.6%	<.001

CABG, Coronary artery bypass graft surgery; *MACCE,* major adverse cardiovascular or cerebrovascular event (death, MI, stroke, or revascularization); *MI,* myocardial infarction; *PES,* paclitaxel-eluting stent; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

between the two treatment strategies. A borderline interaction (P_{int} = .10) was present such that the primary 5-year major adverse cardiovascular and cerebrovascular event (MACCE) end point in the three-vessel disease subgroup was 50% higher in patients assigned to PCI than in those assigned to CABG (24.2% in the CABG group vs. 37.5% in the PCI group, *P* < .0001), whereas no significant difference was apparent between the two strategies of revascularization in the subgroup of patients with left main disease (31.0% in the CABG group vs. 36.9% in the PCI group, *P* = .12).

Further substratification of the SYNTAX results was performed based on angiographically assessed lesion complexity. In these analyses, 5-year rates of the primary end point did not significantly differ among treatment groups in patients in the lower SYNTAX score tertile (≤22) but were significantly higher with PCI than with CABG in patients in the intermediate (23 to 32) and upper (≥33) SYNTAX score tertiles, driven by a better survival, lower MI rates, and less TVR with CABG compared with PCI. As shown in Tables 16-12 and 16-13, however, the threshold of the SYNTAX score beyond which CABG improved outcomes relative to PCI varied depending on whether patients presented with triple-vessel disease or left main disease, with greater equipoise seen among patients with left main disease and those with less extensive disease as a whole.[236,237] However, given the modest sample sizes of these post hoc subgroups, these findings should be considered hypothesis-generating only.

Recently, a new score for risk stratification of patients with multivessel or left main CAD has been developed by fitting multivariable models to the 4-year mortality results of the SYNTAX trial: the SYNTAX score II.[228] This individualized score demonstrates how the threshold of SYNTAX score favoring CABG, rather than PCI, can vary in relation to the presence or absence of additional clinical and angiographic variables that modify the overall trial observations favoring one or the other revascularization modality. Specifically, in the presence of variables that favor CABG—such as young age, female sex, and low left ventricular ejection fraction (LVEF)—lower SYNTAX scores are required to achieve equipoise in mortality between the two revascularization strategies, whereas in the presence of variables that

TABLE 16-13 Five-Year Outcomes From the SYNTAX Trial[237] in Patients With Left Main Disease Stratified by SYNTAX Score Tertiles

	LOW AND INTERMEDIATE SYNTAX TERTILE (≤32)			HIGH SYNTAX TERTILE (≥33)		
	PES ($n = 221$)	CABG ($n = 196$)	*P* value	PES ($n = 135$)	CABG ($n = 149$)	*P* value
MACCE	31.3%	32.1%	0.74	46.5%	29.7%	.003
Death, MI, or stroke	14.8%	19.8%	0.16	26.1%	22.1%	.40
Death	7.9%	15.1%	0.02	20.9%	14.1%	.11
MI	6.1%	3.8%	0.33	11.7%	6.1%	.13
Stroke	1.4%	3.9%	0.11	1.6%	4.9%	.13
Revascularization	22.6%	18.6%	0.35	34.1%	11.6%	<.001

CABG, Coronary artery bypass graft surgery; *MACCE,* major adverse cardiac or cerebrovascular event (death, MI, stroke, or revascularization); *MI,* myocardial infarction; *PES,* paclitaxel-eluting stent; SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

favor PCI—such as old age, presence of left main disease, or chronic obstructive pulmonary disease (COPD)—equipoise between the two treatments is achieved with higher SYNTAX scores.

An updated meta-analysis of CABG versus PCI in MVD included a total of six trials with 6055 randomized patients and has been recently reported.[238] To reflect current practice, only randomized trials with one or more arterial grafts used in at least 90% of patients and one or more stents used in at least 70% of cases were included. After a median follow-up of 4.1 years, CABG was associated with significantly lower rates of mortality compared with PCI (risk ratio [RR] 0.73; 95% CI, 0.62 to 0.86; $P < .01$). In addition, CABG was also associated with significantly lower rates of MI (RR 0.58; 95% CI, 0.48 to 0.72; $P < .001$) and TVR (RR 0.29; 95% CI, 0.21 to 0.41; $P < .001$). In contrast, rates of stroke were significantly higher with CABG compared with PCI, as suggested by other recent meta-analyses.[226,227] Currently, most guidelines generally recommend CABG, rather than PCI, for patients with MVD and a SYNTAX score above 22.[239,240] However, a major limitation of the current evidence base is the fact that all prior randomized trials compared CABG with a first-generation DES. In SYNTAX, 10% of patients treated with a PES had ST by 5 years, and MACEs reported in 8.1% of patients were attributable to ST.[241] As previously discussed, second-generation DESs have markedly improved the safety profile of DES use, and the CoCr-EES in particular may reduce ST by 70% compared with the PES.[95,177]

Prior to the introduction of DES technology, no randomized trials had been done of PCI versus CABG in patients with unprotected left main disease because observational studies had shown a high rate of procedural failure and late sudden cardiac death with balloon angioplasty,[242] and restenosis and MACE rates were unacceptably high with BMS use in this anatomic subgroup.[243] Erglis and colleagues[244] subsequently randomized 103 patients with left main disease to implantation of a BMS versus a PES and demonstrated that PES use resulted in significantly lower 6-month rates of binary restenosis (6% vs. 22%, $P = .02$) and MACEs (13% vs. 30%, $P = .04$). Additional comparisons between stent types have been performed in the Intracoronary Stenting and Antithrombotic Regimen: Drug-Eluting Stents for Unprotected Left Main Stem Disease (ISAR–LEFT MAIN) and ISAR–LEFT MAIN 2 trials. The first trial randomized 650 patients with left main disease to a PES versus an SES[245] and found comparable 1-year rates of composite death, MI, or TLR (13.6% vs. 15.8%, $P = .44$); definite ST (0.3% vs. 0.7%, $P = .57$); and restenosis (16.0% vs. 19.4% $P = .30$) with the two stent types. In the ISAR–LEFT MAIN 2 trial,[106] 650 patients with left main disease were randomized to either the Re-ZES or the CoCr-EES. At 1-year follow-up, the cumulative incidence of the primary end point—a composite of death, MI, and TLR—was 17.5% in the Re-ZES group and 14.3% in the CoCr-EES group ($P = .25$). Three patients in the Re-ZES group (0.9%) and two patients in the CoCr-EES group (0.6%) experienced definite/probable ST ($P = .99$). These results, in addition to the SYNTAX subgroup analyses that demonstrated comparable outcomes with PCI and CABG for patients with left main disease (particularly those with lesser degrees of coexistent disease), have fueled a renewed interest in the percutaneous treatment of left main disease.

To date, four randomized trials to compare CABG against PCI with a first-generation DES have been performed in patients with left main disease, including the left main subset analysis from SYNTAX.[237,246-248] In a meta-analysis of these four trials (1611 randomized patients)[249] with data reported to 1 year, no significant differences in the risk of death or MI were apparent between the two strategies of revascularization. PCI, however, was associated with significantly higher rates of TVR (11.4% vs. 5.4%, $P < .001$) but significantly lower rates of stroke (1.7% vs. 0.1%, $P = .01$) compared with CABG. In the SYNTAX trial left main cohort ($n = 705$) with results to 5 years, no significant difference was found in the rate of the composite primary end point of death, MI, stroke, or clinically driven repeat revascularization (36.9% with a PES vs. 31.0% with CABG, $P = .12$).[250] However, the results with PES were at least as good as CABG in patients with a low or intermediate SYNTAX score (≤32), whereas the results with CABG were superior in those with a high SYNTAX score (≥33). On the basis of these findings, the most recent United States and European Union guidelines have elevated PCI of the left main to either a class IIa or IIb recommendation depending on the relative risk and complexity of both PCI versus CABG.[239,240] The results of PCI in patients with left main disease, especially those with concomitant complex CAD, may be further optimized by use of better stents and pharmacotherapy than were used in SYNTAX[41,251] and with the regular use of IVUS and fractional flow reserve (FFR) guidance,[252,253] which were rarely utilized in SYNTAX. Many of these issues are being addressed in the ongoing large-scale Evaluation of Xience Prime Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) and Nordic-Baltic-British Left Main Revascularization Study (NOBLE) trials, which randomized patients with unprotected left main disease and a low- to moderate-complexity CAD to PCI with a second-generation DES versus CABG.

Chronic Total Occlusions

Clinical and angiographic restenosis rates after both balloon angioplasty and stent implantation are increased following PCI of a chronic total occlusion (CTO) compared with nonoccluded stenoses, which is due principally to an increased incidence of diabetes and greater lesion length, plaque mass, and calcification[254,255] (see Chapter 25, Chronic Total Occlusion). As such, it has been hypothesized that the benefits of DES in reducing clinical restenosis, compared with BMS, would be strongly evident in the treatment of CTO lesions. In a 200-patient randomized trial of the SES versus the BMS, the use of an SES resulted in significant reductions in binary angiographic restenosis (7% vs. 36%, $P < .001$) and TLR (4% vs. 19%, $P < .001$), with reductions in clinical restenosis maintained at up to 4 years of clinical follow-up.[256] A large number of retrospective, nonrandomized and historically controlled

comparisons of the DES and BMS have similarly demonstrated approximately 60% reductions in clinical restenosis end points with DES compared with BMS. However, despite similar hazards of mortality and MI with DES compared with BMS in a meta-analysis aggregating this data, a trend toward increased ST was observed with first-generation DESs (RR 2.79; 95% CI, 0.98 to 7.97; $P = .06$), which merits concern.[257] More recently, 207 patients with CTO lesions were randomized to either a CoCr-EES or SES.[103] In-stent late loss at 9 months was 0.29 mm (±0.60) in patients treated with an SES versus 0.13 mm (±0.69) in patients with a CoCr-EES ($P_{NI} < .01$). A trend was also seen toward lower 1-year rates of major adverse events (15.9% vs. 11.1%, $P = .33$), as well as lower rates of definite/probable ST (3.0% vs. 0.0%, $P = .07$), with a CoCr-EES compared with an SES. Similarly, observational studies have shown improved outcomes with a second-generation DES compared with a first-generation DES for the treatment of CTO lesions.[258]

Bifurcation Lesions

Bifurcation lesions represent 20% or more of stenoses undergoing angioplasty, and PCI of coronary bifurcation lesions is associated with increased procedural complications and worsened long-term outcomes (see Chapter 22, Bifurcations and Branch Vessel Stenting). Because of higher rates of clinical restenosis at bifurcation lesions, the use of a DES for the main vessel of a bifurcation lesion has become standard of care for bifurcation disease. A strategy of provisional stenting of the side branch is the generally accepted current approach to bifurcation disease unless significant high-grade and lengthy disease is present within the side branch.[259,260] A variety of strategies for the treatment of bifurcation disease with drug-eluting balloons (DEBs) are also currently undergoing evaluation,[261,262] but current data using DEBs in native coronary stenoses have been mixed (see Chapter 17, Drug-Coated Balloons).

Several dedicated drug-eluting bifurcation stent systems have been designed and are under investigation. Bifurcation stent systems can be classified as those that facilitate access to the side branch to simplify the PCI procedure or novel stents designed to address the unique geometric challenges of the bifurcated stenosis. Initial experiences with the Axxess (Devax, Lake Forest, CA) self-expanding nitinol stent, coated with the bioabsorbable polymer PLLA and eluting the antiproliferative rapamycin analogue biolimus A9, have demonstrated low rates of restenosis of both the main vessel and side branch in both true bifurcation lesions and in the distal bifurcation of the left main coronary artery (LMCA).[263,264] This "reverse cone" stent is designed to adapt to and cover the main parent vessel and the bifurcation carina and is used in conjunction with a dedicated DES of one or both branches when necessary. Preliminary data have also been published on the use of the Stentys paclitaxel-eluting side branch access stent[265] and the Taxus Petal dedicated bifurcation stent.[266] Finally, the results of the TRYTON Bifurcation Trial: A Randomized Comparison of a Provisional One-Stent Versus a Dedicated Two-Stent Strategy for True Bifurcation Coronary Lesions,[267] in which 704 patients with true bifurcation lesions were randomized to either the Tryton bifurcation two-stent approach versus a provisional one-stent approach, have been recently presented. The Tryton BMS, made from a cobalt-chromium alloy, provides scaffolding within the side branch with minimal coverage in the main vessel. After deployment of the Tryton stent system, a conventional DES is placed in the main vessel and the procedure is completed with a final kissing balloon inflation (facilitated culotte technique). At 9-month follow-up, the primary end point of the study—a composite of cardiac death, target-vessel MI, and ischemia-driven TVR—was 17.4% in the Tryton group versus 12.8% in the provisional group ($P = .11$), which did not meet the criteria for noninferiority because of a greater rate of periprocedural MI with the Tryton. However, side-branch stenosis diameter was significantly lower in the Tryton group than in the provisional group (31.6% vs. 38.6%, respectively, $P = .002$), and outcomes tended to be improved with the Tryton in large side branches. Further clinical data are awaited to determine whether the use of dedicated bifurcation stents offer long-term advantages for the treatment of bifurcation disease compared with a provisional single-stent approach.

Saphenous Vein Grafts

The most common cause of recurrent ischemia following CABG surgery is atheromatous degeneration within the body of a saphenous vein graft (SVG), and BMSs have been associated with improved outcomes compared with balloon angioplasty in SVG intervention.[268,269] Whereas DESs have the potential to further lower rates of restenosis of the target lesion within SVGs, the "tolerated late loss" within SVG lesions is typically greater than in native coronary vessels because of the large caliber of most SVGs, and disease progression at nontarget sites within SVGs is frequent (see Chapter 26, Bypass Graft Intervention). Two small, randomized trials of DESs versus BMSs for critical SVG stenoses have been conducted in patients with SVG lesions and demonstrated lower rates of angiographic restenosis with DESs.[270,271] With extended follow-up to a median of 32 months in one of these studies, however, the antirestenotic advantage of the SES compared with the BMS was lost, and the SES was associated with higher mortality.[272] In the larger Drug-Eluting Versus Bare-Metal Stents in Saphenous Vein Graft Lesions (ISAR-CABG) trial, 610 patients were allocated to either a DES (a PES, SES, or BP-SES) or a BMS.[273] At 1-year follow-up, the primary end point—a composite of death, MI, or TLR—was significantly reduced with the DES compared with the BMS (15% vs. 22%, respectively, $P = .02$). The difference in the primary end point was driven by a significant reduction of TLR with DES compared with BMS (7% vs. 13%, $P = .01$), whereas no significant difference in the risk of death or MI was apparent between treatment groups. Finally, a small pilot study of prophylactic "sealing" of moderate, noncritical SVG lesions with a PES to prevent disease progression within SVGs was superior to medical therapy alone, suggesting a possible preventive role for the DES in degenerating SVG lesions prior to their becoming critical.[274] A large randomized trial is required, however, before such an approach can be recommended in less severe SVG stenoses.

STENT FAILURE MECHANISMS AND MANAGEMENT

Stent Thrombosis

The most feared complication following stent placement is ST, which in more than 40% of patients presents as a large MI and results in death within 30 days in 10% to 25% of patients.[275,276] Whereas it was initially believed that ST with a BMS was largely confined to the first 30 days following PCI, more recent analyses confirm that even with a BMS, ST can occur years after the initial stent implantation.[277] Treatment for ST is almost always emergent repeat PCI, although optimal reperfusion is only achieved in two thirds of patients.[278] Moreover, approximately 20% of patients with a first ST experience a recurrent ST episode within 2 years.[279] Thus understanding and preventing this complication is of paramount importance.

The most widely utilized definition and timing classification of ST was developed by the ARC[280] with definite or probable ST considered by most to represent the best tradeoff between sensitivity and specificity (Table 16-14). ST is considered to be *acute* if it occurs within the first 24 hours, *subacute* if it occurs between 1 and 30 days, *early* if it occurs within the first 30 days, *late* if occurs between 30 days and 1 year, and *very late* if it occurs after 1 year. ST is also classified as *primary* if it is directly related to an implanted stent or *secondary* if it occurs at the stent site after an intervening TLR procedure for restenosis. The ARC definitions specifically pertain to out-of-lab ST; intraprocedural ST (IPST)—that is, ST that occurs within the cardiac catheterization laboratory during or immediately after the index PCI procedure itself—is not captured within the ARC definitions. IPST has been strongly associated with death, MI, and out-of-lab (ARC) ST[281] and should be considered and tracked as a separate entity.

The mechanisms that underlie ST are multifactorial and include patient-, lesion-, procedure-, and stent-related factors. ST occurs more

frequently in complex patients and complex lesions, especially in patients with ACSs and thrombotic lesions (possibly because of stent implantation within or adjacent to a necrotic core),[282] diabetes and renal insufficiency, diffuse disease, small vessels, and bifurcation lesions that require multiple stents.[275,276,283-286] A recent study has suggested an independent association between the risk of ST and the SYNTAX score.[287] Different mechanisms are involved in the risk of early, late, and very late ST.

In general, early ST is related to procedural factors such as stent underexpansion, edge dissection, and residual disease at the stent margins.[288-290] In this regard, the routine use of intravascular imaging such as IVUS may help optimize the procedural results, further decreasing the risk of ST. This is consistent with the results of a large, nonrandomized propensity-adjusted study that suggested lower 30-day and 1-year rates of ST with IVUS guidance compared with angiography guidance[291] and with the results of a substudy of the Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents (ADAPT-DES)[292] trial, a prospective, multicenter, nonrandomized all-comers study in 8582 consecutive patients designed to determine the frequency, timing, and correlates of ST and adverse clinical events after DES implantation. Specifically, in a propensity-adjusted analysis from ADAPT DES, IVUS guidance compared with angiographic guidance was associated with significantly lower propensity-adjusted 1-year rates of definite/probable ST (0.6% vs. 1.0%, $P = .003$), MI (2.5% vs. 3.7%; $P = .004$), and MACEs (3.1% vs. 4.7%; $P = .002$).[293]

In contrast, late and very late ST (Fig. 16-14) have been associated with delayed arterial healing, chronic inflammation with chronic fibrin deposition, neoatherosclerosis,[53,294] late strut fractures,[295] and late acquired stent malapposition (reflecting underlying vascular toxicity from the drug and/or polymer).[296,297] Although late and very late ST also occurs with BMSs,[277] for many years the ongoing and increased risk of ST after first-generation DES use has remained a concern.[66,67,80] In contrast, emerging data from randomized trials,[112] observational studies,[130] and meta-analyses[177,178] suggest that second-generation DESs may be as safe as, if not safer than, BMSs, representing a major paradigm shift.[298] In particular, durable fluoropolymer-coated CoCr-EESs may be associated with the lowest rates of ST not only compared with other DESs but even when compared with BMSs.

TABLE 16-14 Academic Research Consortium Definitions of Stent Thrombosis

Classification	Definition
Definite	An acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion within or adjacent to a stent
Probable	Unexplained death within 30 days after stent implantation or acute myocardial infarction involving the target-vessel territory without angiographic confirmation
Possible	Any unexplained death beyond 30 days after the procedure
Timing	
Acute	Within 24 hours (excluding events within the catheterization laboratory)
Subacute	From 1 to 30 days
Early	Within 30 days (excluding events within the catheterization laboratory)
Late	From 30 days to 1 year
Very late	After 1 year

Dual-Antiplatelet Therapy and Stent Thrombosis

Five randomized trials have demonstrated that ST and MACEs within 30 days of BMS implantation are markedly reduced by addition of the thienopyridine ticlopidine to aspirin,[12-15,299] and in this regard clopidogrel has efficacy comparable to that of ticlopidine with an enhanced safety profile.[300] In patients with ACSs, the rates of ST have also been reduced with more potent thienopyridines such as prasugrel and ticagrelor.[188,189] Whereas observational studies have uniformly documented that premature thienopyridine discontinuation (generally <3 mo) after DES placement is strongly associated with ST,[301,302] whether prolonged DAPT beyond this time will enhance freedom from ST and/or death and MI is controversial; some studies support this hypothesis,[303,304] but others do not.[301,305]

Several randomized trials have not shown benefit of a longer course of DAPT compared with a shorter course, and some studies also suggest an increased risk of bleeding. Specifically, in the Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated With Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic Events (REAL-LATE) and Evaluation of the Long-Term Safety After Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions–Late Coronary Arterial Thrombotic Events (ZEST-LATE) trials,[306] 2701 patients who were event free 1 year after DES placement were randomly allocated to continue aspirin and clopidogrel versus aspirin alone. After a median follow-up of 19.2 months, the primary end point—a composite of cardiac death or MI—did not significantly differ between groups (1.8% with DAPT vs. 1.2% with aspirin alone, $P = .17$). Similar results were apparent in the Optimal Duration of Clopidogrel Therapy After Drug-Eluting Stent Implantation to Reduce Late Coronary Arterial Thrombotic Events (DES-LATE) trial (Fig. 16-15),[307] an extension of the REAL-LATE and ZEST-LATE trials that included

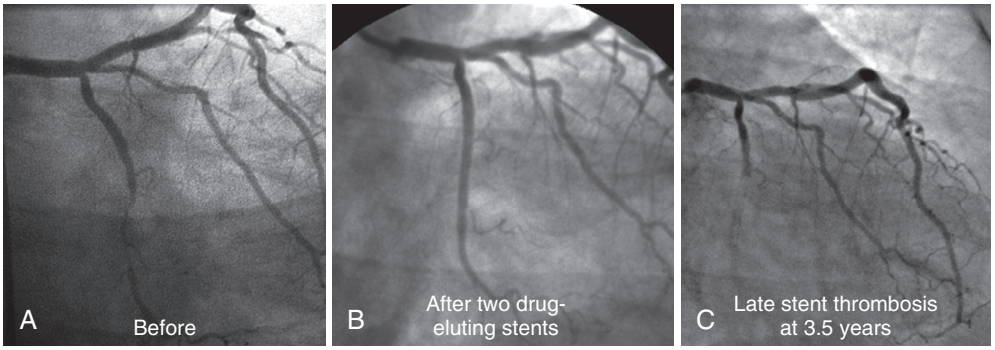

FIGURE 16-14 A high-grade stenosis is present in the midportion of the left circumflex artery (*left panel*). An excellent angiographic result was obtained after placement of two 15-mm long 2.5-mm diameter sirolimus-eluting stents (*middle panel*). The patient was asymptomatic until 3.5 years later, when he presented with acute myocardial infarction due to thrombotic occlusion within the previously implanted stents (*right panel*).

5045 randomized patients, and in the smaller Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation and Interruption Versus Continuation of Double Antiplatelet Therapy (ARCTIC-Interruption) trial[308] that included 1259 randomized patients. On this background, four randomized trials tested the hypothesis that a course of DAPT shorter than 1 year (3 or 6 months) could be noninferior to 1-year or longer DAPT duration.[131,309-311] All these trials consistently reported similar rates of ischemic events between the two strategies of DAPT duration, and some studies also reported an increased risk of bleeding with long (≥1 year) versus short (≤6 months) DAPT duration.[131] These four trials have been amalgamated in a meta-analysis that included 8649 randomized patients with at least 1 year of follow-up.[312] In this analysis, the risk of cardiac death, MI, or ST did not differ between long versus short DAPT duration. In contrast, short DAPT duration was associated with significantly lower rates of bleeding compared with long DAPT duration. Several other moderate-sized to large trials have demonstrated similar findings.[313-315] Finally, observational registries that included real-world patients and post hoc analyses of randomized trials have suggested that interruption of DAPT more than 3 months after implantation of a second-generation DES (Xience or Resolute) is not associated with an increased hazard of ST.[316,317]

The largest randomized trial to examine the issue of prolonged DAPT was the Prospective, Multicenter, Randomized Double-Blind Trial to Assess the Effectiveness and Safety of 12 Versus 30 Months of Dual Antiplatelet Therapy in Subjects Undergoing Percutaneous Coronary Intervention With Either Drug-Eluting Stent or Bare Metal Stent Placement for the Treatment of Coronary Artery Lesions (DAPT)[318] trial, which randomized 9961 DES patients who were free from MACE and bleeding events 1 year after SES, PES, EES, or ZES implantation to aspirin alone or aspirin plus a thienopyridine (either clopidogrel or prasugrel) for an additional 18 months. Among DES-treated patients, continuance of DAPT was associated with reductions in ST (0.4% vs. 1.4%, $P < .001$) and MI (2.1% vs. 4.1%, $P < .001$). Of note, 45% of the benefit in reducing MI was by prevention of ST, whereas 55% of the benefit derived from preventing MI from nontreated sites (secondary prevention). The reduction in ST with prolonged DAPT was present with all stents, although the absolute reduction was least with the CoCr-EES (0.4% absolute reduction over 18 months), and no reduction in MACCEs was reported with use of the CoCr-EES. The ischemic benefits of prolonged DAPT in this trial were offset by increases in moderate/severe bleeding complications (2.5% vs. 1.6%, $P = .001$). Additionally, a strong trend was observed toward increased all-cause mortality among patients randomized to extended-duration DAPT (2.0% vs. 1.5%, $P = .05$), which was explained by an excess of bleeding-, trauma-, and cancer-related deaths among patients randomized to extended-duration DAPT. Of note, the DAPT trial also included a BMS arm of 1687 patients who were event free at 12 months and were also randomized to aspirin alone compared with continued DAPT for an additional 18 months; results of this substratum of the trial were largely consistent with the overall findings and demonstrated numeric—although as expected, not statistically significant—reductions in ST with extended-duration DAPT compared with cessation at 1 year.[319] Other ongoing trials to compare different DAPT durations are summarized in Table 16-15. Taken together, these trials show that although prolonged DAPT is not absolutely mandatory beyond 3 to 6 months,

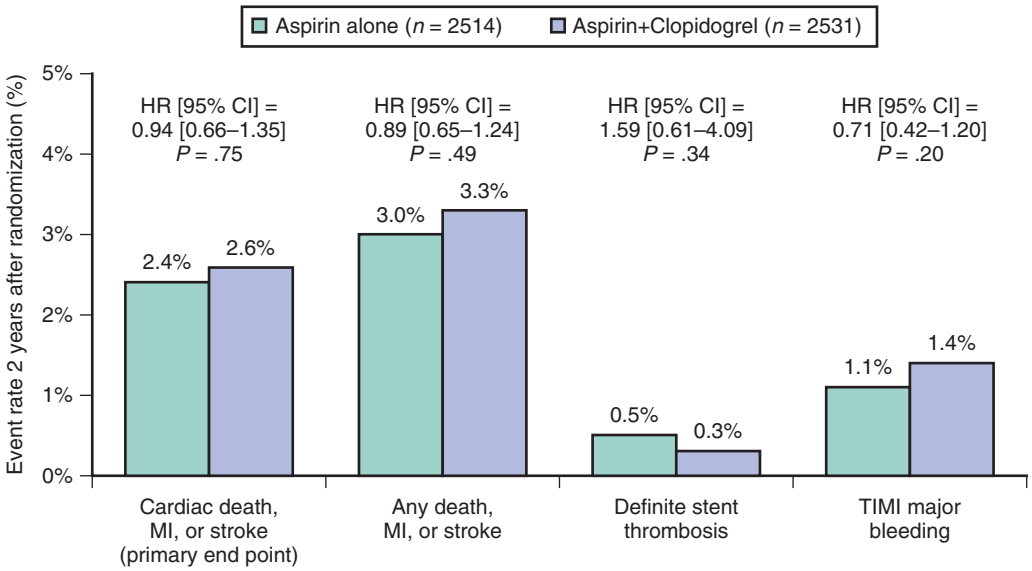

FIGURE 16-15 Outcomes in the DES-LATE randomized trial 2 years after randomizing 5045 patients who were free from adverse cardiovascular events at least 1 year after DES implantation to aspirin alone versus aspirin plus clopidogrel.[307] *CI,* Confidence interval; *HR,* hazard ratio; *MI,* myocardial infarction; *TIMI,* Thrombolysis in Myocardial Infarction (grade).

TABLE 16-15 Ongoing Randomized Controlled Trials Comparing Different Durations of Dual-Antiplatelet Therapy After Drug-Eluting Stent Implantation

Study	N	Months of DAPT	Stent Type	Primary End Point	Months of Follow-Up
DAPT-STEMI	1100	6 vs. 12	DES	All cause death, MI, any revascularization, stroke, or major bleeding	24
NOBORI-DAPT	4590	6 vs. 18	BES	All-cause death, MI, stroke, or major bleeding	18
OPTIDUAL[307a]	1966	12 vs. 48	DES	MI, stroke, or severe bleeding	48

BES, Biolimus-eluting stent; *DAPT,* dual-antiplatelet therapy; *DES,* drug-eluting stent; *MI,* myocardial infarction; *ST,* stent thrombosis; *ZES,* zotarolimus-eluting stent.

some benefit may be gained by continuing DAPT for several years in the prevention of late ST and MI (arising both from the stent site and elsewhere); however, such therapy should be utilized only in patients in whom the benefits of reducing long-term atherothrombotic complications would be expected to outweigh the increased risks of bleeding.

Restenosis

By increasing acute luminal gain[33,34] and eliminating late recoil and negative vessel remodeling,[320] BMS use reduced the rate of restenosis compared with balloon angioplasty.[5,6] However, stents induce more arterial injury than balloon angioplasty, and this results in a greater absolute amount of neointimal hyperplasia developing over the first 6 to 12 months after the procedure,[321] thereby resulting in binary angiographic restenosis in 10% to more than 50% of lesions (depending on patient and lesion complexity). Whereas restenosis most commonly presents with stable angina and exercise-induced ischemia within 1 year of stent implantation, it has become increasingly recognized that restenosis presents as an ACS in as many as 25% of patients, occasionally even with STEMI.[321,322]

Numerous studies have demonstrated that the most reproducible determinants of restenosis after BMS implantation are the presence of diabetes mellitus, especially if insulin is required; small RVD; and long lesion length.[212,213,323-326] Other factors associated with restenosis are treatment of ostial and/or calcified lesions, true bifurcation lesions that require main vessel and side-branch stents, CTOs, and SVGs.[327] The same factors are associated with higher rates of DES restenosis. However, angiographic and clinical restenosis after DES—as well as death, MI, and ST—occurs less frequently in FDA-approved "on-label" lesions (generally noncomplex lesions for which safety and efficacy have been established in large-scale randomized trials) than in less well-studied and more complex "off-label" lesions.[328,329] In nearly all cases, DES use has been shown to reduce TLR compared with BMS use,[38,330,331] including SVG lesions, with a recent randomized trial[273] showing lower rates of restenosis with DESs compared with BMSs in this subset of lesions.

The timing of early angiographic restenosis after BMS peaks within approximately 6 months; thereafter, continued organization of the extracellular matrix results in slight luminal enlargement, and serial angiographic and IVUS studies have rarely shown late restenosis.[332,333] However, during 10-year follow-up after BMS implantation, the minimal luminal diameter continues to slowly decrease,[334] and late neoatherosclerosis with plaque rupture can present as restenosis years later.[335] A monotonically increasing amount of angiographic late loss has also been described for several years after SES and EES use, although this is perhaps somewhat less with PES use.[335-339] These observations imply the existence of low-grade chronic vascular inflammation from either the polymer or the lack of healing. In the largest randomized trial to examine this issue, the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) trial,[340] 1012 patients were randomized to a PES or an SES and were followed for 5 years, with angiographic follow-up performed systematically at 8 months and 5 years. Incremental late loss between these two periods occurred with both stents, although more so with the SES than with the PES. At 1 year, the rate of TLR was less with the SES than with the PES, a benefit that was somewhat mitigated at 5 years. The degree to which routine angiographic follow-up triggered late TLR procedures and therefore confounded the clinical results is unknown.[341] As a result of this ongoing late loss, the BMS, PES, and SES demonstrate an incrementally increasing rate of stent-site specific TLF events during long-term follow-up.[67,337,342-345] The same observations have been made with the best second-generation DESs, such as the CoCr-EES.[122,346]

The causes of restenosis after stenting are multifactorial. In addition to excessive late neointimal hyperplasia, restenosis after BMS and DES use has been associated with stent underexpansion,[347-349] edge dissections and residual untreated disease,[350,351] geographic miss,[352] and strut fractures.[353-355] Some studies,[356] but not all,[357,358] have found an association between nickel allergy and restenosis after BMS or DES use. Genetic mutations in the genes that encode mTOR or polymorphisms in the genes that encode proteins involved in paclitaxel metabolism may result in resistance to SESs and PESs respectively.[359,360] Other genetic polymorphisms have also been associated with restenosis.[361,362] Excessive inflammation from first-generation DES polymers—specifically, eosinophilic reactions to PESs and granulomatous reactions to SESs—may provoke late restenosis.[52,363] And of course, the antiproliferative effects of the DES depend on both the drug (with rapamycin analogues being inherently more potent than paclitaxel) and the release kinetics (with extended release of rapamycin analogues beyond 1 month being necessary for maximal efficacy). The role of neoatherosclerosis as a cause of restenosis has been previously discussed.[335,364] As discussed earlier, newer generation stents—especially the CoCr-EES and Re-ZES—have been shown to have enhanced efficacy and safety. In addition, by facilitating the operator's ability to achieve larger lumen areas, IVUS may reduce restenosis and improve clinical outcomes after DES and BMS use.[365-367] No single randomized trial, however, has been adequately powered to demonstrate a reduction in TLR with IVUS after DES implantation, although the Angiography Versus IVUS Optimization (AVIO)[368] trial demonstrated that the postprocedural minimal luminal diameter was significantly greater in DES with IVUS guidance.

Patients who develop in-stent restenosis are at high risk for recurrence after percutaneous treatment, especially if the pattern of restenosis is diffuse.[369,370] IVUS imaging is highly useful in patients with restenosis to differentiate neointimal hyperplasia from stent underexpansion, geographic miss, strut fracture, and other rare occurrences such as chronic recoil and stent embolization, which require directed approaches to successfully manage.[371] Radiofrequency IVUS, optical coherence tomography (OCT), and near-infrared spectroscopy can identify neoatherosclerosis as a cause of restenosis or ST, either with or without plaque rupture.[372-374]

Treatment of Restenosis

Isolated restenosis at the stent edge can often be effectively treated with only balloon angioplasty or with an additional short stent. Treatment options for diffuse BMS restenosis due to neointimal hyperplasia have been extensively studied. In the BMS era, neither cutting balloons, directional or rotational atherectomy, or repeat BMS proved better than balloon angioplasty for diffuse in-stent restenosis (ISR).[375] Vascular brachytherapy with either locally applied beta or gamma radiation was effective in reducing recurrent restenosis within 1 year[376,377] but was logistically complex, and the resultant vascular toxicity with prolonged inflammation and obliteration of normal cell lines resulted in high rates of late ST, especially when new BMSs were implanted, and restenosis.[378,379] Subsequently, two multicenter randomized trials demonstrated that SESs and PESs significantly reduce angiographic restenosis and improve event-free survival at 9 months compared with either beta or gamma vascular brachytherapy in patients with BMS restenosis.[380,381] With follow-up to 2 to 3 years in these two trials,[382,383] event-free survival was reduced with the PES and was noninferior with the SES compared with brachytherapy. In the Intracoronary Stenting or Angioplasty for Restenosis Reduction–Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE) trial,[384] 300 patients with BMS restenosis were randomized to balloon angioplasty alone, an SES, or a PES. Angiographic follow-up at 6 months showed recurrent restenosis after balloon angioplasty in 44.6% of patients, versus 14.3% for the SES ($P < .001$) and 21.7% for the PES ($P = .001$), with TVR rates of 33%, 8%, and 19%, respectively ($P < .001$ and $P = .02$ compared with balloon angioplasty, respectively). Based on the results of these trials, DESs have supplanted brachytherapy and other approaches for treatment of nearly all cases of BMS restenosis as a result of intimal hyperplasia, except possibly isolated edge stenoses.

Implanting a second stent, even a DES, to treat BMS restenosis is not inherently desirable because of the obligate reduction in luminal diameter with layered devices. As a result, drug-eluting balloons have

been investigated as a treatment for BMS in-stent restenosis (see Chapter 17). Three small, randomized trials with angiographic end points suggested that the Paccocath (Bayer HealthCare, Germany) paclitaxel-eluting balloon was more effective than balloon angioplasty alone and at least as effective as a PES for the treatment of BMS restenosis.[385-387] In the Restenosis Intrastent of Bare Metal Stents: Paclitaxel-Eluting Balloon Versus Everolimus-Eluting Stent (RIBS V)[388] trial, 189 patients with BMS restenosis were randomized to receive the CoCr-EES or the Sequent Please (B. Braun Vascular Systems, Germany) paclitaxel-eluting balloon. The mean in-segment diameter stenosis at 9 months was less with the CoCr-EES than with the DEB (13% ± 17% vs. 25% ± 20%, $P < .001$), and restenosis tended to be reduced with EES use, although no differences were reported in the 1-year MACE rates, which were low in both arms. Given the superior angiographic results in this trial, which was underpowered for MACE, most cases of BMS restenosis should be treated with a potent second-generation DES unless the RVD is very small, in which case a DEB may be a preferable first choice.

Compared with BMS restenosis, DES restenosis tends to be focal and is diffuse in less than 25% of patients. However, recurrence rates after treatment of DES restenosis are higher than after treatment of BMS restenosis.[389,390] If the DES restenosis is isolated to the margin of the stent or is focal within the stent, either balloon angioplasty or implantation of a short DES of the same type is often selected. Management of diffuse DES restenosis has been less well studied. In the Prospective Randomized Trial of Sirolimus-Eluting Stents Compared to Balloon Angioplasty for Restenosis of Drug-Eluting Coronary Stents (CRISTAL),[391] 197 patients with diffuse restenosis (mean length ~14 mm) of either an SES or a PES were randomized to treatment with an SES or balloon angioplasty. Follow-up at 12 months demonstrated a significantly larger minimal luminal diameter (MLD) with an SES compared with balloon angioplasty only (2.14 ± 0.62 mm vs. 1.71 ± 0.55 mm, $P < .0001$), with a trend toward less TLR (5.9% vs. 13.1%, $P = .10$). If IVUS demonstrates adequate stent expansion, many operators consider diffuse ISR after DES implantation to represent "drug failure" and will treat with a different class of agent (e.g., a PES after SES failure). Consistent with this hypothesis are data from the Restenosis Intrastent: Balloon Angioplasty Versus Drug-Eluting Stent (RIBS III)[392] registry, a nonrandomized, multicenter registry that included 363 consecutive patients with DES ISR who were treated with either a different DES (switch strategy) or a conventional strategy that included balloon angioplasty, a BMS, or the same DES. After a median follow-up of 2 years, the switch strategy was associated with significantly lower restenosis rates compared with the conventional strategy. Notably, the use of a second-generation DES compared with a first-generation DES, as well as IVUS guidance compared with angiography guidance, resulted in better long-term outcomes. However, these findings were not confirmed in the Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis (ISAR-DESIRE-2) trial,[393] in which 450 patients with SES restenosis were randomized to an SES or a PES. At 6- to 8-month follow-up, no differences were observed between the SES and PES in late loss (0.40 ± 0.65 mm vs. 0.38 ± 0.59 mm; $P = .85$), binary restenosis (19.6% vs. 20.6%; $P = .69$), or TLR (16.6% vs. 14.6%; $P = .52$).

DES restenosis has also been treated with DEBs. In a small study that included 50 patients with DES restenosis, DEBs were superior to plain old balloon angioplasty (POBA) for angiographic and clinical outcomes.[394] The efficacy of DEBs for the treatment of DES restenosis has been subsequently confirmed in a multicenter randomized trial that included 110 patients.[395] More recently, the Randomized Trial of Paclitaxel-Eluting Balloon, Paclitaxel-Eluting Stent, and Plain Balloon Angioplasty for Restenosis in Limus-Eluting Coronary Stents (ISAR-DESIRE-3) trial[396] randomized 402 patients with DES restenosis 1 : 1 : 1 to a PES, a Sequent Please paclitaxel-eluting balloon, or POBA. At 8-month follow-up, paclitaxel-eluting balloons were superior to BMSs and noninferior to PESs for the primary end point of diameter stenosis (38.0% with paclitaxel-eluting balloons vs. 54.1% with POBA vs. 37.4% with the PES, P value for superiority [P_{SUP}] < .0001 and P_{NI} = .007). Finally, in the Restenosis Intrastent of Drug-Eluting Stents: Paclitaxel-Eluting Balloon Versus Everolimus-Eluting Stent (RIBS IV) study,[397] 309 patients with DES restenosis were randomized to the Sequent Please paclitaxel-eluting balloon or a CoCr-EES. At 9-month angiographic follow-up, the in-segment stenosis diameter was significantly lower with the EES ($P = .009$), and a strong trend was present for less binary restenosis with EES use (11% vs. 19%, $P = .06$). At 1 year the rates of TLR (4% vs. 13%, $P = .008$) and MACE (cardiac death, MI, or TVR; 10% vs. 18%, $P = .04$) were significantly lower with the EES, establishing a potent second-generation DES as the treatment of choice for most patients with restenosis of previously implanted DESs.

CONCLUSIONS AND FUTURE DIRECTIONS

The development and evolution of the coronary stent has resulted in remarkable progress in less invasive treatment of CAD. The evolution from BMSs to first-generation DESs further reduced restenosis at the cost of an increased rate of very late ST and MI and a dependence on longer-term DAPT. Best-in-class second-generation DESs have eliminated these very late risks, resulting in devices that are more effective and possibly even safer than BMSs, although the optimal duration of DAPT after all stents is still debated. Novel DESs are under active development to enhance the rate and completeness of endothelialization to further reduce reliance on DAPT and enhance long-term safety,[398] as are polymer-free systems. Dual-agent DESs may also confer improved safety and efficacy. Fully bioabsorbable stents[399,400] may represent the greatest opportunity for further major improvement in outcomes, offering the potential to reduce or eliminate the problems that can arise from a permanent metallic cage and durable polymers, including neoatherosclerosis, late strut fractures, compliance mismatch, altered vascular physiology, and the inability of the vessel to remodel to accommodate plaque progression (see Chapter 34, Bioresorbable Coronary Scaffolds). In the future, stents will continue to improve in deliverability and ease of use, and further advances in adjunctive drugs and devices will enable PCI for the most complex patients and coronary anatomies.

REFERENCES

1. Sigwart U, Puel J, Mirkovitch V, et al: Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med* 316(12):701–706, 1987.
2. Serruys PW, Strauss BH, Beatt KJ, et al: Angiographic follow-up after placement of a self-expanding coronary-artery stent. *N Engl J Med* 324(1):13–17, 1991.
3. George BS, Voorhees WD, 3rd, Roubin GS, et al: Multicenter investigation of coronary stenting to treat acute or threatened closure after percutaneous transluminal coronary angioplasty: clinical and angiographic outcomes. *J Am Coll Cardiol* 22(1):135–143, 1993.
4. Schatz RA, Baim DS, Leon M, et al: Clinical experience with the Palmaz-Schatz coronary stent. Initial results of a multicenter study. *Circulation* 83(1):148–161, 1991.
5. Fischman DL, Leon MB, Baim DS, et al: A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med* 331(8):496–501, 1994.
6. Serruys PW, de Jaegere P, Kiemeneij F, et al: A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med* 331(8):489–495, 1994.
7. Cutlip DE, Chhabra AG, Baim DS, et al: Beyond restenosis: five-year clinical outcomes from second-generation coronary stent trials. *Circulation* 110(10):1226–1230, 2004.
8. Kimura T, Abe K, Shizuta S, et al: Long-term clinical and angiographic follow-up after coronary stent placement in native coronary arteries. *Circulation* 105(25):2986–2991, 2002.
9. Yamaji K, Kimura T, Morimoto T, et al: Very long-term (15 to 20 years) clinical and angiographic outcome after coronary bare metal stent implantation/clinical perspective. *Circ Cardiovasc Interv* 3(5):468–475, 2010.
10. Colombo A, Hall P, Nakamura S, et al: Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. *Circulation* 91(6):1676–1688, 1995.
11. Nakamura S, Colombo A, Gaglione A, et al: Intracoronary ultrasound observations during stent implantation. *Circulation* 89(5):2026–2034, 1994.
12. Bertrand ME, Legrand V, Boland J, et al: Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting. The full anticoagulation versus aspirin and ticlopidine (FANTASTIC) study. *Circulation* 98(16):1597–1603, 1998.
13. Leon MB, Baim DS, Popma JJ, et al: A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med* 339(23):1665–1671, 1998.

14. Schömig A, Neumann FJ, Kastrati A, et al: A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 334(17):1084–1089, 1996.
15. Urban P, Macaya C, Rupprecht HJ, et al: Randomized evaluation of anticoagulation versus antiplatelet therapy after coronary stent implantation in high-risk patients: the multicenter aspirin and ticlopidine trial after intracoronary stenting (MATTIS). *Circulation* 98(20):2126–2132, 1998.
16. Hehrlein C, Zimmermann M, Metz J, et al: Influence of surface texture and charge on the biocompatibility of endovascular stents. *Coron Artery Dis* 6(7):581–586, 1995.
17. Garasic JM, Edelman ER, Squire JC, et al: Stent and artery geometry determine intimal thickening independent of arterial injury. *Circulation* 101(7):812–818, 2000.
18. Rogers C, Edelman ER: Endovascular stent design dictates experimental restenosis and thrombosis. *Circulation* 91(12): 2995–3001, 1995.
19. Kastrati A, Mehilli J, Dirschinger J, et al: Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. *Circulation* 103(23):2816–2821, 2001.
20. Kolandaivelu K, Swaminathan R, Gibson WJ, et al: Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. *Circulation* 123(13):1400–1409, 2011.
21. Ormiston JA, Webber B, Webster MW: Stent longitudinal integrity bench insights into a clinical problem. *JACC Cardiovasc Interv* 4(12):1310–1317, 2011.
22. Mamas MA, Williams PD: Longitudinal stent deformation: insights on mechanisms, treatments and outcomes from the Food and Drug Administration Manufacturer and User Facility Device Experience database. *EuroIntervention* 8(2):196–204, 2012.
23. van der Giessen WJ, Lincoff AM, Schwartz RS, et al: Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation* 94(7):1690–1697, 1996.
24. Han RO, Schwartz RS, Kobayashi Y, et al: Comparison of self-expanding and balloon-expandable stents for the reduction of restenosis. *Am J Cardiol* 88(3):253–259, 2001.
25. Amoroso G, van Geuns RJ, Spaulding C, et al: Assessment of the safety and performance of the STENTYS self-expanding coronary stent in acute myocardial infarction: results from the APPOSITION I study. *EuroIntervention* 7(4):428–436, 2011.
26. Shin ES, Garcia-Garcia HM, Okamura T, et al: Comparison of acute vessel wall injury after self-expanding stent and conventional balloon-expandable stent implantation: a study with optical coherence tomography. *J Invasive Cardiol* 22(9):435–439, 2010.
27. van Geuns RJ, Tamburino C, Fajadet J, et al: Self-expanding versus balloon-expandable stents in acute myocardial infarction: results from the APPOSITION II study: self-expanding stents in ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv* 5(12):1209–1219, 2012.
28. Haude M, Hopp HW, Rupprecht HJ, et al: Immediate stent implantation versus conventional techniques for the treatment of abrupt vessel closure or symptomatic dissections after coronary balloon angioplasty. *Am Heart J* 140(5):e26, 2000.
29. Antoniucci D, Valenti R, Santoro GM, et al: Restenosis after coronary stenting in current clinical practice. *Am Heart J* 135(3):510–518, 1998.
30. Agostoni P, Biondi-Zoccai GG, Gasparini GL, et al: Is bare-metal stenting superior to balloon angioplasty for small vessel coronary artery disease? Evidence from a meta-analysis of randomized trials. *Eur Heart J* 26(9):881–889, 2005.
31. Nordmann AJ, Hengstler P, Leimenstoll BM, et al: Clinical outcomes of stents versus balloon angioplasty in non-acute coronary artery disease. A meta-analysis of randomized controlled trials. *Eur Heart J* 25(1):69–80, 2004.
32. Al Suwaidi J, Berger PB, Holmes DR, Jr: Coronary artery stents. *JAMA* 284(14):1828–1836, 2000.
33. Kuntz RE, Safian RD, Carrozza JP, et al: The importance of acute luminal diameter in determining restenosis after coronary atherectomy or stenting. *Circulation* 86(6):1827–1835, 1992.
34. Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS: Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy. *J Am Coll Cardiol* 21(1): 15–25, 1993.
35. Morice MC, Serruys PW, Sousa JE, et al: A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 346(23):1773–1780, 2002.
36. Moses JW, Leon MB, Popma JJ, et al: Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 349(14):1315–1323, 2003.
37. Stone GW, Ellis SG, Cox DA, et al: A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 350(3):221–231, 2004.
38. Kirtane AJ, Gupta A, Iyengar S, et al: Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. *Circulation* 119(25):3198–3206, 2009.
39. Leon MB, Kandzari DE, Eisenstein EL, et al: Late safety, efficacy, and cost-effectiveness of a zotarolimus-eluting stent compared with a paclitaxel-eluting stent in patients with de novo coronary lesions: 2-year follow-up from the ENDEAVOR IV trial (Randomized, Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Taxus Paclitaxel-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions). *JACC Cardiovasc Interv* 2(12):1208–1218, 2009.
40. Leon MB, Mauri L, Popma JJ, et al: A randomized comparison of the ENDEAVOR zotarolimus-eluting stent versus the TAXUS paclitaxel-eluting stent in de novo native coronary lesions: 12-month outcomes from the ENDEAVOR IV trial. *J Am Coll Cardiol* 55(6):543–554, 2010.
41. Stone GW, Rizvi A, Newman W, et al: Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med* 362(18):1663–1674, 2010.
42. Marx SO, Marks AR: Bench to bedside: the development of rapamycin and its application to stent restenosis. *Circulation* 104(8):852–855, 2001.
43. Aslan JE, Tormoen GW, Loren CP, et al: S6K1 and mTOR regulate Rac1-driven platelet activation and aggregation. *Blood* 118(11):3129–3136, 2011.
44. Weyrich AS, Denis MM, Schwertz H, et al: mTOR-dependent synthesis of Bcl-3 controls the retraction of fibrin clots by activated human platelets. *Blood* 109(5):1975–1983, 2007.
45. Daemen J, Serruys PW: Drug-eluting stent update 2007: part I. A survey of current and future generation drug-eluting stents: meaningful advances or more of the same? *Circulation* 116(3): 316–328, 2007.
46. Axel DI, Kunert W, Goggelmann C, et al: Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. *Circulation* 96(2):636–645, 1997.
47. Sollott SJ, Cheng L, Pauly RR, et al: Taxol inhibits neointimal smooth muscle cell accumulation after angioplasty in the rat. *J Clin Invest* 95(4):1869–1876, 1995.
48. Belotti D, Vergani V, Drudis T, et al: The microtubule-affecting drug paclitaxel has antiangiogenic activity. *Clin Cancer Res* 2(11):1843–1849, 1996.
49. Hui A, Min WX, Tang J, Cruz TF: Inhibition of activator protein 1 activity by paclitaxel suppresses interleukin-1–induced collagenase and stromelysin expression by bovine chondrocytes. *Arthritis Rheum* 41(5):869–876, 1998.
50. Lansky AJ, Costa RA, Mintz GS, et al: Non-polymer-based paclitaxel-coated coronary stents for the treatment of patients with de novo coronary lesions: angiographic follow-up of the DELIVER clinical trial. *Circulation* 109(16):1948–1954, 2004.
51. Finn AV, Joner M, Nakazawa G, et al: Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation* 115(18):2435–2441, 2007.
52. Finn AV, Kolodgie FD, Harnek J, et al: Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation* 112(2):270–278, 2005.
53. Virmani R, Guagliumi G, Farb A, et al: Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 109(6):701–705, 2004.
54. Joner M, Nakazawa G, Finn AV, et al: Endothelial cell recovery between comparator polymer-based drug-eluting stents. *J Am Coll Cardiol* 52(5):333–342, 2008.
55. Cook S, Ladich E, Nakazawa G, et al: Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation* 120(5):391–399, 2009.
56. Liu T-Y, Lin W-C, Huang L-Y, et al: Surface characteristics and hemocompatibility of PAN/PVDF blend membranes. *Polym Adv Technol* 16(5):413–419, 2005.
57. Waksman R, Pakala R: Coating bioabsorption and chronic bare metal scaffolding versus fully bioabsorbable stent. *EuroIntervention* 5(Suppl F):F36–F42, 2009.
58. De Jong WH, Eelco Bergsma J, Robinson JE, Bos RR: Tissue response to partially in vitro predegraded poly-L-lactide implants. *Biomaterials* 26(14):1781–1791, 2005.
59. Gallo R, Padurean A, Jayaraman T, et al: Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle. *Circulation* 99(16):2164–2170, 1999.
60. Suzuki T, Kopia G, Hayashi S-I, et al: Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. *Circulation* 104(10):1188–1193, 2001.
61. Sousa JE, Costa MA, Abizaid A, et al: Four-year angiographic and intravascular ultrasound follow-up of patients treated with sirolimus-eluting stents. *Circulation* 111(18):2326–2329, 2005.
62. Morice MC, Serruys PW, Sousa JE, et al: A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 346:1773–1780, 2002.
63. Schampaert E, Cohen EA, Schluter M, et al: The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). *J Am Coll Cardiol* 43(6):1110–1115, 2004.
64. Tu JV, Bowen J, Chiu M, et al: Effectiveness and safety of drug-eluting stents in Ontario. *N Engl J Med* 357(14):1393–1402, 2007.
65. Caixeta A, Leon MB, Lansky AJ, et al: 5-year clinical outcomes after sirolimus-eluting stent implantation insights from a patient-level pooled analysis of 4 randomized trials comparing sirolimus-eluting stents with bare-metal stents. *J Am Coll Cardiol* 54(10):894–902, 2009.
66. Daemen J, Wenaweser P, Tsuchida K, et al: Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* 369(9562):667–678, 2007.
67. Wenaweser P, Daemen J, Zwahlen M, et al: Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice: 4-year results from a large 2-institutional cohort study. *J Am Coll Cardiol* 52(14):1134–1140, 2008.
68. Drachman DE, Edelman ER, Seifert P, et al: Neointimal thickening after stent delivery of paclitaxel: change in composition and arrest of growth over six months. *J Am Coll Cardiol* 36(7):2325–2332, 2000.
69. Farb A, Heller PF, Shroff S, et al: Pathological analysis of local delivery of paclitaxel via a polymer-coated stent. *Circulation* 104(4):473–479, 2001.
70. Stone GW, Ellis SG, Cox DA, et al: A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 350(3):221–231, 2004.
71. Stone GW, Ellis SG, Colombo A, et al: Long-term safety and efficacy of paclitaxel-eluting stents final 5-year analysis from the TAXUS Clinical Trial Program. *JACC Cardiovasc Interv* 4(5):530–542, 2011.
72. Morice M-C, Colombo A, Meier B, et al: Sirolimus- vs paclitaxel-eluting stents in de novo coronary artery lesions: the REALITY trial: a randomized controlled trial. *JAMA* 295(8):895–904, 2006.
73. Lee SW, Park SW, Kim YH, et al: A randomized comparison of sirolimus- versus paclitaxel-eluting stent implantation in patients with diabetes mellitus. *J Am Coll Cardiol* 52(9):727–733, 2008.
74. Galloe AM, Thuesen L, Kelbaek H, et al: Comparison of paclitaxel- and sirolimus-eluting stents in everyday clinical practice: the SORT OUT II randomized trial. *JAMA* 299(4):409–416, 2008.
75. Petronio AS, De Carlo M, Branchitta G, et al: Randomized comparison of sirolimus and paclitaxel drug-eluting stents for long lesions in the left anterior descending artery: an intravascular ultrasound study. *J Am Coll Cardiol* 49(5):539–546, 2007.
76. Birkmeier KA, Kastrati A, Byrne RA, et al: Five-year clinical outcomes of sirolimus-eluting versus paclitaxel-eluting stents in high-risk patients. *Catheter Cardiovasc Interv* 77(4):494–501, 2011.
77. Eisenstein EL, Anstrom KJ, Kong DF, et al: Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 297(2):159–168, 2007.
78. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al: Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol* 48(12):2584–2591, 2006.
79. Ong AT, McFadden EP, Regar E, et al: Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol* 45(12):2088–2092, 2005.
80. Camenzind E, Steg PG, Wijns W: Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation* 115(11):1440–1455, discussion 1455, 2007.
81. Joner M, Finn AV, Farb A, et al: Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 48(1):193–202, 2006.
82. Krone RJ, Rao SV, Dai D, et al: Acceptance, panic, and partial recovery the pattern of usage of drug-eluting stents after introduction in the U.S. (a report from the American College of Cardiology/National Cardiovascular Data Registry). *JACC Cardiovasc Interv* 3(9):902–910, 2010.
83. Ellis SG, Colombo A, Grube E, et al: Incidence, timing, and correlates of stent thrombosis with the polymeric paclitaxel drug-eluting stent: a TAXUS II, IV, V, and VI meta-analysis of 3,445 patients followed for up to 3 years. *J Am Coll Cardiol* 49(10):1043–1051, 2007.
84. Kastrati A, Mehilli J, Pache J, et al: Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 356(10):1030–1039, 2007.
85. Mauri L, Hsieh WH, Massaro JM, et al: Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 356(10):1020–1029, 2007.
86. Spaulding C, Daemen J, Boersma E, et al: A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 356(10):989–997, 2007.
87. Stone GW, Moses JW, Ellis SG, et al: Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 356(10):998–1008, 2007.
88. Stone GW, Ellis SG, Colombo A, et al: Offsetting impact of thrombosis and restenosis on the occurrence of death and myocardial infarction after paclitaxel-eluting and bare metal stent implantation. *Circulation* 115(22):2842–2847, 2007.
89. Lin JC, Tiong SL, Chen CY: Surface characterization and platelet adhesion studies on fluorocarbons prepared by plasma-induced graft polymerization. *J Biomater Sci Polym Ed* 11(7):701–714, 2000.
90. Simon C, Palmaz JC, Sprague EA: Influence of topography on endothelialization of stents: clues for new designs. *J Long Term Eff Med Implants* 10(1–2):143–151, 2000.
91. Grube E, Chevalier B, Guagliumi G, et al: The SPIRIT V diabetic study: a randomized clinical evaluation of the XIENCE V everolimus-eluting stent vs the TAXUS Liberté paclitaxel-eluting stent in diabetic patients with de novo coronary artery lesions. *Am Heart J* 163(5):867–875.e1, 2012.

92. Kedhi E, Joesoef KS, McFadden E, et al: Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *Lancet* 375(9710):201–209, 2010.
93. Ribichini F, Romano M, Rosiello R, et al: A clinical and angiographic study of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with multivessel coronary artery disease: the EXECUTIVE trial (EXecutive RCT: evaluating XIENCE V in a multi vessel disease). *JACC Cardiovasc Interv* 6(10):1012–1022, 2013.
94. Serruys PW, Ruygrok P, Neuzner J, et al: A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. *EuroIntervention* 2(3):286–294, 2006.
95. Stone GW, Midei M, Newman W, et al: Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. *JAMA* 299(16): 1903–1913, 2008.
96. Burzotta F, Trani C, Todaro D, et al: Prospective randomized comparison of sirolimus- or everolimus-eluting stent to treat bifurcated lesions by provisional approach. *JACC Cardiovasc Interv* 4(3):327–335, 2011.
97. Byrne RA, Kastrati A, Kufner S, et al: Randomized, non-inferiority trial of three limus agent–eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Trial. *Eur Heart J* 30(20):2441–2449, 2009.
98. Hofma SH, Brouwer J, Velders MA, et al: Second-generation everolimus-eluting stents versus first-generation sirolimus-eluting stents in acute myocardial infarction. 1-year results of the randomized XAMI (XienceV Stent vs. Cypher Stent in Primary PCI for Acute Myocardial Infarction) trial. *J Am Coll Cardiol* 60(5):381–387, 2012.
99. Jensen LO, Thayssen P, Hansen HS, et al: Randomized comparison of everolimus-eluting and sirolimus-eluting stents in patients treated with percutaneous coronary intervention: the Scandinavian Organization for Randomized Trials with Clinical Outcome IV (SORT OUT IV). *Circulation* 125(10):1246–1255, 2012.
100. Kaiser C, Galatius S, Erne P, et al: Drug-eluting versus bare-metal stents in large coronary arteries. *N Engl J Med* 363(24): 2310–2319, 2013.
101. Kim WJ, Lee SW, Park SW, et al: Randomized comparison of everolimus-eluting stent versus sirolimus-eluting stent implantation for de novo coronary artery disease in patients with diabetes mellitus (ESSENCE-DIABETES): results from the ESSENCE-DIABETES trial. *Circulation* 124(8):886–892, 2011.
102. Kadota K, Muramatsu T, Iwabuchi M, et al: Randomized comparison of the Nobori biolimus A9-eluting stent with the sirolimus-eluting stent in patients with stenosis in native coronary arteries. *Catheter Cardiovasc Interv* 80(5):789–796, 2012.
103. Moreno R, Garcia E, Teles R, et al: Randomized comparison of sirolimus-eluting and everolimus-eluting coronary stents in the treatment of total coronary occlusions: results from the chronic coronary occlusion treated by everolimus-eluting stent randomized trial. *Circ Cardiovasc Interv* 6(1):21–28, 2013.
104. Park DW, Kim YH, Song HG, et al: Comparison of everolimus- and sirolimus-eluting stents in patients with long coronary artery lesions: a randomized LONG-DES-III (Percutaneous Treatment of LONG Native Coronary Lesions With Drug-Eluting Stent-III) Trial. *JACC Cardiovasc Interv* 4(10):1096–1103, 2011.
105. Park KW, Chae IH, Lim DS, et al: Everolimus-eluting versus sirolimus-eluting stents in patients undergoing percutaneous coronary intervention: the EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) randomized trial. *J Am Coll Cardiol* 58(18):1844–1854, 2011.
106. Mehilli J, Richardt G, Valgimigli M, et al: Zotarolimus- versus everolimus-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol* 62(22):2075–2082, 2013.
107. Serruys PW, Silber S, Garg S, et al: Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med* 363(2):136–146, 2010.
108. von Birgelen C, Basalus MW, Tandjung K, et al: A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: the TWENTE trial. *J Am Coll Cardiol* 59(15): 1350–1361, 2012.
109. Fajadet J, Garcia E, Neumann F, et al: A Prospective, Randomized, Multicenter Trial to Assess the Everolimus-Eluting Coronary Stent System (PROMUS Element) for Coronary Revascularization in a Population of Unrestricted Patients. Paper presented at Transcatheter Cardiovascular Therapeutics, San Francisco, October 29, 2013.
110. Stone GW, Teirstein PS, Meredith IT, et al: A prospective, randomized evaluation of a novel everolimus-eluting coronary stent: the PLATINUM (a Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of Up to Two de Novo Coronary Artery Lesions) trial. *J Am Coll Cardiol* 57(16):1700–1708, 2011.
111. de Belder A, de la Torre Hernandez JM, Lopez-Palop R, et al: A prospective randomized trial of everolimus-eluting stents versus bare-metal stents in octogenarians: the XIMA Trial (Xience or Vision Stents for the Management of Angina in the Elderly). *J Am Coll Cardiol* 63(14):1371–1375, 2014.
112. Sabate M, Cequier A, Iniguez A, et al: Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet* 380(9852):1482–1490, 2012.
113. Serruys PW, Ong AT, Piek JJ, et al: A randomized comparison of a durable polymer everolimus-eluting stent with a bare metal coronary stent: the SPIRIT first trial. *EuroIntervention* 1(1):58–65, 2005.
114. Kaiser C, Galatius S, Jeger R, et al: Long-term efficacy and safety of biodegradable-polymer biolimus-eluting stents: main results of the Basel Stent Kosten-Effektivitäts Trial-PROspective Validation Examination II (BASKET-PROVE II), a randomized, controlled noninferiority 2-year outcome trial. *Circulation* 131(1): 74–81, 2015.
115. Natsuaki M, Kozuma K, Morimoto T, et al: Two-year outcome of a randomized trial comparing second-generation drug-eluting stents using biodegradable or durable polymer. *JAMA* 311(20):2125–2127, 2014.
116. Smits PC, Hofma S, Togni M, et al: Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. *Lancet* 381(9867):651–660, 2013.
117. Byrne RA, Kufner S, Tiroch K, et al: Randomised trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis: 2-year follow-up results. *Heart* 95(18):1489–1494, 2009.
118. Gao RL, Xu B, Lansky AJ, et al: A randomised comparison of a novel abluminal groove-filled biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent: clinical and angiographic follow-up of the TARGET I trial. *EuroIntervention* 9(1):75–83, 2013.
119. Pilgrim T, Heg D, Roffi M, et al: Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial. *Lancet* 384(9960):2111–2122, 2014.
120. Saito S, Valdes-Chavarri M, Richardt G, et al: A randomized, prospective, intercontinental evaluation of a bioresorbable polymer sirolimus-eluting coronary stent system: the CENTURY II (Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients with Coronary Artery Disease) trial. *Eur Heart J* 35(30):2021–2031, 2014.
121. Windecker S, Witzenbichler B, Stangl K, et al: Safety and Clinical Performance of the Drug-Eluting Orsiro Stent in the Treatment of Subjects With Single De Novo Coronary Artery Lesions II (BIOFLOW II). Paper presented at Transcatheter Cardiovascular Therapeutics, San Francisco, October 29, 2013.
122. Brener SJ, Kereiakes DJ, Simonton CA, et al: Everolimus-eluting stents in patients undergoing percutaneous coronary intervention: final 3-year results of the Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions trial. *Am Heart J* 166(6):1035–1042, 2013.
123. Smits PC, Sheikjoesoef K, van de Ent M, et al: Final 5 Year Results From the All-Comer COMPARE Trial: A Prospective Randomized Comparison Between Xience-V and Taxus Liberté. Paper presented at Transcatheter Cardiovascular Therapeutics, San Francisco, October 29, 2013.
124. Kimura T, Morimoto T, Natsuaki M, et al: Comparison of everolimus-eluting and sirolimus-eluting coronary stents: 1-year outcomes from the Randomized Evaluation of Sirolimus-eluting Versus Everolimus-eluting stent Trial (RESET). *Circulation* 126(10):1225–1236, 2012.
125. Jensen LO, Thayssen P, Christiansen EH, et al: Improved Safety and Reduction in Stent Thrombosis After Everolimus-Eluting Stents Versus Sirolimus-Eluting Stents in Patients With Coronary Artery Disease: SORT OUT IV 5-Year. Paper presented at Transcatheter Cardiovascular Therapeutics, Washington D.C., September 14, 2014.
126. Baber U, Mehran R, Sharma SK, et al: Impact of the everolimus-eluting stent on stent thrombosis: a meta-analysis of 13 randomized trials. *J Am Coll Cardiol* 58(15):1569–1577, 2011.
127. Palmerini T, Kirtane AJ, Serruys PW, et al: Stent thrombosis with everolimus-eluting stents: meta-analysis of comparative randomized controlled trials. *Circ Cardiovasc Interv* 5(3):357–364, 2012.
128. de Waha A, Cassese S, Park DW, et al: Everolimus-eluting versus sirolimus-eluting stents: an updated meta-analysis of randomized trials. *Clin Res Cardiol* 101(6):461–467, 2012.
129. Raber L, Juni P, Nuesch E, et al: Long-term comparison of everolimus-eluting and sirolimus-eluting stents for coronary revascularization. *J Am Coll Cardiol* 57(21):2143–2151, 2011.
130. Raber L, Magro M, Stefanini GG, et al: Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. *Circulation* 125(9):1110–1121, 2012.
131. Valgimigli M, Campo G, Monti M, et al: Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation* 125(16):2015–2026, 2012.
132. Valgimigli M, Sabate M, Kaiser C, et al: Effects of cobalt-chromium everolimus eluting stents or bare metal stent on fatal and non-fatal cardiovascular events: patient level meta-analysis. *BMJ* 349:g6427, 2014.
133. Meredith IT, Verheye S, Dubois CL, et al: Primary endpoint results of the EVOLVE trial: a randomized evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent. *J Am Coll Cardiol* 59(15):1362–1370, 2012.
134. Natsuaki M, Kozuma K, Morimoto T, et al: Biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent: a randomized, controlled, noninferiority trial. *J Am Coll Cardiol* 62(3):181–190, 2013.
135. Wilson GJ, Huibregtse BA, Stejskal EA, et al: Vascular response to a third generation everolimus-eluting stent. *EuroIntervention* 6(4):512–519, 2010.
136. Meredith IT, Whitbourn R, Scott D, et al: PLATINUM QCA: a prospective, multicentre study assessing clinical, angiographic, and intravascular ultrasound outcomes with the novel platinum chromium thin-strut PROMUS Element everolimus-eluting stent in de novo coronary stenosis. *EuroIntervention* 7(1):84–90, 2011.
137. Kim H, Park K, Kang HJ, et al: *Randomized Comparison of PtCr-EES vs CoCr-ZES in All-Comers Receiving PCI: The HOST-ASSURE Randomized Trial*, Paper presented at the American College of Cardiology, San Francisco, March 9, 2013.
138. von Birgelen C, Sen H, Lam MK, et al: Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients requiring a percutaneous coronary intervention (DUTCH PEERS): a randomised, single-blind, multicentre, non-inferiority trial. *Lancet* 383(9915):413–423, 2014.
139. Meredith IT, Teirstein PS, Bouchard A, et al: Three-year results comparing platinum-chromium PROMUS element and cobalt-chromium XIENCE V everolimus-eluting stents in de novo coronary artery narrowing (from the PLATINUM Trial). *Am J Cardiol* 113(7):1117–1123, 2014.
140. Williams PD, Mamas MA, Morgan KP, et al: Longitudinal stent deformation: a retrospective analysis of frequency and mechanisms. *EuroIntervention* 8(2):267–274, 2012.
141. Ormiston JA, Webber B, Ubod B, et al: Stent longitudinal strength assessed using point compression: insights from a second-generation, clinically related bench test. *Circ Cardiovasc Interv* 7(1):62–69, 2014.
142. Whelan DM, van der Giessen WJ, Krabbendam SC, et al: Biocompatibility of phosphorylcholine coated stents in normal porcine coronary arteries. *Heart* 83(3):338–345, 2000.
143. Meredith IT, Ormiston J, Whitbourn R, et al: First-in-human study of the Endeavor ABT-578-eluting phosphorylcholine-encapsulated stent system in de novo native coronary artery lesions: ENDEAVOR I Trial. *EuroIntervention* 1(2):157–164, 2005.
144. Mauri L, Orav EJ, Kuntz RE: Late loss in lumen diameter and binary restenosis for drug-eluting stent comparison. *Circulation* 111(25):3435–3442, 2005.
145. Pocock SJ, Lansky AJ, Mehran R, et al: Angiographic surrogate end points in drug-eluting stent trials: a systematic evaluation based on individual patient data from 11 randomized, controlled trials. *J Am Coll Cardiol* 51(1):23–32, 2008.
146. Eisenstein EL, Wijns W, Fajadet J, et al: Long-term clinical and economic analysis of the Endeavor drug-eluting stent versus the Driver bare-metal stent: 4-year results from the ENDEAVOR II trial (Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesions). *JACC Cardiovasc Interv* 2(12):1178–1187, 2009.
147. Fajadet J, Wijns W, Laarman GJ, et al: Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions. Clinical and angiographic results of the ENDEAVOR II Trial. *Minerva Cardioangiol* 55(1):1–18, 2007.
148. Fajadet J, Wijns W, Laarman GJ, et al: Long-term follow-up of the randomised controlled trial to evaluate the safety and efficacy of the zotarolimus-eluting driver coronary stent in de novo native coronary artery lesions: five year outcomes in the ENDEAVOR II study. *EuroIntervention* 6(5):562–567, 2010.
149. Kandzari DE, Leon MB, Popma JJ, et al: Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. *J Am Coll Cardiol* 48(12):2440–2447, 2006.
150. Byrne RA, Mehilli J, Iijima R, et al: A polymer-free dual drug-eluting stent in patients with coronary artery disease: a randomized trial vs. polymer-based drug-eluting stents. *Eur Heart J* 30(8):923–931, 2009.
151. Kang WC, Ahn T, Lee K, et al: Comparison of zotarolimus-eluting stents versus sirolimus-eluting stents versus paclitaxel-eluting stents for primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction: results from the Korean Multicentre Endeavor (KOMER) acute myocardial infarction (AMI) trial. *EuroIntervention* 7(8):936–943, 2011.
152. Briguori C, Airoldi F, Visconti G, et al: Novel approaches for preventing or limiting events in diabetic patients (Naples-diabetes) trial: a randomized comparison of 3 drug-eluting stents in diabetic patients. *Circ Cardiovasc Interv* 4(2):121–129, 2011.
153. Lee CW, Park DW, Lee SH, et al: Comparison of the efficacy and safety of zotarolimus-, sirolimus-, and paclitaxel-eluting stents in patients with ST-elevation myocardial infarction. *Am J Cardiol* 104(10):1370–1376, 2009.
154. Rasmussen K, Maeng M, Kaltoft A, et al: Efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care (SORT OUT III): a randomised controlled superiority trial. *Lancet* 375(9720):1090–1099, 2010.
155. Maeng M, Tilsted HH, Jensen LO, et al: Differential clinical outcomes after 1 year versus 5 years in a randomised comparison of zotarolimus-eluting and sirolimus-eluting coronary stents (the SORT OUT III study): a multicentre, open-label, randomised superiority trial. *Lancet* 383(9934):2047–2056, 2014.

156. Camenzind E, Wijns W, Mauri L, et al: Stent thrombosis and major clinical events at 3 years after zotarolimus-eluting or sirolimus-eluting coronary stent implantation: a randomised, multicentre, open-label, controlled trial. *Lancet* 380(9851):1396–1405, 2012.
157. Camenzind E: Patient related outcomes with Endeavor versus Cypher stenting trial: 5-year outcomes. Paper presented at the European Society of Cardiology Congress, Barcelona, September 3, 2014.
158. RESOLUTE Investigators: Clinical and angiographic results with the next-generation resolute stent system: a prospective, multicenter, first-in-human trial. *JACC Cardiovasc Interv* 2(10):977–985, 2009.
159. Taniwaki M, Stefanini GG, Silber S, et al: 4-Year clinical outcomes and predictors of repeat revascularization in patients treated with new-generation drug-eluting stents: a report from the RESOLUTE all-comers trial (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention). *J Am Coll Cardiol* 63(16):1617–1625, 2014.
160. Tandjung K, Sen H, Lam MK, et al: Clinical outcome following stringent discontinuation of dual antiplatelet therapy after 12 months in real-world patients treated with second-generation zotarolimus-eluting Resolute and everolimus-eluting Xience V stents: 2-year follow-up of the randomized TWENTE trial. *J Am Coll Cardiol* 61(24):2406–2416, 2013.
161. Park KW, Kang SH, Kang HJ, et al: A randomized comparison of platinum chromium-based everolimus-eluting stents versus cobalt chromium-based zotarolimus-eluting stents in all-comers receiving percutaneous coronary intervention: HOST-ASSURE (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-Safety & Effectiveness of Drug-Eluting Stents & Anti-platelet Regimen), a randomized, controlled, noninferiority trial. *J Am Coll Cardiol* 63(25 Pt A):2805–2816, 2014.
162. Windecker S, Serruys PW, Wandel S, et al: Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 372(9644):1163–1173, 2008.
163. Raber L, Kelbaek H, Ostojic M, et al: Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. *JAMA* 308(8):777–787, 2012.
164. Stefanini GG, Kalesan B, Serruys PW, et al: Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. *Lancet* 378(9807):1940–1948, 2011.
165. Stefanini GG, Byrne RA, Serruys PW, et al: Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. *Eur Heart J* 33(10):1214–1222, 2012.
166. Mehilli J, Byrne RA, Wieczorek A, et al: Randomized trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis. *Eur Heart J* 29(16):1975–1982, 2008.
167. Chevalier B, Serruys PW, Silber S, et al: Randomised comparison of Nobori, biolimus A9-eluting coronary stent with a Taxus(R), paclitaxel-eluting coronary stent in patients with stenosis in native coronary arteries: the Nobori 1 trial. *EuroIntervention* 2(4):426–434, 2007.
168. Chevalier B, Silber S, Park SJ, et al: Randomized comparison of the Nobori Biolimus A9-eluting coronary stent with the Taxus Liberté paclitaxel-eluting coronary stent in patients with stenosis in native coronary arteries: the NOBORI 1 trial–Phase 2. *Circ Cardiovasc Interv* 2(3):188–195, 2009.
169. Christiansen EH, Jensen LO, Thayssen P, et al: Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V): a randomised non-inferiority trial. *Lancet* 381(9867):661–669, 2013.
170. Christiansen EH, Jensen LO, Thayssen P, et al: Biolimus-eluting biodegradable polymer-coated stent versus a durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention SORT-OUT V: 3-year outcome, *EuroPCR*, Paris, France, 2014.
171. Smits PC, Hofma S, Goy JJ, et al: COMPARE II trial: 3 year follow-up data, *EuroPCR*, Paris, France, 2014.
172. Krucoff MW, Kereiakes DJ, Petersen JL, et al: A novel bioresorbable polymer paclitaxel-eluting stent for the treatment of single and multivessel coronary disease: primary results of the COSTAR (Cobalt Chromium Stent With Antiproliferative for Restenosis) II study. *J Am Coll Cardiol* 51(16):1543–1552, 2008.
173. Haude M, Lee SW, Worthley SG, et al: The REMEDEE trial: a randomized comparison of a combination sirolimus-eluting endothelial progenitor cell capture stent with a paclitaxel-eluting stent. *JACC Cardiovasc Interv* 6(4):334–343, 2013.
174. Ormiston J: MiStent SES Clinical Program: DESSOLVE I and II Trials 2-Year Follow-up. Paper presented at Transcatheter Cardiovascular Therapeutics, San Francisco, 2013.
175. Kereiakes DJ, Meredith IT, Windecker S, et al: *Primary outcomes of the EVOLVE II trial: a Prospective Randomized Investigation of a Novel Bioabsorbable Polymer-Coated, Everolimus-Eluting Coronary Stent*, Paper presented at the American Heart Association Congress, Chicago, November 17, 2014.
176. Song F, Harvey I, Lilford R: Adjusted indirect comparison may be less biased than direct comparison for evaluating new pharmaceutical interventions. *J Clin Epidemiol* 61(5):455–463, 2008.
177. Palmerini T, Biondi-Zoccai G, Della Riva D, et al: Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 379(9824):1393–1402, 2012.
178. Bangalore S, Kumar S, Fusaro M, et al: Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. *Circulation* 125(23):2873–2891, 2012.
179. Bangalore S, Toklu B, Amoroso N, et al: Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis. *BMJ* 347:f6625, 2013.
180. Kang SH, Park KW, Kang DY, et al: Biodegradable-polymer drug-eluting stents vs. bare metal stents vs. durable-polymer drug-eluting stents: a systematic review and bayesian approach network meta-analysis. *Eur Heart J* 35(17):1147–1158, 2014.
181. Navarese EP, Tandjung K, Claessen B, et al: Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: comprehensive network meta-analysis. *BMJ* 347:f6530, 2013.
182. Palmerini T, Biondi-Zoccai G, Della Riva D, et al: Clinical outcomes with bioabsorbable polymer- versus durable polymer-based drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol* 63(4):299–307, 2013.
183. Navarese EP, Kowalewski M, Cortese B, et al: Short- and long-term safety and efficacy of polymer-free vs. durable polymer drug-eluting stents. A comprehensive meta-analysis of randomized trials including 6178 patients. *Atherosclerosis* 233(1):224–231, 2014.
184. Virmani R, Burke AP, Farb A, Kolodgie FD: Pathology of the vulnerable plaque. *J Am Coll Cardiol* 47(8 Suppl):C13–C18, 2006.
185. Keeley EC, Boura JA, Grines CL: Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 361(9351):13–20, 2003.
186. De Luca G, Suryapranata H, Stone GW, et al: Coronary stenting versus balloon angioplasty for acute myocardial infarction: a meta-regression analysis of randomized trials. *Int J Cardiol* 126(1):37–44, 2008.
187. Nakazawa G, Finn AV, Joner M, et al: Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. *Circulation* 118(11):1138–1145, 2008.
188. Cannon CP, Harrington RA, James S, et al: Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet* 375(9711):283–293, 2010.
189. Montalescot G, Wiviott SD, Braunwald E, et al: Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet* 373(9665):723–731, 2009.
190. Di Lorenzo E, De Luca G, Sauro R, et al: The PASEO (PaclitAxel or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty) Randomized Trial. *JACC Cardiovasc Interv* 2(6):515–523, 2009.
191. Valgimigli M, Campo G, Percoco G, et al: Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTISTRATEGY randomized trial. *JAMA* 299(15):1788–1799, 2008.
192. Spaulding C, Henry P, Teiger E, et al: Sirolimus-eluting versus uncoated stents in acute myocardial infarction. *N Engl J Med* 355(11):1093–1104, 2006.
193. van der Hoeven BL, Liem SS, Jukema JW, et al: Sirolimus-eluting stents versus bare-metal stents in patients with ST-segment elevation myocardial infarction: 9-month angiographic and intravascular ultrasound results and 12-month clinical outcome results from the MISSION! Intervention Study. *J Am Coll Cardiol* 51(6):618–626, 2008.
194. Menichelli M, Parma A, Pucci E, et al: Randomized trial of Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction (SESAMI). *J Am Coll Cardiol* 49(19):1924–1930, 2007.
195. Valgimigli M, Campo G, Arcozzi C, et al: Two-year clinical follow-up after sirolimus-eluting versus bare-metal stent implantation assisted by systematic glycoprotein IIb/IIIa inhibitor infusion in patients with myocardial infarction: results from the STRATEGY study. *J Am Coll Cardiol* 50(2):138–145, 2007.
196. Laarman GJ, Suttorp MJ, Dirksen MT, et al: Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. *N Engl J Med* 355(11):1105–1113, 2006.
197. Tierala I, Syvänne M, Kupari M: Comparison of Paclitaxel-Eluting With Bare Metal Stents in Acute Myocardial Infarction. Paper presented at Transcatheter Cardiovascular Therapeutics, San Francisco, 2006.
198. Chechi T, Vittori G, Biondi-Zoccai GG, et al: Single-center randomized evaluation of paclitaxel-eluting versus conventional stent in acute myocardial infarction (SELECTION). *J Interv Cardiol* 20(4):282–291, 2007.
199. Pasceri V, Pristipino C, Pelliccia F, et al: A randomized trial of a rapamycin-eluting stent in acute myocardial infarction: preliminary results. *Am J Cardiol* 92(6 Suppl 1):1, 2003.
200. Sanchez PL, Gimeno F, Ancillo P, et al: Role of the paclitaxel-eluting stent and tirofiban in patients with ST-elevation myocardial infarction undergoing postfibrinolysis angioplasty: the GRACIA-3 randomized clinical trial. *Circ Cardiovasc Interv* 3(4):297–307, 2010.
201. Stone GW, Lansky AJ, Pocock SJ, et al: Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. *N Engl J Med* 360(19):1946–1959, 2009.
202. Di Lorenzo E, De Luca G, Sauro R, et al: The PASEO (PaclitAxel or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty) Randomized Trial. *J Am Coll Cardiol Interv* 2:515–523, 2009.
203. Juwana YB, Suryapranata H, Ottervanger JP, et al: Comparison of rapamycin- and paclitaxel-eluting stents in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Am J Cardiol* 104(2):205–209, 2009.
204. De Luca G, Dirksen MT, Spaulding C, et al: Drug-eluting vs bare-metal stents in primary angioplasty: a pooled patient-level meta-analysis of randomized trials. *Arch Intern Med* 172(8):611–621, discussion 621–612, 2012.
205. Sabate M, Brugaletta S, Cequier A, et al: The EXAMINATION trial (Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction): 2-year results from a multicenter randomized controlled trial. *JACC Cardiovasc Interv* 7(1):64–71, 2014.
206. Raber L, Kelbaek H, Taniwaki M, et al: Biolimus-eluting stents with biodegradable polymer versus bare-metal stents in acute myocardial infarction: two-year clinical results of the COMFORTABLE AMI trial. *Circ Cardiovasc Interv* 7(3):355–364, 2014.
207. Palmerini T, Biondi-Zoccai G, Della Riva D, et al: Clinical outcomes with drug-eluting and bare-metal stents in patients with ST-segment elevation myocardial infarction: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol* 62(6):496–504, 2013.
208. Bangalore S, Amoroso N, Fusaro M, et al: Outcomes with various drug-eluting or bare metal stents in patients with ST-segment-elevation myocardial infarction: a mixed treatment comparison analysis of trial level data from 34 068 patient-years of follow-up from randomized trials. *Circ Cardiovasc Interv* 6(4):378–390, 2013.
209. Henriques JP, Zijlstra F, Ottervanger JP, et al: Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. *Eur Heart J* 23(14):1112–1117, 2002.
210. Jain AK, Rothman MT: Thrombus entrapment by a novel mesh-covered stent in ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 58(22):e39, 2011.
211. Stone GW, Abizaid A, Silber S, et al: Prospective, Randomized, Multicenter Evaluation of a Polyethylene Terephthalate Micronet Mesh-Covered Stent (MGuard) in ST-Segment Elevation Myocardial Infarction: The MASTER Trial. *J Am Coll Cardiol* 60(19):1975–1984, 2012.
212. Elezi S, Kastrati A, Pache J, et al: Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. *J Am Coll Cardiol* 32(7):1866–1873, 1998.
213. Singh M, Gersh BJ, McClelland RL, et al: Clinical and angiographic predictors of restenosis after percutaneous coronary intervention: insights from the Prevention of Restenosis With Tranilast and Its Outcomes (PRESTO) trial. *Circulation* 109(22):2727–2731, 2004.
214. Fajadet J, Wijns W, Laarman GJ, et al: Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation* 114(8):798–806, 2006.
215. Hermiller JB, Raizner A, Cannon L, et al: Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: the TAXUS-IV trial. *J Am Coll Cardiol* 45(8):1172–1179, 2005.
216. Moussa I, Leon MB, Baim DS, et al: Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. *Circulation* 109(19):2273–2278, 2004.
217. Dawkins KD, Stone GW, Colombo A, et al: Integrated analysis of medically treated diabetic patients in the TAXUS(R) program: benefits across stent platforms, paclitaxel release formulations, and diabetic treatments. *EuroIntervention* 2(1):61–68, 2006.
218. Mitsuuchi Y, Johnson SW, Selvakumaran M, et al: The phosphatidylinositol 3-kinase/AKT signal transduction pathway plays a critical role in the expression of p21WAF1/CIP1/SDI1 induced by cisplatin and paclitaxel. *Cancer Res* 60(19):5390–5394, 2000.
219. Rocic P: Differential phosphoinositide 3-kinase signaling: implications for PTCA? *Am J Physiol Heart Circ Physiol* 297(6):H1970–H1971, 2009.
220. Dibra A, Kastrati A, Mehilli J, et al: Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med* 353(7):663–670, 2005.
221. Stone GW, Kedhi E, Kereiakes DJ, et al: Differential clinical responses to everolimus-eluting and paclitaxel-eluting coronary

stents in patients with and without diabetes mellitus. *Circulation* 124(8):893–900, 2011.
222. Bangalore S, Kumar S, Fusaro M, et al: Outcomes with various drug eluting or bare metal stents in patients with diabetes mellitus: mixed treatment comparison analysis of 22,844 patient years of follow-up from randomised trials. *BMJ* 345:e5170, 2012.
223. Daemen J, Boersma E, Flather M, et al: Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation* 118(11): 1146–1154, 2008.
224. Kapur A, Hall RJ, Malik IS, et al: Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. *J Am Coll Cardiol* 55(5):432–440, 2010.
225. Farkouh ME, Domanski M, Sleeper LA, et al: Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 367(25):2375–2384, 2012.
226. Palmerini T, Biondi-Zoccai G, Reggiani LB, et al: Risk of stroke with coronary artery bypass graft surgery compared with percutaneous coronary intervention. *J Am Coll Cardiol* 60(9):798–805, 2012.
227. Palmerini T, Biondi-Zoccai G, Riva DD, et al: Risk of stroke with percutaneous coronary intervention compared with on-pump and off-pump coronary artery bypass graft surgery: evidence from a comprehensive network meta-analysis. *Am Heart J* 165(6):910–917.e14, 2013.
228. Farooq V, van Klaveren D, Steyerberg EW, et al: Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 381(9867):639–650, 2013.
229. Hlatky MA, Boothroyd DB, Bravata DM, et al: Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 373(9670): 1190–1197, 2009.
230. Booth J, Clayton T, Pepper J, et al: Randomized, controlled trial of coronary artery bypass surgery versus percutaneous coronary intervention in patients with multivessel coronary artery disease: six-year follow-up from the Stent or Surgery Trial (SoS). *Circulation* 118(4):381–388, 2008.
231. Hueb W, Lopes NH, Gersh BJ, et al: Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 115(9):1082–1089, 2007.
232. Rodriguez AE, Baldi J, Fernandez Pereira C, et al: Five-year follow-up of the Argentine randomized trial of coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple vessel disease (ERACI II). *J Am Coll Cardiol* 46(4):582–588, 2005.
233. Serruys PW, Ong AT, van Herwerden LA, et al: Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol* 46(4):575–581, 2005.
234. Serruys PW, Morice MC, Kappetein AP, et al: Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 360(10):961–972, 2009.
235. Mohr FW, Morice MC, Kappetein AP, et al: Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 381:629–638, 2013.
236. Head SJ, Davierwala PM, Serruys PW, et al: Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial. *Eur Heart J* 35(40):2821–2830, 2014.
237. Morice MC, Serruys PW, Kappetein AP, et al: Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation* 129(23): 2388–2394, 2014.
238. Sipahi I, Akay MH, Dagdelen S, et al: Coronary artery bypass grafting vs percutaneous coronary intervention and long-term mortality and morbidity in multivessel disease: meta-analysis of randomized clinical trials of the arterial grafting and stenting era. *JAMA Intern Med* 174(2):223–230, 2014.
239. Patel MR, Dehmer GJ, Hirshfeld JW, et al: ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 Appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 59(9): 857–881, 2012.
240. Windecker S, Kolh P, Alfonso F, et al: 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 35(37):2541–2619, 2014.
241. Farooq V, Serruys PW, Zhang Y, et al: Short-term and long-term clinical impact of stent thrombosis and graft occlusion in the SYNTAX trial at 5 years: Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial. *J Am Coll Cardiol* 62(25):2360–2369, 2013.
242. O'Keefe JH, Jr, Hartzler GO, Rutherford BD, et al: Left main coronary angioplasty: early and late results of 127 acute and elective procedures. *Am J Cardiol* 64(3):144–147, 1989.
243. Tan WA, Tamai H, Park SJ, et al: Long-term clinical outcomes after unprotected left main trunk percutaneous revascularization in 279 patients. *Circulation* 104(14):1609–1614, 2001.
244. Erglis A, Narbute I, Kumsars I, et al: A randomized comparison of paclitaxel-eluting stents versus bare-metal stents for treatment of unprotected left main coronary artery stenosis. *J Am Coll Cardiol* 50(6):491–497, 2007.
245. Mehilli J, Kastrati A, Byrne RA, et al: Paclitaxel- versus sirolimus-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol* 53(19):1760–1768, 2009.
246. Boudriot E, Thiele H, Walther T, et al: Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. *J Am Coll Cardiol* 57(5):538–545, 2011.
247. Buszman PE, Kiesz SR, Bochenek A, et al: Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol* 51(5):538–545, 2008.
248. Park SJ, Kim YH, Park DW, et al: Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med* 364(18):1718–1727, 2011.
249. Capodanno D, Stone GW, Morice MC, et al: Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. *J Am Coll Cardiol* 58(14):1426–1432, 2011.
250. Mohr JP, Parides MK, Stapf C, et al: Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. *Lancet* 383(9917):614–621, 2013.
251. Rassen JA, Mittleman MA, Glynn RJ, et al: Safety and effectiveness of bivalirudin in routine care of patients undergoing percutaneous coronary intervention. *Eur Heart J* 31(5):561–572, 2010.
252. Park SJ, Kim YH, Park DW, et al: Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. *Circ Cardiovasc Interv* 2(3):167–177, 2009.
253. Tonino PA, De Bruyne B, Pijls NH, et al: Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 360(3):213–224, 2009.
254. Stone GW, Kandzari DE, Mehran R, et al: Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. *Circulation* 112(15):2364–2372, 2005.
255. Stone GW, Reifart NJ, Moussa I, et al: Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part II. *Circulation* 112(16):2530–2537, 2005.
256. Suttorp MJ, Laarman GJ, Rahel BM, et al: Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISON II): a randomized comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions. *Circulation* 114(9):921–928, 2006.
257. Colmenarez HJ, Escaned J, Fernandez C, et al: Efficacy and safety of drug-eluting stents in chronic total coronary occlusion recanalization: a systematic review and meta-analysis. *J Am Coll Cardiol* 55(17):1854–1866, 2010.
258. Jaguszewski M, Gilis-Siek N, Ciecwierz D, et al: Early-generation versus new-generation drug-eluting stents in isolated chronic total occlusion: on the road to extinction? *J Invasive Cardiol* 26(5):209–214, 2014.
259. King SB, 3rd, Smith SC, Jr, Hirshfeld JW, Jr, et al: 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *J Am Coll Cardiol* 51(2):172–209, 2008.
260. Brar SS, Gray WA, Dangas G, et al: Bifurcation stenting with drug-eluting stents: a systematic review and meta-analysis of randomised trials. *EuroIntervention* 5(4):475–484, 2009.
261. Fanggiday JC, Stella PR, Guyomi SH, Doevendans PA: Safety and efficacy of drug-eluting balloons in percutaneous treatment of bifurcation lesions the DEBIUT (drug-eluting balloon in bifurcaton Utrecht) registry. *Catheter Cardiovasc Interv* 71(5): 629–635, 2008.
262. Stella PR: Are Drug-Eluting Balloons Likely to Assist Bifurcation Stenting? Rationale and the DEBIUT Experience. Paper presented at Transcatheter Cardiovascular Therapeutics, Washington, D.C., 2010.
263. Hasegawa T, Ako J, Koo BK, et al: Analysis of left main coronary artery bifurcation lesions treated with biolimus-eluting DEVAX AXXESS plus nitinol self-expanding stent: intravascular ultrasound results of the AXXENT trial. *Catheter Cardiovasc Interv* 73(1):34–41, 2009.
264. Verheye S, Agostoni P, Dubois CL, et al: 9-month clinical, angiographic, and intravascular ultrasound results of a prospective evaluation of the Axxess self-expanding biolimus A9-eluting stent in coronary bifurcation lesions: the DIVERGE (Drug-Eluting Stent Intervention for Treating Side Branches Effectively) study. *J Am Coll Cardiol* 53(12):1031–1039, 2009.
265. Verheye S, Grube E, Ramcharitar S, et al: First-in-man (FIM) study of the Stentys bifurcation stent–30 days results. *EuroIntervention* 4(5):566–571, 2009.
266. Ormiston JA, Lefevre T, Grube E, et al: First human use of the TAXUS Petal paclitaxel-eluting bifurcation stent. *EuroIntervention* 6(1):46–53, 2010.
267. Leon M: The TRYTON Bifurcation Trial: A Randomized Comparison of a Provisional One-Stent Versus a Dedicated Two-Stent Strategy for True Bifurcation Coronary Lesions. Paper presented at Transcatheter Cardiovascular Therapeutics, Washington, D.C., 2013.
268. Hanekamp CE, Koolen JJ, Den Heijer P, et al: Randomized study to compare balloon angioplasty and elective stent implantation in venous bypass grafts: the VENESTENT study. *Catheter Cardiovasc Interv* 60(4):452–457, 2003.
269. Savage MP, Douglas JS, Jr, Fischman DL, et al: Stent placement compared with balloon angioplasty for obstructed coronary bypass grafts. Saphenous Vein De Novo Trial Investigators. *N Engl J Med* 337(11):740–747, 1997.
270. Vermeersch P, Agostoni P, Verheye S, et al: Randomized double-blind comparison of sirolimus-eluting stent versus bare-metal stent implantation in diseased saphenous vein grafts: six-month angiographic, intravascular ultrasound, and clinical follow-up of the RRISC Trial. *J Am Coll Cardiol* 48(12):2423–2431, 2006.
271. Brilakis ES, Lichtenwalter C, de Lemos JA, et al: A randomized controlled trial of a paclitaxel-eluting stent versus a similar bare-metal stent in saphenous vein graft lesions the SOS (Stenting of Saphenous Vein Grafts) trial. *J Am Coll Cardiol* 53(11):919–928, 2009.
272. Vermeersch P, Agostoni P, Verheye S, et al: Increased late mortality after sirolimus-eluting stents versus bare-metal stents in diseased saphenous vein grafts: results from the randomized DELAYED RRISC Trial. *J Am Coll Cardiol* 50(3):261–267, 2007.
273. Mehilli J, Pache J, Abdel-Wahab M, et al: Drug-eluting versus bare-metal stents in saphenous vein graft lesions (ISAR-CABG): a randomised controlled superiority trial. *Lancet* 378(9796): 1071–1078, 2011.
274. Rodes-Cabau J, Bertrand OF, Larose E, et al: Comparison of plaque sealing with paclitaxel-eluting stents versus medical therapy for the treatment of moderate nonsignificant saphenous vein graft lesions: the moderate vein graft lesion stenting with the taxus stent and intravascular ultrasound (VELETI) pilot trial. *Circulation* 120(20):1978–1986, 2009.
275. Holmes DR, Jr, Kereiakes DJ, Garg S, et al: Stent thrombosis. *J Am Coll Cardiol* 56(17):1357–1365, 2010.
276. Iakovou I, Schmidt T, Bonizzoni E, et al: Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 293(17):2126–2130, 2005.
277. Doyle B, Rihal CS, O'Sullivan CJ, et al: Outcomes of stent thrombosis and restenosis during extended follow-up of patients treated with bare-metal coronary stents. *Circulation* 116(21): 2391–2398, 2007.
278. Burzotta F, Parma A, Pristipino C, et al: Angiographic and clinical outcome of invasively managed patients with thrombosed coronary bare metal or drug-eluting stents: the OPTIMIST study. *Eur Heart J* 29(24):3011–3021, 2008.
279. van Werkum JW, Heestermans AA, de Korte FI, et al: Long-term clinical outcome after a first angiographically confirmed coronary stent thrombosis: an analysis of 431 cases. *Circulation* 119(6):828–834, 2009.
280. Cutlip DE, Windecker S, Mehran R, et al: Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 115(17):2344–2351, 2007.
281. Brener SJ, Cristea E, Kirtane AJ, et al: Intra-procedural stent thrombosis: a new risk factor for adverse outcomes in patients undergoing percutaneous coronary intervention for acute coronary syndromes. *JACC Cardiovasc Interv* 6(1):36–43, 2013.
282. Finn AV, Nakazawa G, Ladich E, et al: Does underlying plaque morphology play a role in vessel healing after drug-eluting stent implantation? *JACC Cardiovasc Imaging* 1(4):485–488, 2008.
283. Aoki J, Lansky AJ, Mehran R, et al: Early stent thrombosis in patients with acute coronary syndromes treated with drug-eluting and bare metal stents: the Acute Catheterization and Urgent Intervention Triage Strategy trial. *Circulation* 119(5): 687–698, 2009.
284. Cutlip DE, Baim DS, Ho KK, et al: Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation* 103(15):1967–1971, 2001.
285. Kuchulakanti PK, Chu WW, Torguson R, et al: Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. *Circulation* 113(8):1108–1113, 2006.
286. Mishkel GJ, Moore AL, Markwell S, Shelton ME: Correlates of late and very late thrombosis of drug eluting stents. *Am Heart J* 156(1):141–147, 2008.
287. Yadav M, Généreux P, Palmerini T, et al: SYNTAX score and the risk of stent thrombosis after percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes: an ACUITY trial substudy. *Catheter Cardiovasc Interv* 85(1):1–10, 2014.
288. Fujii K, Carlier SG, Mintz GS, et al: Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol* 45(7):995–998, 2005.

289. Liu X, Doi H, Maehara A, et al: A volumetric intravascular ultrasound comparison of early drug-eluting stent thrombosis versus restenosis. *JACC Cardiovasc Interv* 2(5):428–434, 2009.
290. Okabe T, Mintz GS, Buch AN, et al: Intravascular ultrasound parameters associated with stent thrombosis after drug-eluting stent deployment. *Am J Cardiol* 100(4):615–620, 2007.
291. Roy P, Steinberg DH, Sushinsky SJ, et al: The potential clinical utility of intravascular ultrasound guidance in patients undergoing percutaneous coronary intervention with drug-eluting stents. *Eur Heart J* 29(15):1851–1857, 2008.
292. Stone GW, Witzenbichler B, Weisz G, et al: Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet* 382(9892):614–623, 2013.
293. Witzenbichler B, Maehara A, Weisz G, et al: Relationship between intravascular ultrasound guidance and clinical outcomes after drug-eluting stents: the assessment of dual antiplatelet therapy with drug-eluting stents (ADAPT-DES) study. *Circulation* 129(4):463–470, 2014.
294. Cook S, Ladich E, Nakazawa G, et al: Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation* 120:391–399, 2009.
295. Nakazawa G, Finn AV, Vorpahl M, et al: Incidence and predictors of drug-eluting stent fracture in human coronary artery a pathologic analysis. *J Am Coll Cardiol* 54(21):1924–1931, 2009.
296. Cook S, Wenaweser P, Togni M, et al: Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation* 115(18):2426–2434, 2007.
297. Hassan AK, Bergheanu SC, Stijnen T, et al: Late stent malapposition risk is higher after drug-eluting stent compared with bare-metal stent implantation and associates with late stent thrombosis. *Eur Heart J* 31(10):1172–1180, 2010.
298. Palmerini T, Biondi-Zoccai G, Della Riva D, et al: Stent thrombosis with drug-eluting stents: is the paradigm shifting? *J Am Coll Cardiol* 62(21):1915–1921, 2013.
299. Hall P, Nakamura S, Maiello L, et al: A randomized comparison of combined ticlopidine and aspirin therapy versus aspirin therapy alone after successful intravascular ultrasound-guided stent implantation. *Circulation* 93(2):215–222, 1996.
300. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH: Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). *Circulation* 102(6):624–629, 2000.
301. Airoldi F, Colombo A, Morici N, et al: Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. *Circulation* 116(7):745–754, 2007.
302. van Werkum JW, Heestermans AA, Zomer AC, et al: Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. *J Am Coll Cardiol* 53(16):1399–1409, 2009.
303. Jimenez-Quevedo P, Sabate M, Angiolillo DJ, et al: Long-term clinical benefit of sirolimus-eluting stent implantation in diabetic patients with de novo coronary stenoses: long-term results of the DIABETES trial. *Eur Heart J* 28(16):1946–1952, 2007.
304. Brar SS, Kim J, Brar SK, et al: Long-term outcomes by clopidogrel duration and stent type in a diabetic population with de novo coronary artery lesions. *J Am Coll Cardiol* 51(23):2220–2227, 2008.
305. Harjai KJ, Shenoy C, Orshaw P, Boura J: Dual antiplatelet therapy for more than 12 months after percutaneous coronary intervention: insights from the Guthrie PCI Registry. *Heart* 95(19):1579–1586, 2009.
306. Park SJ, Park DW, Kim YH, et al: Duration of dual antiplatelet therapy after implantation of drug-eluting stents. *N Engl J Med* 362(15):1374–1382, 2010.
307. Lee CW, Ahn JM, Park DW, et al: Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a randomized, controlled trial. *Circulation* 129(3):304–312, 2013.
307a. Helft G, Le Feuvre C, Georges JL, et al: Efficacy and safety of 12 versus 48 months of dual antiplatelet therapy after implantation of a drug-eluting stent: the OPTImal DUAL antiplatelet therapy (OPTIDUAL) trial: study protocol for a randomized controlled trial. *Trials* 14:56, 2013.
308. Collet JP, Silvain J, Barthélémy O, et al: Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. *Lancet* 384(9954):1577–1585, 2014.
309. Feres F, Costa RA, Abizaid A, et al: Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA* 310(23):2510–2522, 2013.
310. Gwon HC, Hahn JY, Park KW, et al: Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation* 125(3):505–513, 2012.
311. Kim BK, Hong MK, Shin DH, et al: A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol* 60(15):1340–1348, 2012.
312. Stefanini GG, Siontis GC, Cao D, et al: Short versus long duration of DAPT after DES implantation: a meta-analysis. *J Am Coll Cardiol* 64(9):953–954, 2014.
313. Colombo A, Chieffo A, Frasheri A, et al: Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. *J Am Coll Cardiol* 64(20):2086–2097, 2014.
314. Gilard M, Barragan P, Noryani A, et al: 6- Versus 24-month dual antiplatelet therapy after implantation of drug eluting stents in patients non-resistant to aspirin: the randomized, multicenter ITALIC trial. *J Am Coll Cardiol* 65(8):777–786, 2015.
315. Schulz-Schüpke S, Byrne RA, Ten Berg JM, et al: ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J* 36:1252–1263, 2015.
316. Palmerini T: Difficult Decisions with Dual Antiplatelet Therapy: DES, STEMI, Unplanned Treatment Interruption, *EuroPCR*, Paris, France, 2012.
317. Silber S, Kirtane AJ, Belardi JA, et al: Lack of association between dual antiplatelet therapy use and stent thrombosis between 1 and 12 months following resolute zotarolimus-eluting stent implantation. *Eur Heart J* 35(29):1949–1956, 2014.
318. Mauri L, Kereiakes DJ, Yeh RW, et al: Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 371(23):2155–2166, 2014.
319. Kereiakes DJ, Yeh RW, Massaro JM, et al: *Comparison of ischemic and bleeding events after drug-eluting stents or bare metal stents in subjects receiving dual antiplatelet therapy: results from the randomized Dual Antiplatelet Therapy (DAPT) study*, Chicago, 2014, American Heart Association.
320. Mintz GS, Popma JJ, Hong MK, et al: Intravascular ultrasound to discern device-specific effects and mechanisms of restenosis. *Am J Cardiol* 78(3A):18–22, 1996.
321. Chen MS, John JM, Chew DP, et al: Bare metal stent restenosis is not a benign clinical entity. *Am Heart J* 151(6):1260–1264, 2006.
322. Nayak AK, Kawamura A, Nesto RW, et al: Myocardial infarction as a presentation of clinical in-stent restenosis. *Circ J* 70(8):1026–1029, 2006.
323. Cutlip DE, Chauhan MS, Baim DS, et al: Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. *J Am Coll Cardiol* 40(12):2082–2089, 2002.
324. Kastrati A, Schömig A, Elezi S, et al: Predictive factors of restenosis after coronary stent placement. *J Am Coll Cardiol* 30(6):1428–1436, 1997.
325. Mercado N, Boersma E, Wijns W, et al: Clinical and quantitative coronary angiographic predictors of coronary restenosis: a comparative analysis from the balloon-to-stent era. *J Am Coll Cardiol* 38(3):645–652, 2001.
326. West NE, Ruygrok PN, Disco CM, et al: Clinical and angiographic predictors of restenosis after stent deployment in diabetic patients. *Circulation* 109(7):867–873, 2004.
327. Lemos PA, Hoye A, Goedhart D, et al: Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. *Circulation* 109(11):1366–1370, 2004.
328. Beohar N, Davidson CJ, Kip KE, et al: Outcomes and complications associated with off-label and untested use of drug-eluting stents. *JAMA* 297(18):1992–2000, 2007.
329. Win HK, Caldera AE, Maresh K, et al: Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA* 297(18):2001–2009, 2007.
330. Ko DT, Chiu M, Guo H, et al: Safety and effectiveness of drug-eluting and bare-metal stents for patients with off- and on-label indications. *J Am Coll Cardiol* 53(19):1773–1782, 2009.
331. Marroquin OC, Selzer F, Mulukutla SR, et al: A comparison of bare-metal and drug-eluting stents for off-label indications. *N Engl J Med* 358(4):342–352, 2008.
332. Kimura T, Yokoi H, Nakagawa Y, et al: Three-year follow-up after implantation of metallic coronary-artery stents. *N Engl J Med* 334(9):561–566, 1996.
333. Mintz GS, Weissman NJ: Intravascular ultrasound in the drug-eluting stent era. *J Am Coll Cardiol* 48(3):421–429, 2006.
334. Yamaji K, Kimura T, Morimoto T, et al: Very long-term (15 to 20 years) clinical and angiographic outcome after coronary bare metal stent implantation. *Circ Cardiovasc Interv* 3(5):468–475, 2010.
335. Hasegawa K, Ito M, Oda M, et al: Intravascular ultrasonic imaging of vulnerable plaque in a bare metal stent 10 years after implantation. *Circulation* 122(13):1341, 2010.
336. Claessen BE, Beijk MA, Legrand V, et al: Two-year clinical, angiographic, and intravascular ultrasound follow-up of the XIENCE V everolimus-eluting stent in the treatment of patients with de novo native coronary artery lesions: the SPIRIT II trial. *Circ Cardiovasc Interv* 2(4):339–347, 2009.
337. Raber L: SIRTAX-LATE: Five-Year Clinical and Angiographic Follow-up from a Prospective Randomized Trial of Sirolimus-Eluting and Paclitaxel-Eluting Stents. Paper presented at Transcatheter Cardiovascular Therapeutics, Washington, D.C., September 24, 2010.
338. Tsuchida K, Piek JJ, Neumann FJ, et al: One-year results of a durable polymer everolimus-eluting stent in de novo coronary narrowings (the SPIRIT FIRST trial). *EuroIntervention* 1(3):266–272, 2005.
339. Tsuchida K, Serruys PW, Bruining N, et al: Two-year serial coronary angiographic and intravascular ultrasound analysis of in-stent angiographic late lumen loss and ultrasonic neointimal volume from the TAXUS II trial. *Am J Cardiol* 99(5):607–615, 2007.
340. Raber L: SIRTAX-LATE: Five-Year Clinical and Angiographic Follow-up from a Prospective Randomized Trial of Sirolimus-Eluting and Paclitaxel-Eluting Stents. Paper presented at Transcatheter Cardiovascular Therapeutics, San Francisco, September 23, 2009.
341. Pinto DS, Stone GW, Ellis SG, et al: Impact of routine angiographic follow-up on the clinical benefits of paclitaxel-eluting stents: results from the TAXUS-IV trial. *J Am Coll Cardiol* 48(1):32–36, 2006.
342. Byrne RA, Kastrati A, Tiroch K, et al: 2-year clinical and angiographic outcomes from a randomized trial of polymer-free dual drug-eluting stents versus polymer-based Cypher and Endeavor [corrected] drug-eluting stents. *J Am Coll Cardiol* 55(23):2536–2543, 2010.
343. Ellis SG, Stone GW, Cox DA, et al: Long-term safety and efficacy with paclitaxel-eluting stents: 5-year final results of the TAXUS IV clinical trial (TAXUS IV-SR: Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent). *JACC Cardiovasc Interv* 2(12):1248–1259, 2009.
344. SPIRIT II and III Investigators: Clinical follow-up 3 years after everolimus- and paclitaxel-eluting stents: a pooled analysis from the SPIRIT II (A Clinical Evaluation of the XIENCE V Everolimus eluting Coronary Stent System in the Treatment of Patients with De Novo Native coronary Atery Lesions) and SPIRIT III (A Clinical Evaluation of the Investigational Device XIENCE V Everolimus Eluting Coronary Stent System [EECSS] in the Treament of Subjects With De Novo Native Coronary Atery Lesions) randomized trials. *JACC Cardiovasc Interv* 3(12):1220–1228, 2010.
345. Stone GW: SPIRIT IV: Two-Year Results from a Prospective Randomized Trial of Everolimus-Eluting Stents Compared to Paclitaxel-Eluting Stents in Patients with Coronary Artery Disease. Paper presented at Transcatheter Cardiovascular Therapeutics, Washington, D.C., September 24, 2010.
346. Gada H, Kirtane AJ, Newman W, et al: 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). *JACC Cardiovasc Interv* 6(12):1263–1266, 2013.
347. Doi H, Maehara A, Mintz GS, et al: Impact of post-intervention minimal stent area on 9-month follow-up patency of paclitaxel-eluting stents: an integrated intravascular ultrasound analysis from the TAXUS IV, V, and VI and TAXUS ATLAS Workhorse, Long Lesion, and Direct Stent Trials. *JACC Cardiovasc Interv* 2(12):1269–1275, 2009.
348. Morino Y, Honda Y, Okura H, et al: An optimal diagnostic threshold for minimal stent area to predict target lesion revascularization following stent implantation in native coronary lesions. *Am J Cardiol* 88(3):301–303, 2001.
349. Sonoda S, Morino Y, Ako J, et al: Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the SIRIUS trial. *J Am Coll Cardiol* 43(11):1959–1963, 2004.
350. Liu J, Maehara A, Mintz GS, et al: An integrated TAXUS IV, V, and VI intravascular ultrasound analysis of the predictors of edge restenosis after bare metal or paclitaxel-eluting stents. *Am J Cardiol* 103(4):501–506, 2009.
351. Sakurai R, Ako J, Morino Y, et al: Predictors of edge stenosis following sirolimus-eluting stent deployment (a quantitative intravascular ultrasound analysis from the SIRIUS trial). *Am J Cardiol* 96(9):1251–1253, 2005.
352. Costa MA, Angiolillo DJ, Tannenbaum M, et al: Impact of stent deployment procedural factors on long-term effectiveness and safety of sirolimus-eluting stents (final results of the multicenter prospective STLLR trial). *Am J Cardiol* 101(12):1704–1711, 2008.
353. Kandzari DE, Rao SV, Moses JW, et al: Clinical and angiographic outcomes with sirolimus-eluting stents in total coronary occlusions: the ACROSS/TOSCA-4 (Approaches to Chronic Occlusions With Sirolimus-Eluting Stents/Total Occlusion Study of Coronary Arteries-4) trial. *JACC Cardiovasc Interv* 2(2):97–106, 2009.
354. Aoki J, Nakazawa G, Tanabe K, et al: Incidence and clinical impact of coronary stent fracture after sirolimus-eluting stent implantation. *Catheter Cardiovasc Interv* 69(3):380–386, 2007.
355. Popma JJ, Tiroch K, Almonacid A, et al: A qualitative and quantitative angiographic analysis of stent fracture late following sirolimus-eluting stent implantation. *Am J Cardiol* 103(7):923–929, 2009.
356. Koster R, Vieluf D, Kiehn M, et al: Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. *Lancet* 356(9245):1895–1897, 2000.
357. Nakazawa G, Tanabe K, Aoki J, et al: Sirolimus-eluting stents suppress neointimal formation irrespective of metallic allergy. *Circ J* 72(6):893–896, 2008.
358. Norgaz T, Hobikoglu G, Serdar ZA, et al: Is there a link between nickel allergy and coronary stent restenosis? *Tohoku J Exp Med* 206(3):243–246, 2005.
359. Hanioka N, Matsumoto K, Saito Y, Narimatsu S: Functional characterization of CYP2C8.13 and CYP2C8.14: catalytic activities toward paclitaxel. *Basic Clin Pharmacol Toxicol* 107(1):565–569, 2010.

360. Huang S, Houghton PJ: Mechanisms of resistance to rapamycins. *Drug Resist Updat* 4(6):378–391, 2001.
361. Monraats PS, de Vries F, de Jong LW, et al: Inflammation and apoptosis genes and the risk of restenosis after percutaneous coronary intervention. *Pharmacogenet Genomics* 16(10):747–754, 2006.
362. Vogiatzi K, Apostolakis S, Voudris V, et al: Interleukin 8 gene polymorphisms and susceptibility to restenosis after percutaneous coronary intervention. *J Thromb Thrombolysis* 29(1):134–140, 2010.
363. Nakazawa G, Ladich E, Finn AV, Virmani R: Pathophysiology of vascular healing and stent mediated arterial injury. *EuroIntervention* 4(Suppl C):C7–C10, 2008.
364. Otsuka F, Vorpahl M, Nakano M, et al: Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. *Circulation* 129(2):211–223, 2014.
365. Ferlini M, De Silvestri A, Raisaro A, et al: IVUS Guided Implantation of DES: A Meta-Analysis. *EuroPCR*, Paris, France, 2014.
366. Sanidas E, Mintz G, Maehara A, et al: Intracoronary ultrasound for optimizing stent implantation. *Curr Cardiovasc Imaging Rep* 3(4):230–236, 2010.
367. Zhang Y, Farooq V, Garcia-Garcia HM, et al: Comparison of intravascular ultrasound versus angiography-guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients. *EuroIntervention* 8(7):855–865, 2012.
368. Colombo A: AVIO: A Prospective Randomized Trial of Intravascular Ultrasound-Guided Compared to Angiography-Guided Stent Implantation in Complex Coronary Lesions. Paper presented at Transcatheter Cardiovascular Therapeutics, Washington, D.C., September 25, 2010.
369. Elezi S, Kastrati A, Hadamitzky M, et al: Clinical and angiographic follow-up after balloon angioplasty with provisional stenting for coronary in-stent restenosis. *Catheter Cardiovasc Interv* 48(2):151–156, 1999.
370. Mehran R, Dangas G, Abizaid AS, et al: Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation* 100(18):1872–1878, 1999.
371. Mintz GS: Features and parameters of drug-eluting stent deployment discoverable by intravascular ultrasound. *Am J Cardiol* 100(8B):26M–35M, 2007.
372. Ali ZA, Roleder T, Narula J, et al: Increased thin-cap neoatheroma and periprocedural myocardial infarction in drug-eluting stent restenosis: multimodality intravascular imaging of drug-eluting and bare-metal stents. *Circ Cardiovasc Interv* 6(5):507–517, 2013.
373. Kozuki A, Shinke T, Otake H, et al: Temporal course of vessel healing and neoatherosclerosis after DES implantation. *JACC Cardiovasc Imaging* 6(10):1121–1123, 2013.
374. Tian J, Ren X, Uemura S, et al: Spatial heterogeneity of neoatherosclerosis and its relationship with neovascularization and adjacent plaque characteristics: optical coherence tomography study. *Am Heart J* 167(6):884–892.e2, 2014.
375. Mintz GS, Mehran R, Waksman R, et al: Treatment of in-stent restenosis. *Semin Interv Cardiol* 3(2):117–121, 1998.
376. Leon MB, Teirstein PS, Moses JW, et al: Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. *N Engl J Med* 344(4):250–256, 2001.
377. Waksman R, Raizner AE, Yeung AC, et al: Use of localised intracoronary beta radiation in treatment of in-stent restenosis: the INHIBIT randomised controlled trial. *Lancet* 359(9306):551–557, 2002.
378. Grise MA, Massullo V, Jani S, et al: Five-year clinical follow-up after intracoronary radiation: results of a randomized clinical trial. *Circulation* 105(23):2737–2740, 2002.
379. Waksman R, Ajani AE, White RL, et al: Five-year follow-up after intracoronary gamma radiation therapy for in-stent restenosis. *Circulation* 109(3):340–344, 2004.
380. Holmes DR, Jr, Teirstein P, Satler L, et al: Sirolimus-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the SISR randomized trial. *JAMA* 295(11):1264–1273, 2006.
381. Stone GW, Ellis SG, O'Shaughnessy CD, et al: Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the TAXUS V ISR randomized trial. *JAMA* 295(11):1253–1263, 2006.
382. Ellis SG, O'Shaughnessy CD, Martin SL, et al: Two-year clinical outcomes after paclitaxel-eluting stent or brachytherapy treatment for bare metal stent restenosis: the TAXUS V ISR trial. *Eur Heart J* 29(13):1625–1634, 2008.
383. Holmes DR, Jr, Teirstein PS, Satler L, et al: 3-year follow-up of the SISR (Sirolimus-Eluting Stents Versus Vascular Brachytherapy for In-Stent Restenosis) trial. *JACC Cardiovasc Interv* 1(4):439–448, 2008.
384. Kastrati A, Mehilli J, von Beckerath N, et al: Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. *JAMA* 293(2):165–171, 2005.
385. Scheller B, Hehrlein C, Bocksch W, et al: Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med* 355(20):2113–2124, 2006.
386. Scheller B, Hehrlein C, Bocksch W, et al: Two year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *Clin Res Cardiol* 97(10):773–781, 2008.
387. Unverdorben M, Vallbracht C, Cremers B, et al: Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation* 119(23):2986–2994, 2009.
388. Alfonso F, Perez-Vizcayno MJ, Cardenas A, et al: A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent-in-stent restenosis: the RIBS V clinical trial (Restenosis Intra-stent of Bare Metal Stents: paclitaxel-eluting balloon vs. everolimus-eluting stent). *J Am Coll Cardiol* 63(14):1378–1386, 2014.
389. Latib A, Mussardo M, Ielasi A, et al: Long-term outcomes after the percutaneous treatment of drug-eluting stent restenosis. *JACC Cardiovasc Interv* 4(2):155–164, 2011.
390. Maluenda G, Ben-Dor I, Gaglia MA, Jr, et al: Clinical outcomes and treatment after drug-eluting stent failure: the absence of traditional risk factors for in-stent restenosis. *Circ Cardiovasc Interv* 5(1):12–19, 2012.
391. Chevalier B: CRISTAL: A Prospective Randomized Trial of Sirolimus-Eluting Stents Compared to Balloon Angioplasty for Restenosis of Drug-Eluting Coronary Stents. Paper presented at Transcatheter Cardiovascular Therapeutics, Washington, D.C., September 25, 2010.
392. Alfonso F, Perez-Vizcayno MJ, Dutary J, et al: Implantation of a drug-eluting stent with a different drug (switch strategy) in patients with drug-eluting stent restenosis. Results from a prospective multicenter study (RIBS III [Restenosis Intra-Stent: Balloon Angioplasty Versus Drug-Eluting Stent]). *JACC Cardiovasc Interv* 5(7):728–737, 2012.
393. Mehilli J, Byrne RA, Tiroch K, et al: Randomized trial of paclitaxel- versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents: the ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) study. *J Am Coll Cardiol* 55(24):2710–2716, 2010.
394. Habara S, Mitsudo K, Kadota K, et al: Effectiveness of paclitaxel-eluting balloon catheter in patients with sirolimus-eluting stent restenosis. *JACC Cardiovasc Interv* 4(2):149–154, 2011.
395. Rittger H, Brachmann J, Sinha AM, et al: A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study. *J Am Coll Cardiol* 59(15):1377–1382, 2012.
396. Byrne RA, Neumann FJ, Mehilli J, et al: Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. *Lancet* 381(9865):461–467, 2013.
397. Alfonso F: A Prospective, Randomized Trial of Paclitaxel-Eluting Balloons Versus Everolimus-Eluting Stents in Patients with Coronary In-Stent Restenosis of Drug-Eluting Stents: The RIBS IV Clinical Trial. Paper presented at Transcatheter Cardiovascular Therapeutics, Washington D.C., 2014.
398. Chong E, Poh KK, Liang S, et al: Two-year clinical registry follow-up of endothelial progenitor cell capture stent versus sirolimus-eluting bioabsorbable polymer-coated stent versus bare metal stents in patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction. *J Interv Cardiol* 23(2):101–108, 2010.
399. Ormiston JA, Serruys PW, Regar E, et al: A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. *Lancet* 371(9616):899–907, 2008.
400. Serruys PW, Ormiston JA, Onuma Y, et al: A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. *Lancet* 373(9667):897–910, 2009.
401. Schofer J, Schluter M, Gershlick AH, et al: Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet* 362(9390):1093–1099, 2003.
402. Diaz de la Llera LS, Ballesteros S, Nevado J, et al: Sirolimus-eluting stents compared with standard stents in the treatment of patients with primary angioplasty. *Am Heart J* 154(1):164.e1–164.e6, 2007.
403. Baumgart D, Klauss V, Baer F, et al: One-year results of the SCORPIUS study: a German multicenter investigation on the effectiveness of sirolimus-eluting stents in diabetic patients. *J Am Coll Cardiol* 50(17):1627–1634, 2007.
404. Chan C, Zambahari R, Kaul U, et al: A randomized comparison of sirolimus-eluting versus bare metal stents in the treatment of diabetic patients with native coronary artery lesions: the DECODE study. *Catheter Cardiovasc Interv* 72(5):591–600, 2008.
405. Kelbaek H, Thuesen L, Helqvist S, et al: The Stenting Coronary Arteries in Non-stress/benestent Disease (SCANDSTENT) trial. *J Am Coll Cardiol* 47(2):449–455, 2006.
406. Ardissino D, Cavallini C, Bramucci E, et al: Sirolimus-eluting vs uncoated stents for prevention of restenosis in small coronary arteries: a randomized trial. *JAMA* 292(22):2727–2734, 2004.
407. Pache J, Dibra A, Mehilli J, et al: Drug-eluting stents compared with thin-strut bare stents for the reduction of restenosis: a prospective, randomized trial. *Eur Heart J* 26(13):1262–1268, 2005.
408. Ortolani P, Marzocchi A, Marrozzini C, et al: Randomized comparative trial of a thin-strut bare metal cobalt-chromium stent versus a sirolimus-eluting stent for coronary revascularization. *Catheter Cardiovasc Interv* 69(6):790–798, 2007.
409. Grube E, Silber S, Hauptmann KE, et al: TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation* 107(1):38–42, 2003.
410. Colombo A, Drzewiecki J, Banning A, et al: Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 108(7):788–794, 2003.
411. Stone GW, Ellis SG, Cannon L, et al: Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. *JAMA* 294(10):1215–1223, 2005.
412. Dawkins KD, Grube E, Guagliumi G, et al: Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice. *Circulation* 112(21):3306–3313, 2005.
413. Stone GW, Lansky AJ, Pocock SJ, et al: Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. *N Engl J Med* 360(19):1946–1959, 2009.
414. Zhang Q, Zhang RY, Zhang JS, et al: One-year clinical outcomes of Chinese sirolimus-eluting stent in the treatment of unselected patients with coronary artery disease. *Chin Med J (Engl)* 119(2):165–168, 2006.
415. Windecker S, Remondino A, Eberli FR, et al: Sirolimus-Eluting and Paclitaxel-Eluting Stents for Coronary Revascularization. *N Engl J Med* 353(7):653–662, 2005.
416. Goy JJ, Stauffer JC, Siegenthaler M, et al: A prospective randomized comparison between paclitaxel and sirolimus stents in the real world of interventional cardiology: the TAXi trial. *J Am Coll Cardiol* 45(2):308–311, 2005.
417. Kim MH, Hong SJ, Cha KS, et al: Effect of paclitaxel-eluting versus sirolimus-eluting stents on coronary restenosis in Korean diabetic patients. *J Interv Cardiol* 21(3):225–231, 2008.
418. Maeng M, Jensen LO, Galloe AM, et al: Comparison of the sirolimus-eluting versus paclitaxel-eluting coronary stent in patients with diabetes mellitus: the diabetes and drug-eluting stent (DiabeDES) randomized angiography trial. *Am J Cardiol* 103(3):345–349, 2009.
419. de Lezo JS, Medina A, Pan M: Drug-eluting stent for complex lesions: latest angiographic data from randomized rapamycin versus paclitaxel CORPAL study. *J Am Coll Cardiol (Suppl)* 45:75A, 2005.
420. Kim Y-H, Park S-W, Lee S-W, et al: Sirolimus-eluting stent versus paclitaxel-eluting stent for patients with long coronary artery disease. *Circulation* 114(20):2148–2153, 2006.
421. Han YL, Wang XZ, Jing QM, et al: [Comparison of rapamycin and paclitaxel eluting stent in patients with multi-vessel coronary disease]. *Zhonghua Xin Xue Guan Bing Za Zhi* 34(2):123–126, 2006.
422. Mehilli J, Dibra A, Kastrati A, et al: Randomized trial of paclitaxel- and sirolimus-eluting stents in small coronary vessels. *Eur Heart J* 27(3):260–266, 2006.
423. Pan M, Suarez de Lezo J, Medina A, et al: Drug-eluting stents for the treatment of bifurcation lesions: a randomized comparison between paclitaxel and sirolimus stents. *Am Heart J* 153(1):15 e11–e17, 2007.
424. Cervinka P, Costa MA, Angiolillo DJ, et al: Head-to-head comparison between sirolimus-eluting and paclitaxel-eluting stents in patients with complex coronary artery disease: an intravascular ultrasound study. *Catheter Cardiovasc Interv* 67(6):846–851, 2006.
425. Lee JH, Kim HS, Lee SW, et al: Prospective randomized comparison of sirolimus- versus paclitaxel-eluting stents for the treatment of acute ST-elevation myocardial infarction: pROSIT trial. *Catheter Cardiovasc Interv* 72(1):25–32, 2008.
426. Stettler C, Wandel S, Allemann S, et al: Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet* 370(9591):937–948, 2007.
427. Onuma Y, Miquel-Hebert K, Serruys PW: Five-year long-term clinical follow-up of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with de novo coronary artery disease: the SPIRIT II trial. *EuroIntervention* 8(9):1047–1051, 2013.
428. Byrne RA, Kastrati A, Massberg S, et al: Biodegradable polymer versus permanent polymer drug-eluting stents and everolimus-versus sirolimus-eluting stents in patients with coronary artery disease: 3-year outcomes from a randomized clinical trial. *J Am Coll Cardiol* 58(13):1325–1331, 2011.
429. Kimura T: Three-year Follow-up of a Randomized Comparison of Nobori I, Biolimus A9 Eluting Stent With Cypher, Sirolimus Eluting Stent for Coronary Revascularization in Japanese Population. Paper presented at Transcatheter Cardiovascular Therapeutics, Miami, 2012.
430. Valgimigli M, Tebaldi M, Borghesi M, et al: Two-year outcomes after first- or second-generation drug-eluting or bare-metal stent implantation in all-comer patients undergoing percutaneous coronary intervention: a pre-specified analysis from the PRODIGY study (PROlonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia studY). *JACC Cardiovasc Interv* 7(1):20–28, 2014.
431. Wiemer M, Serruys PW, Miquel-Hebert K, et al: Five-year long-term clinical follow-up of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with de novo coronary artery lesions: the SPIRIT FIRST trial. *Catheter Cardiovasc Interv* 75(7):997–1003, 2010.

432. Park GM, Lee SW, Park SW, et al: Comparison of zotarolimus-eluting stent versus sirolimus-eluting stent for de novo coronary artery disease in patients with diabetes mellitus from the ESSENCE-DIABETES II trial. *Am J Cardiol* 112(10):1565–1570, 2013.
433. Park HJ, Kim HY, Lee JM, et al: Randomized comparison of the efficacy and safety of zotarolimus-eluting stents vs. sirolimus-eluting stents for percutaneous coronary intervention in chronic total occlusion–CAtholic Total Occlusion Study (CATOS) trial. *Circ J* 76(4):868–875, 2012.
434. Jensen LO, Maeng M, Thayssen P, et al: Late lumen loss and intima hyperplasia after sirolimus-eluting and zotarolimus-eluting stent implantation in diabetic patients: the diabetes and drug-eluting stent (DiabeDES III) angiography and intravascular ultrasound trial. *EuroIntervention* 7(3):323–331, 2011.
435. Kandzari DE, Mauri L, Popma JJ, et al: Late-term clinical outcomes with zotarolimus- and sirolimus-eluting stents. 5-year follow-up of the ENDEAVOR III (A Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions). *JACC Cardiovasc Interv* 4(5):543–550, 2011.
436. Kirtane AJ, Leon MB, Ball MW, et al: The "final" 5-year follow-up from the ENDEAVOR IV trial comparing a zotarolimus-eluting stent with a paclitaxel-eluting stent. *JACC Cardiovasc Interv* 6(4):325–333, 2013.
437. Leon MB, Nikolsky E, Cutlip DE, et al: Improved late clinical safety with zotarolimus-eluting stents compared with paclitaxel-eluting stents in patients with de novo coronary lesions: 3-year follow-up from the ENDEAVOR IV (Randomized Comparison of Zotarolimus- and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease) trial. *JACC Cardiovasc Interv* 3(10):1043–1050, 2010.
438. Serruys PW, Garg S, Abizaid A, et al: A randomised comparison of novolimus-eluting and zotarolimus-eluting coronary stents: 9-month follow-up results of the EXCELLA II study. *EuroIntervention* 6(2):195–205, 2010.
439. Park DW, Kim YH, Yun SC, et al: Comparison of zotarolimus-eluting stents with sirolimus- and paclitaxel-eluting stents for coronary revascularization: the ZEST (comparison of the efficacy and safety of zotarolimus-eluting stent with sirolimus-eluting and paclitaxel-eluting stent for coronary lesions) randomized trial. *J Am Coll Cardiol* 56(15):1187–1195, 2010.
440. Park SJ: The ZEST Trial: Two-year Final Outcomes. Paper presented at Transcatheter Cardiovascular Therapeutics, Washington, DC, September 22, 2010.
441. Botelho R: The CARDIOMIND® Sparrow® DES Program (CARE II): A Bioabsorbable Polymer Sirolimus-eluting "Micro-Stent." Paper presented at Transcatheter Cardiovascular Therapeutics, Washington, D.C., 2009.
442. Reifart N, Hauptmann KE, Rabe A, et al: Short and long term comparison (24 months) of an alternative sirolimus-coated stent with bioabsorbable polymer and a bare metal stent of similar design in chronic coronary occlusions: the CORACTO trial. *EuroIntervention* 6(3):356–360, 2010.
443. Wijns W, Vrolix M, Verheye S, et al: Randomised study of a bioabsorbable polymer-coated sirolimus-eluting stent: results of the DESSOLVE II trial. *EuroIntervention* 10(12):1383–1390, 2015.
444. Rodriguez AE, Vigo CF, Delacasa A, et al: Efficacy and safety of a double-coated paclitaxel-eluting coronary stent: the EUCATAX trial. *Catheter Cardiovasc Interv* 77(3):335–342, 2011.
445. Rodriguez-Granillo AM, Mieres J, Fernandez-Pereira C, et al: Two-Year Reports of Efficacy and Safety End Points from the Randomised, Multicentre and Controlled EUCATAX trial. *EuroPCR*, Paris, France, 2012.
446. Junbo G: Sirolimus Eluting Stent with Biodegradable Polymer versus Sirolimus Eluting Stent with Durable Polymer for the Treatment of Patients with de novo Coronary Artery Lesions (EVOLUTION): A Randomized Non-inferiority Trial. *EuroPCR*, Paris, France, 2012.
447. Junbo G: Sirolimus Eluting Stent with Biodegradable Polymer versus Sirolimus Eluting Stent with Durable Polymer for the Treatment of Patients with de novo Coronary Artery Lesions (EVOLUTION): A Randomized Non-inferiority Trial: Two-year Follow-up. Paper presented at the European Society of Cardiology Congress, Amsterdam, 2013.
448. Ribeiro EE, Campos CM, Ribeiro HB, et al: First-in-man randomised comparison of a novel sirolimus-eluting stent with abluminal biodegradable polymer and thin-strut cobalt-chromium alloy: INSPIRON-I trial. *EuroIntervention* 9(12):1380–1384, 2014.
449. Lemos P: Inspiron Sirolimus-Eluting Stent: Clinical Research Program Update. Paper presented at Transcatheter Cardiovascular Therapeutics, Miami, 2012.
450. Chevalier B: Nobori DES—Clinical Update. *EuroPCR*, Paris, France, 2011.
451. Chevalier B, Serruys PW, Silber S, et al: Nobori 1—Long-Term Results: 3 Years Phase 1 and 2 and 4 Years Phase 1. *EuroPCR*, Paris, France, 2010.
452. Kefei D, Xu B, Yang Y, Gao R: NOYA I: A Single Blind Multicenter Randomized Trial of NOYA Bioabsorbable Polymer Versus Firebird 2 Durable Polymer Sirolimus-Eluting Stent—Nine-Month Angiographic and 24-Month Clinical Results. Paper presented at Transcatheter Cardiovascular Therapeutics, Miami, 2012.
453. Xu B, Dou K, Yang Y, et al: Nine-month angiographic and 2-year clinical follow-up of the NOYA biodegradable polymer sirolimus-eluting stent in the treatment of patients with de novo native coronary artery lesions: the NOYA I trial. *EuroIntervention* 8(7):796–802, 2012.
454. Guagliumi G, Sirbu V, Musumeci G, et al: Strut coverage and vessel wall response to a new-generation paclitaxel-eluting stent with an ultrathin biodegradable abluminal polymer: Optical Coherence Tomography Drug-Eluting Stent Investigation (OCTDESI). *Circ Cardiovasc Interv* 3(4):367–375, 2010.
455. Lemos PA, Moulin B, Perin MA, et al: Randomized evaluation of two drug-eluting stents with identical metallic platform and biodegradable polymer but different agents (paclitaxel or sirolimus) compared against bare stents: 1-year results of the PAINT trial. *Catheter Cardiovasc Interv* 74(5):665–673, 2009.
456. Xu B: Firehawk Abluminal Groove-Filled Biodegradable Polymer Sirolimus-Eluting Stent: Update on the FIH, TARGET I, and TARGET II Trials. Paper presented at the Transcatheter Cardiovascular Therapeutics, San Francisco, 2013.
457. Carrié D, Berland J, Verheye S, et al: A multicenter randomized trial comparing amphilimus- with paclitaxel-eluting stents in de novo native coronary artery lesions. *J Am Coll Cardiol* 59(15):1371–1376, 2012.
458. Dang Q, Li YJ, Gao L, et al: Six-month angiographic and one-year clinical outcomes of polymer-free paclitaxel-eluting stent in patients with ST-segment elevation myocardial infarction: a comparison with permanent polymer sirolimus-eluting stent. *Chin Med J (Engl)* 125(19):3393–3397, 2012.
459. King L, Byrne RA, Mehilli J, et al: Five-year clinical outcomes of a polymer-free sirolimus-eluting stent versus a permanent polymer paclitaxel-eluting stent: final results of the intracoronary stenting and angiographic restenosis—test equivalence between two drug-eluting stents (ISAR-TEST) trial. *Catheter Cardiovasc Interv* 81(1):E23–E28, 2013.
460. Mehilli J, Kastrati A, Wessely R, et al: Randomized trial of a nonpolymer-based rapamycin-eluting stent versus a polymer-based paclitaxel-eluting stent for the reduction of late lumen loss. *Circulation* 113(2):273–279, 2006.
461. Massberg S, Byrne RA, Kastrati A, et al: Polymer-free sirolimus- and probucol-eluting versus new generation zotarolimus-eluting stents in coronary artery disease: the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting versus Zotarolimus-eluting Stents (ISAR-TEST 5) trial. *Circulation* 124(5):624–632, 2011.
462. Desch S, Schloma D, Mobius-Winkler S, et al: Randomized comparison of a polymer-free sirolimus-eluting stent versus a polymer-based paclitaxel-eluting stent in patients with diabetes mellitus: the LIPSIA Yukon trial. *JACC Cardiovasc Interv* 4(4):452–459, 2011.
463. Stiermaier T, Heinz A, Schloma D, et al: Five-year clinical follow-up of a randomized comparison of a polymer-free sirolimus-eluting stent versus a polymer-based paclitaxel-eluting stent in patients with diabetes mellitus (LIPSIA Yukon trial). *Catheter Cardiovasc Interv* 83(3):418–424, 2014.
464. Zhang Y, Shen J, Li Z, et al: Two-year clinical outcomes of different drug-eluting stents with different polymer coating strategies in coronary artery heart disease: a multi-centre, randomised, controlled clinical trial. *Int J Cardiol* 168(3):2646–2652, 2013.
465. Stone GW, Witzenbichler B, Guagliumi G, et al: Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. *Lancet* 377(9784):2193–2204, 2011.
466. Boden H, van der Hoeven BL, Liem SS, et al: Five-year clinical follow-up from the MISSION! Intervention Study: sirolimus-eluting stent versus bare metal stent implantation in patients with ST-segment elevation myocardial infarction, a randomised controlled trial. *EuroIntervention* 7(9):1021–1029, 2012.
467. Valgimigli M, Campo G, Gambetti S, et al: Three-year follow-up of the MULTIcentre evaluation of Single high-dose Bolus TiRofiban versus Abciximab with Sirolimus-eluting STEnt or Bare-Metal Stent in Acute Myocardial Infarction StudY (MULTISTRATEGY). *Int J Cardiol* 165(1):134–141, 2013.
468. Di Lorenzo E, Sauro R, Varricchio A, et al: Benefits of drug-eluting stents as compared to bare metal stent in ST-segment elevation myocardial infarction: four year results of the PaclitAxel or Sirolimus-Eluting stent vs bare metal stent in primary angiOplasty (PASEO) randomized trial. *Am Heart J* 158(4):e43–e50, 2009.
469. Dirksen MT, Vink MA, Suttorp MJ, et al: Two year follow-up after primary PCI with a paclitaxel-eluting stent versus a bare-metal stent for acute ST-elevation myocardial infarction (the PASSION trial): a follow-up study. *EuroIntervention* 4(1):64–70, 2008.
470. Vink MA, Dirksen MT, Suttorp MJ, et al: 5-year follow-up after primary percutaneous coronary intervention with a paclitaxel-eluting stent versus a bare-metal stent in acute ST-segment elevation myocardial infarction: a follow-up study of the PASSION (Paclitaxel-Eluting Versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation) trial. *JACC Cardiovasc Interv* 4(1):24–29, 2011.
471. Kim HS, Lee JH, Lee SW, et al: Long-term safety and efficacy of sirolimus- vs. paclitaxel-eluting stent implantation for acute ST-elevation myocardial infarction: 3-year follow-up of the PROSIT trial. *Int J Cardiol* 147(2):253–257, 2011.
472. Musto C, Fiorilli R, De Felice F, et al: Long-term outcome of sirolimus-eluting vs bare-metal stent in the setting of acute myocardial infarction: 5-year results of the SESAMI trial. *Int J Cardiol* 166(2):399–403, 2013.
473. Violini R, Musto C, De Felice F, et al: Maintenance of long-term clinical benefit with sirolimus-eluting stents in patients with ST-segment elevation myocardial infarction 3-year results of the SESAMI (sirolimus-eluting stent versus bare-metal stent in acute myocardial infarction) trial. *J Am Coll Cardiol* 55(8):810–814, 2010.
474. Tebaldi M, Arcozzi C, Campo G, et al: The 5-year clinical outcomes after a randomized comparison of sirolimus-eluting versus bare-metal stent implantation in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 54(20):1900–1901, 2009.
475. Spaulding C, Teiger E, Commeau P, et al: Four-year follow-up of TYPHOON (trial to assess the use of the CYPHer sirolimus-eluting coronary stent in acute myocardial infarction treated with BallOON angioplasty). *JACC Cardiovasc Interv* 4(1):14–23, 2011.

17 Drug-Coated Balloons

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KEY POINTS

- Drug-coated balloon catheters are the most advanced proven alternative to drug-eluting stents for local intravascular drug delivery.
- Preclinical data indicate effective inhibition of restenosis; however, there is no uniform class effect on drug-coated balloons.
- Randomized clinical trials have shown the efficacy and safety of these devices in the treatment of coronary in-stent restenosis and treatment of de novo and nonstented restenotic lesions in the superficial femoral artery (SFA).
- The role of drug-coated balloons in other indications such as coronary de novo disease, SFA in-stent restenosis, and below the knee has to be further determined.

Coronary angioplasty was introduced into clinical use by Andreas Grüntzig in 1977.[1] In the field of coronary intervention, the most important advance has been the introduction of stents. Stenting overcomes the weaknesses of balloon angioplasty alone, which include acute recoil and dissection, as well as longer-term negative vessel remodeling, but not restenosis because of continued or increased neointimal proliferation with stents. Local intravascular drug delivery by drug-eluting stents (DESs) that elute paclitaxel, sirolimus, and their associated analogues have successfully addressed this cellular basis of restenosis in the coronary territory. However, stents cannot be implanted or may be suboptimal at coronary sites where neointimal proliferation may limit the long-term benefit of angioplasty, such as in small vessels and bifurcations. Moreover, DESs that use sirolimus and its analogues have not been found to be effective in the treatment of atherosclerotic disease of the femoropopliteal territory. In the coronary arteries, sometimes delayed or incomplete reendothelialization with the need for long-term dual-antiplatelet therapy to reduce the risk of late stent thrombosis can limit the use of this technology in certain patients at risk for hemorrhagic complications, or it can limit the need for planned surgery. Sustained drug release seems to be essential for stent-based local drug delivery owing to the inhomogeneous drug distribution from DESs to the arterial wall,[2] the time course of the inflammation related to the initial trauma of the procedure, and the provocation of neointimal hyperplasia due to the implanted prosthesis and any associated polymeric coating. About 75% to 85% of the stented vessel wall area is not covered by the stent struts, resulting in low tissue levels of the antiproliferative agent in these areas. Cell culture experiments indicate that low drug concentrations require much longer exposure times to achieve sufficient inhibition of cell proliferation than do higher concentrations.[3] Therefore high drug concentrations on the stent struts, including a controlled and sustained release, are mandatory for stent-based local drug delivery,[4] with the consequence of delayed and incomplete reendothelialization of the stent struts. Autopsy studies show that even beyond 40 months, some DESs can demonstrate incomplete endothelial coverage.[5] Furthermore, the polymeric matrices on the stent that are meant to control the release kinetics of the antiproliferative drug can induce inflammation and thrombosis.[6] On the other hand, incomplete suppression of neointimal hyperplasia at the stent margins or between the struts may limit the efficacy of DESs.[2] Alternative approaches to overcome the limitations of DESs have included modifying the sustained drug release from stent struts to allow for earlier reendothelialization, using bioerodable polymers or nonpolymeric release mechanisms (such as surface-modified stent struts), and using thinner struts that require less coverage.

Antiproliferative taxanes, such as paclitaxel, seem to be suitable for the prevention of local intravascular restenosis because of their high lipophilicity and tight binding to various cell constituents compared with sirolimus and its analogues; this results in effective local retention at the site of delivery.[3] The addition of a contrast agent surprisingly resulted in a solubility of taxanes far beyond the concentrations applied in previous investigations.[7] In the porcine coronary model, the intracoronary bolus administration of a taxane–contrast medium formulation led to a significant reduction of neointimal formation after experimental coronary stent implantation despite the short application time.[8,9] Paclitaxel in a contrast agent was better tolerated and led to higher local tissue concentrations than diluted Taxol, indicating the impact of additional compounds for local drug transfer.[10] The surprising discovery was that sustained drug release is not a precondition for long-lasting restenosis inhibition. In 2001, the basic premise of a more lesion- than vessel-specific method of intramural drug delivery became embodied in the concept of a drug-coated balloon.[11] By coating paclitaxel onto the surface of a conventional angioplasty balloon used to dilate the stenotic artery, an exclusively local effect could theoretically be achieved, with the drug transferred to the dilated segment as the balloon was inflated. In this way, an effective local drug concentration is achieved with very low systemic exposure. However, several properties of the balloon coating are crucial for ensuring effective drug delivery to the target site: (1) its form on the balloon surface; (2) the homogeneity of distribution along the surface of the balloon; (3) its stability during production, handling, and storage; (4) the degree of premature loss while transiting to the target vessel segment; (5) the ability to release during balloon expansion; (6) the transfer efficiency to the vessel wall; and (7) the amount of particulate material released to the distal circulation.

PRECLINICAL DATA

Using various coating procedures, Speck and colleagues coated conventional coronary balloon catheters with different doses of paclitaxel and studied their pharmacokinetics in a porcine coronary model.[10] The paclitaxel dose was variable on the coated balloons, between 1.3 to 3 $\mu g/mm^2$, corresponding to a total dose of approximately 220 to 650 µg paclitaxel, depending on the balloon size. About 10% of the initial amount of paclitaxel on the balloon was lost while the catheter was being advanced to the lesion through the hemostatic valve and the guiding catheter, and about 80% of the dose was released during inflation. Most of the dose released at the target site is distributed as particulate distally in the bloodstream, with less than 20% being directly taken up into the vessel wall. In this way, paclitaxel-coated balloons deliver drug to the target site in a very short time, and the dosing is higher than that released by stents over the course of several weeks elution. At 5-week follow-up, the implantation of bare-metal stents (BMSs) premounted on paclitaxel-coated balloons was found to have caused a marked dose-dependent and statistically significant reduction in late lumen loss and an equally impressive statistically significant increase in minimal lumen diameter compared with

controls. Quantitative coronary angiography revealed no edge effects or signs of malapposition or aneurysm. Histomorphometry showed a statistically significant increase in lumen diameter and lumen area and a corresponding decrease in maximal neointimal thickness and neointimal area in the vessels treated with paclitaxel-coated balloons (a reduction of neointimal area by 63% in the paclitaxel-coated balloon group vs. the uncoated balloon group).[11] Furthermore, the drug is more evenly distributed on the vessel surface compared with that delivered by a DES.[12] However, studies suggest that the amount of paclitaxel in the arterial tissue varies widely depending on the dose of drug on the balloon and particularly on the coating formulation. An adequate inhibition of neointimal proliferation was observed when balloons were coated with paclitaxel mixed with the contrast agent iopromide dissolved in acetone; the effect was markedly lower when ethyl acetate was used as a solvent without iopromide. The difference in efficacy of these two coating formulations may be primarily explained by the presence of the hydrophilic iodinated contrast medium in the case of the acetone version, thus suggesting that a proper solubilizing agent is important.[13]

Paclitaxel admixed with a small amount of the hydrophilic contrast medium iopromide had also been registered under the name Paccocath (Charite University Hospital, Berlin, Germany). These balloons were standard angioplasty balloons coated with a more uniform paclitaxel dose of 3 μg/mm^2 of balloon surface. The situation in the peripheral arteries is not directly comparable with that in the coronary arteries, and treatment is much more complex in several respects. Specifically, the incidence of restenosis in the SFA is considerably higher and can reach up to 50% within the first 6 months after intervention in longer lesions.[13a] Given the clinical need, it was very encouraging when Albrecht and colleagues[14] developed early preclinical data that demonstrated local intraarterial administration of paclitaxel using drug-coated balloons or an admixture of paclitaxel to contrast medium could inhibit in-stent stenosis of peripheral arteries in the porcine overstretch model: in-stent stenosis in the control group was 38% (± 20%, uncoated balloons). In the treatment groups, it was reduced: treatment group I used balloons coated with 330 μg paclitaxel, and in-stent stenosis was 18% (± 22%); treatment group II used balloons coated with 480 μg paclitaxel, and the rate was 12% (± 18%); and treatment group III used 6.4 mg paclitaxel dissolved in 50 mL iopromide 370 + 5 mL ethanol), and the rate was 18% (± 20%; $P < .05$). Cremers and coworkers subsequently evaluated the effects of various inflation times (10, 60, and 2 × 60 seconds) on the efficacy of restenosis inhibition and the safety of different doses (5 μg; 2 × 5 μg paclitaxel/mm^2 balloon surface) in pigs. Treatment with a drug-coated balloon (5 μg paclitaxel/mm^2 balloon surface with iopromide) for 10 seconds reduced the neointimal area to the same extent as contact with the vessel wall for two times 60 seconds (by 57% and 56%, respectively, compared with control). Furthermore, neointimal proliferation and all other parameters that characterize in-stent restenosis were not further decreased by inflating two drug-coated balloons (each containing 5 μg paclitaxel/mm^2 balloon surface) in the same vessel segment for 60 seconds each. These results suggest that balloons coated with the paclitaxel-iopromide formulation release most of the drug rapidly during the first seconds of inflation. Thus the initial contact of the coated balloon membrane with the vessel wall appears to produce the desired effect of inhibiting neointimal proliferation. The results of this study indicate that it may be sufficient to inflate the balloon for a few seconds only to achieve adequate protection from restenosis. The results also show that doses of up to 10 μg paclitaxel/mm^2 balloon surface applied by the inflation of two drug-coated balloons does not appear to be linked with clinical toxicity, such as increasing the risk of thrombosis or aneurysm.[15] In addition, persistence of detectable drug in the vessel has been demonstrated to at least 30 days.[16]

Since this initial research was published, several manufacturers have started commercializing or developing drug-coated balloons. Currently, paclitaxel is the drug of choice, the typical dosage being 3 μg/mm^2 of balloon surface. The critical factor enabling successful drug transfer is the formulation used to coat the balloon. Current products range from those with no additive and very tight binding of the drug to the balloon membrane to those applied in conjunction with contrast agents or other beneficial additives. A number of these developers have undertaken extensive research into this issue and with the assumption that the formulation will be critical to successful product performance and adoption (Table 17-1). The matrix coating of the SeQuent Please

TABLE 17-1 Paclitaxel-Coated Balloons Currently on the Market or in Development

Company/Origin	Product	Drug Formulation	Indication	Development/Launch Status
University (Charité, Germany)	Paccocath (prototype)	Paclitaxel with iopromide (Ultravist)	CAD/PAD	Not pursued
B. Braun Melsungen AG (Germany)	SeQuent Please	Modified Paccocath	CAD	CE (since 2009)
Medrad Interventional/ Possis (U.S.)	Cotavance	Modified Paccocath	PAD	CE (since 2011), withdrawn
Eurocor GmbH (Germany)	Dior I Dior II	Rough balloon surface Mixture of paclitaxel and shellac	CAD	CE (since 2007)
Lutonix, Inc. (U.S.)	Moxy	Paclitaxel, matrix not disclosed	CAD/PAD	CE (since 2011) FDA (since 2014)
Medtronic Invatec, S.p.A. (Italy)	In.Pact (four different catheters)	Paclitaxel, hydrophilic FreePac	CAD/PAD	CE (since 2009)
Aachen Resonance GmbH (Germany)	Elutax I Elutax II	Structured balloon surface Coating = two layers of paclitaxel (elastic and drug depot)	CAD CAD/PAD	CE (since 2008)
Cook Group, Inc. (U.S.)	Advance 18 PTX	Paclitaxel, matrix not disclosed	PAD	Late-stage development
Biotronik AG (Germany)	Pantera Lux	Paclitaxel and BTHC matrix	CAD PAD	CE (since 2010) CE (since 2014)
Angioscore (U.S.)	Coated AngioSculpt	Paclitaxel, matrix not disclosed	CAD/PAD	Late-stage development
Cordis (U.S.)	Not disclosed	Sirolimus, matrix not disclosed	?	?
Minvasys (France)	Not disclosed	Paclitaxel and BTHC matrix	?	CE (since ?)
Boston Scientific (U.S.)	Ranger	Paclitaxel and BTHC matrix	?	CE (since 2014)

BTHC, Butyryl-trihexyl citrate; *CE,* CE Mark approval in Europe; *CAD,* coronary artery disease; *FDA,* U.S. Food and Drug Administration; *PAD,* peripheral artery disease.

balloon catheter (B. Braun Melsungen AG, Germany) for percutaneous transluminal coronary angioplasty (PTCA) consists of a mixture of paclitaxel and iopromide, identical in composition to Paccocath. The preclinical data compare very well with the results from the Paccocath program. Buszman and colleagues reported histologic results showing the Cotavance coating (Bayer-Schering, Berlin, Germany), an iterative coating formula based on Paccocath, to be superior to an uncoated balloon in treating coronary artery and SFA lesions in pigs. In an additional pilot study, single or overlapping Cotavance balloons were compared with single nonoverlapping balloons coated with a contrast medium (iopromide) without paclitaxel in a healthy porcine iliofemoral stent model. Balloon angioplasty was followed by self-expandable BMS implantation. After 28 days, Cotavance balloons decreased neointimal proliferation in a dose-dependent manner when assessed by quantitative angiography (late lumen loss [LLL] with Cotavance single 1.5 ± 0.7 mm vs. Cotavance overlap 0.7 ± 0.6 mm compared with contrast-coated control 1.7 ± 0.4 mm).[17,18] Unfortunately, this balloon is no longer produced, nor is it available for use.

FreePac (Medtronic Invatec, Italy) is a proprietary hydrophilic coating formulation in which urea serves as the matrix substance. Urea is a nontoxic, ubiquitous endogenous compound commonly used in pharmacy; it is meant to enhance the release of paclitaxel during the short time of contact with the vessel wall. In the porcine coronary model, similar amounts of paclitaxel were transferred to the vessel wall with the Paccocath coating (214 ± 106 µg paclitaxel) and the FreePac coating (175 ± 101 µg paclitaxel) 15 to 25 minutes after stent implantation. Twenty-eight days after balloon dilation, the original Paccocath coating caused the known strong inhibition of neointimal formation in the porcine coronary model (minimal lumen diameter [MLD]: 2.7 ± 0.3 mm; LLL, 0.3 ± 0.2 mm). The FreePac coating was equally efficacious and equally well tolerated (MLD: 2.7 ± 0.2 mm; LLL, 0.4 ± 0.2 mm).[19] The aim of another preclinical study was to determine the minimum effective dose and local toxicity at extremely high doses of the FreePac formulation. The balloons were coated with 1 to 9 µg paclitaxel/mm^2 balloon surface. In the highest-dose group, three balloons each coated with 9 µg paclitaxel/mm^2 balloon surface were expanded in the same vessel segment. FreePac paclitaxel-coated balloon catheters efficaciously inhibited neointimal proliferation starting with the lowest dose tested (1 µg/mm^2) and were well tolerated up to three times the preferred dose of 3 µg/mm^2. Stent occlusions observed at the highest dose level and repeated treatment (3 × 9 µg/mm^2) indicate that the limit of tolerance was reached.[19]

As early as 2007, a paclitaxel-coated balloon catheter, Dior (Eurocor GmbH, Germany), received approval in Europe (CE Mark). A study of first-generation Dior balloon catheters reported a tissue paclitaxel concentration of the dilated segment in porcine arteries 1.5 hours after dilation of 1.82 µmol/L (± 1.60), which decreased significantly to 0.73 (± 0.27; $P = .03$), 0.62 (± 0.34), and 0.44 µmol/L (± 0.31) at 12, 24, and 48 hours, respectively.[20] In a direct comparison with the Paccocath balloon, the roughened Dior balloon failed to produce statistically significant effects on angiographic measures of stenosis or morphometric parameters such as maximal neointimal thickness and luminal area. Use of the matrix-coated Paccocath balloon led to a highly significant ($P < .01$) reduction in all parameters, indicating improved neointimal proliferation compared with both uncoated control and Dior balloons at 28-day follow-up.[21] Only about 50% of the drug coating was released from the roughened balloons during the recommended balloon inflation time of 45 to 60 seconds. In contrast, the iopromide matrix was found to release the full amount of the drug (4.5% ± 0.7 % of the total paclitaxel dose on balloons after the procedure), which may contribute to its superiority in inhibiting restenosis. The second-generation Dior II balloon is a coronary dilation balloon for human use with a paclitaxel coating of 3.0 µg/mm^2 on the balloon surface, which is applied using a completely different coating technique: The drug is mixed with shellac composed of a network of hydroxy fatty acid esters and sesquiterpene acid esters with a molecular weight of about 1000. The 1:1 mixture of paclitaxel and shellac is coated onto regular balloon catheters. A balloon inflation time dependency study in the porcine model of coronary artery overstretch showed almost maximal tissue paclitaxel concentrations after balloon inflation times of 30 seconds and demonstrated release of 75% of the drug from the balloon surface, which resulted in an up to twentyfold higher tissue concentration compared with the first-generation Dior. Two weeks after overstretch injury, histomorphometry showed significantly smaller neointimal hyperplasia and neointimal thickness in the Dior group compared with the conventional uncoated balloon group. As a result, the area of the coronary artery lumen was larger in the Dior-treated arteries compared with those treated with the conventional balloon (1.20 ± 0.27 mm^2 vs. 0.5 ± 0.22 mm^2, $P < .001$).[22]

Elutax (Aachen Resonance, Germany) uses pure paclitaxel without a matrix coated on a structured balloon surface, and preclinical data on the Moxy paclitaxel-coated balloon catheter (Lutonix, Inc., USA) were recently published. It has a paclitaxel dose of 2 µg/mm^2 using polysorbate and sorbitol as excipients, resulting in paclitaxel tissue concentrations of 58.8 ng/mg at 1 hour and 0.3 ng/mg at 30 days. The treated arteries showed a long-term dose-dependent drug effect.[23]

Pantera Lux (Biotronik AG, Berlin, Germany) uses butyryl-trihexyl citrate (BTHC) as a carrier for paclitaxel. BTHC is used in different medical devices and cosmetics and is approved for blood contact in blood bags.[24] The same excipient is used with lower paclitaxel doses for the Danubio (Minvasys, Paris, France) and the Ranger DCB (Boston Scientific, Marlborough, MA).

A different, alternative mode of local drug delivery into the target artery segment has been developed using the Genie balloon (Acrostak Corp., Winterthur, Switzerland). Paclitaxel is delivered by a system consisting of a balloon with a distal and proximal occlusive segment and a central segment that allows transfer of paclitaxel to the vessel wall by infusion of paclitaxel solution into the vascular chamber created between the balloons.[25] Preclinical investigations in the coronary arteries of pigs demonstrated that the administration via Genie of 10 µM paclitaxel (Taxol, diluted paclitaxel in a mixture of 50% cremophor and 50% ethanol [2.9 ± 1.6 mL 10 µM paclitaxel in this study equals 24.8 ± 13.7 µg paclitaxel]) markedly reduced LLL (0.9 ± 0.1 mm) compared with controls (2.2 ± 0.2 mm, $P < .001$). The histologic examination showed a statistically significant increase in the lumen area (5.2 ± 1.0 mm^2) and a corresponding decrease in maximal neointimal thickness (0.1 ± 0.01 mm) and neointimal area (1.0 ± 0.1 mm^2) in the stented artery treated with paclitaxel versus the control group (3.0 ± 0.3 mm^2, 0.3 ± 0.04 mm, 2.4 ± 0.2 mm^2).[24] These preclinical results suggest that a solid form (crystalline or amorphous) of paclitaxel is not a requisite for effectiveness.

Preclinical data with a paclitaxel-coated scoring balloon (AngioScore, Fremont, CA) showed increased luminal areas of 6.8 (± 1.6) mm^2 compared with uncoated scoring balloons (2.3 ± 1.5 mm^2; $P = .001$).[26] This concept of drug-coated specialty balloons dedicated to plaque modification may allow for better initial lumen gain and a reduced risk of dissections, leading to less stent usage.

The lipophilic nature of the antiproliferative drug zotarolimus makes it a potential candidate for drug-coated balloon applications. A coronary study in pigs aimed to evaluate the safety and efficacy of a novel zotarolimus-coated balloon in comparison with a zotarolimus-eluting stent, and in both zotarolimus groups, a clear reduction was noted in the neointimal area compared with the control group, which did not receive any drug on the balloon or the stent. The effect of neointimal inhibition was slightly more pronounced with the zotarolimus-coated balloon (control 4.32 ± 1.45 mm^2, zotarolimus-coated balloon 2.79 ± 1.43 mm^2, and zotarolimus-eluting stent 3.32 ± 1.11 mm^2; $P = .001$). The inflammation score was significantly reduced in vessels treated with the zotarolimus-coated balloon.[27] Currently, sirolimus as an alternative for a drug-coated balloon (DCB) is under investigation.[28]

CLINICAL DATA ON DRUG-COATED BALLOONS

At the time of this publication, only one DCB device has been approved for human use in the United States, the Bard Lutonix device, with

another release imminent for the Medtronic In.Pact device. In Europe, regulatory approval currently exists for several coronary and also peripheral devices. In spite of the multiple device approvals, there is a comparative paucity of data in the literature regarding the clinical safety and utility of DCBs as a stand-alone therapy or in combination with other modalities. The use of DCBs in combination with BMSs or debulking devices has both positive and negative potential: the potential for a better, more secure initial patency comes with questions of efficacy, given the potential for edge effect and geographic miss, as well as safety.

Human Pharmacokinetics of Current Drug-Coated-Balloon Technology

Data on the current first generation of DCBs suggest that the amount of drug delivered by the coated balloon to the vessel wall is a minor fraction of the total dose loaded and that the majority of the drug is distributed into the bloodstream either before or during balloon inflation. Therefore defining the possible systemic dose of drug delivered with this technology is important, especially given the requirement to use larger, longer, and possibly multiple coated balloons in certain peripheral vascular applications. In a pharmacokinetic study,[29] 14 patients treated at two sites for femoropopliteal disease with DCB had blood sampling at multiple time intervals before and after treatment with balloons ranging up to 10 cm, with monitoring of vital signs and electrocardiography (ECG) analysis, which demonstrated no untoward effects. Mean blood levels of paclitaxel in the immediate postintervention phase were roughly an order of magnitude less than the mean chemotherapeutic levels, and blood levels at 2 hours in more than half the samples were below the lower limit of quantification. Although the study was small, with a considerable heterogeneity of both patients and balloon sizes, a reasonable safety margin of systemic paclitaxel was demonstrated. Still to be determined is what, if any, systemic effects the use of longer or multiple balloons in more extensive SFA disease will have.

Data From the Coronary Application of Drug-Coated Balloons

Although a DES is overwhelmingly the device of choice for most coronary lesions, and their efficacy and safety continue to improve to remarkable degrees, specific challenges remain to their delivery and use in specific coronary territories such as bifurcations, small vessels, saphenous vein grafts, long lesions, and diabetic disease, all of which have less robust outcomes with DES use than do simpler lesions. In addition, the current need for prolonged dual-antiplatelet therapy (DAPT) can be clinically challenging for some patients with medication intolerance or bleeding tendencies. Although improved antiplatelet medication duration appears to be shortening and is also available to address the possible consequences of nonresponders to clopidogrel, antiplatelet efficacy often is traded for increased bleeding risk. DCBs have the potential to improve outcomes regarding difficult vascular stent territories with a more limited duration of DAPT.

Whereas all of the mechanisms of DCB efficacy have yet to be determined, several randomized clinical studies suggest efficacy of the technology in both coronary and peripheral territories. However, it is important to note that not all DCBs have the same formulation, and this can have implications for clinical effectiveness.[21] In the discussion of clinical trial results below, specifics as to the formulations used are designated for the DCB tested to the extent that they are known.

Coronary In-Stent Restenosis

DCB use in humans was first described in a 2006 publication.[30] In this multicenter study, 52 patients with coronary in-stent restenosis (ISR) were randomized to receive angioplasty with either an uncoated balloon or a 3 μg/mm^2 iopromide-paclitaxel–coated balloon (Paccocath); aspirin and clopidogrel were given for 1 month, followed by aspirin alone. Baseline demographics, angiography, and short-term procedural outcomes were not different between the two groups. As determined by angiography at 6 months, the Paccocath group demonstrated a clear advantage in the primary end point of less in-segment LLL (0.74 ± 0.86 vs. 0.03 ± 0.48 mm; $P = .002$), as well as in the 6-month secondary end points of MLD and binary restenosis. An additional 56 patients with coronary ISR were randomized, and the combined cohort of 108 patients was followed for 5 years.[31] The primary end point of 6-month angiographic in-segment LLL was similar to that in the original report, with in-segment binary restenosis of only 6% for the DCB group compared with 51% for the standard balloon group; no differential effects were found by gender or diabetes mellitus. Further, a sustained clinical effect of Paccocath was noted up to 5 years, as manifest by a significant reduction in target-lesion revascularization (TLR); no subacute thrombosis or other safety issues were seen in the DCB group.[32] Another group of investigators initiated a series of studies called PEPCAD (Paclitaxel-Eluting PTCA Catheter in Coronary Disease) to test the same DCB Paccocath formulation (SeQuent Please, licensed by B. Braun) using a variety of coronary therapy comparisons. PEPCAD II was a multicenter, randomized trial of the SeQuent Please DCB versus the Taxus Liberté DES in 131 patients with coronary ISR.[33] In the two groups of patients with reference vessels averaging 3.0 mm in diameter, the primary end point of 6-month in-segment LLL was significantly less with the DCB compared with the DES (0.17 ± 0.42 vs. 0.38 ± 0.61 mm; $P = .03$). At 12 months, TLR trended in favor of the DCB (6% vs. 15%; $P = 0.15$), suggesting that the DCB was at least as effective as the DES for coronary ISR and without the need for repeat stent implantation.[33,34] Meanwhile, eight randomized trials have been published studying the SeQuent Please DCB in BMS ISR[32,33,35] and DES ISR.[36-40] Based on these trials, the 2014 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines on myocardial revascularization state, with a class I level A recommendation, that DCBs are recommended for the treatment of ISR (within a BMS or DES).[41]

A nonrandomized single-center trial investigated the treatment of coronary in-stent restenosis with the urea paclitaxel coated In.Pact Falcon DCB (Medtronic Invatec, Italy). A total of 26 restenotic BMSs in 23 patients with lesions 22.8 (± 11.1) mm in length and a reference vessel diameter of 2.64 (± 0.31) mm were treated. Up to 6 months and including the 6-month angiographic control, only one TLR was necessary; in total, the rate of major adverse cardiovascular events (MACEs) up to the 6-month follow-up was 4.3%. In-stent LLL was 0.07 (± 0.37) mm and in-segment LLL was 0.02 (± 0.50) mm. Binary restenosis was present in one patient (4.3%).[42]

Coronary De Novo Disease

Initial concepts for the use of DCB in de novo coronary disease included the combination with a BMS to create a "polymer-free" DES. However, results from the PEPCAD III trial to compare such a BMS-DCB combination with the Cypher sirolimus-eluting stent (Cordis/Johnson & Johnson, Miami Lakes, FL) revealed this concept as an inferior approach. The primary angiographic end point of 9-month in-stent LLL was significantly better for the DES compared with the BMS-DCB combination (0.16 ± 0.39 vs. 0.41 ± 0.51 mm; $P = .001$), although there was less difference for in-segment LLL. The 9-month clinical efficacy end points of TLR and target-vessel revascularization (TVR) favored the DES approach; however, the difference in total MACEs was not significant (15% vs 18%).[43,44] Other approaches that combined BMS and DCB as stand-alone devices in the same lesion also failed.[45-48] These results have been partially explained by suboptimal PCI technique and inferior DCB coatings.[21,49] Nevertheless, even with optimized PCI technique and mature coatings, no benefit was found compared with current generation DESs.[50,51] A Prospective, Randomized Trial Evaluating a Paclitaxel-Eluting Balloon in Patients Treated With Endothelial Progenitor Cell Capturing Stents for De Novo Coronary Artery Disease (PERfECT STENT)[51] randomized 120 patients with implantation of the CD34 antibody–coated Genous stent (OrbusNeich, Hong Kong). In-segment LLL was reduced from 0.61 mm to 0.16 mm by postdilation with a longer SeQuent Please DCB ($P < .001$). Furthermore, binary restenosis (23.2% vs. 5.1%), TLR

(15.5% vs. 4.8%), and MACE (17.2% vs. 4.8%) were significantly less frequent.

PEPCAD I was a nonrandomized study that investigated the safety and efficacy of the SeQuent Please DCB with provisional BMS implantation in small-vessel (mean reference vessel diameter, 2.36 mm) de novo lesions in 120 patients.[52] At the 6-month follow-up, in-segment LLL was significantly less with DCB alone compared with DCB plus a stent (0.18 and 0.73 mm, respectively); the majority of the restenosis was noted at the stent edges, ostensibly where DCB coverage was inadequate. Although this trial was not adequately powered to assess stent thrombosis, vessel thrombosis occurred less frequently in the DCB-alone group despite a shorter duration of dual antiplatelet therapy (1 vs. 3 months). In patients with additional BMS implantation, geographic mismatch between coated balloon dilation and stent implantation was frequently associated with the occurrence of restenosis.[43,53]

As a consequence of these findings, a DCB-only strategy has been proposed that includes a rigorous approach to establish the concept of leaving nothing behind. It includes a careful lesion preparation with a balloon/vessel ratio of 0.8:1.0. Depending on the result after predilation, the operator can decide whether to proceed with DCB only in case of an acceptable angiographic result or use a stent or scaffold in case of a major dissection (type C or higher), significant residual stenosis, or reduced flow. The strengths of this concept include a low need for stent implantation and a shortening of DAPT (4 weeks in DCB stand-alone procedures).[54,55]

This strategy has been investigated successfully in two large registries[56,57] and in the randomized Balloon Elution and Late Loss Optimization (BELLO) study,[58] in which 182 patients with small coronary vessel disease were treated with either an In.Pact Falcon balloon, applying the DCB-only approach, or with a Taxus stent. The primary end point, LLL at 6 months, was significantly lower in the DCB arm (0.08 ± 0.38 mm vs. 0.29 ± 0.44 mm; $P = .001$), demonstrating superiority of the DCB-only approach over DES implantation in terms of angiographic end points.

Clinical Data From the Peripheral Vascular Application of Drug-Coated Balloons

There are a variety of vascular beds for which the DCB technology could be applied, but the focus has largely been on the femoropopliteal and, more recently, the infrapopliteal territories. These vascular territories are the most relevant, with the greatest demonstrated need for reduced restenosis rates. The contiguous SFA and popliteal artery (femoropopliteal) are responsible for most lifestyle-limiting claudication. Taken together, these vessels are the longest nonaortic conduits in the body (at times >300 mm in length) and carry a significant atherosclerotic burden; they are often significantly calcified and chronically occluded throughout their length. As important as their biologic descriptors are their physical ones: the vessel is subject not only to the potential for external compression but also other complex forces during hip and knee flexion (bending, torsion, and axial elongation/shortening). Balloon angioplasty has proved to be inferior to stent implantation for moderate-length lesions (<13 cm),[59,60] but 1-year patency rates even with stents are still suboptimal at 63% and are worse for longer lesions. Until recently, DESs have not proved to be effective in reducing restenosis in the femoropopliteal territory; at least two trials with self-expanding nitinol stents coated with either sirolimus[61] or everolimus using a durable polymer failed to show efficacy.[62] However, a third trial evaluated the Zilver PTX stent, which uses paclitaxel without a polymer, and demonstrated effectiveness compared with angioplasty alone (percutaneous transluminal angioplasty [PTA]) and BMS, but in a relatively constrained (~5- to 6-cm) lesion length.[63] Many involved in this field believe that among the explanations for the failure to date of most of the attempts at DES placement in the femoropopliteal region is the tendency for stents to fracture because of the forces mentioned earlier; this appeared to be associated with restenosis in an early nonrandomized analysis,[64] the ongoing irritant of a rigid stent interacting with a vessel constantly in motion, and the lack of the correct "formula" of drug dose and duration when accounting for stent provocation of intimal hyperplasia in this unique vessel. However, the 24-month patency data for the Zilver PTX treatment cohort did show a durable effect with this device.[63]

The development of DCB technology holds the promise of improved outcomes without a permanent stent prosthesis. The first human examination of a DCB in a noncoronary territory, the Local Taxane With Short Exposure for Reduction of Restenosis in Distal Arteries (THUNDER) trial, a multicenter European study that involved the three-way randomization of 154 patients with lesions of the femoropopliteal segment to standard balloon angioplasty (control), an iopromide-paclitaxel–coated (3 μg/mm^2, Paccocath) balloon, or to paclitaxel mixed with iopromide contrast (0.171 mg/cm^3) and used for a standard balloon procedure up to a maximum dose of 17.1 mg.[65] With a moderate mean lesion length of about 7.5 cm, a marked reduction was seen in the iopromide-paclitaxel balloon group for the primary end point of 6-month angiographic LLL compared with both the control balloon and paclitaxel in contrast groups (0.4 ± 1.2 vs. 1.7 ± 1.8 vs. 2.2 ± 1.6 mm; $P < .001$ for DCB vs. control). TLR at 6 months was reduced in the DCB group compared with the control group (4% vs. 29%; $P = .001$); again, no effect was seen with the paclitaxel and contrast groups (29%; $P = .41$). Notably, vis-à-vis the prior DES concerns, the comparative benefits of DCBs were sustained at 24-month and 5-year follow-ups.[66] A second study using the same coating technology produced remarkably similar results. In the Femoral-Paclitaxel (Fem-Pac)[67] trial, 87 patients underwent 1:1 randomization between control balloon angioplasty and iopromide-paclitaxel–coated balloon angioplasty in relatively short (~6 cm) lesions in the femoropopliteal arteries. For the primary end point of LLL, the coated balloon arm showed results that were superior to those of the control balloon at 6 months (0.5 ± 1.1 vs. 1.0 ± 1.1 mm; $P = .031$), with significantly fewer TLR events (6.7% vs. 33%; $P = .002$); this difference in TLR was sustained beyond 18 months. Of note, no safety issues related to the balloon coating were manifest in either study.

In the Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis (LEVANT I)[68] study, 101 patients with femoropopliteal disease were assigned to either a balloon-only strategy or a stent-assisted strategy if it was felt that a bail-out stent would be required after initial PTA predilation. Thereafter each group was randomized to treatment with either the Lutonix DCB coated with 2 μg/mm^2 paclitaxel and a polysorbate/sorbitol carrier or standard PTA balloon. With a reasonable mean lesion length of about 8 cm, at 6 months, the DCB groups—both PTA and stent—demonstrated significantly better primary end point LLL compared with that of the PTA group (0.46 ± 1.13 mm vs. 1.09 ± 1.07 mm, $P = .016$).

In the United States, 543 patients were enrolled in the Lutonix/Bard LEVANT II pivotal trial aimed at FDA approval; in this trial, 476 subjects were randomized 2:1 to Lutonix DCB ($n = 316$) and PTA ($n = 160$). Target lesion length was 6.1 cm, including 21% total occlusions. At 1 year, freedom from the primary safety end point—perioperative death, index limb amputation or reintervention, or limb-related death—was 84% for DCB and 79% for PTA ($P = .005$ intention to treat (ITT); $P = .08$ per protocol). Primary patency (freedom from target lesion binary restenosis defined by Doppler ultrasound plus TLR) was 65.2% for DCB and 52.6% for PTA ($P = .015$ ITT; $P = .11$ per protocol). Of interest, no difference in target lesion reintervention was observed at 1 year (38.0% vs. 37.5%; $P = .5$).[68b]

In the Paclitaxel-Coated Balloons in Femoral Indication to Defeat Restenosis (PACIFIER) trial,[69] patients with symptomatic femoropopliteal atherosclerotic disease were randomized to In.Pact Pacific or uncoated balloons ($n = 91$). Average lesion length was 7.0 (± 5.3) and 6.6 (± 5.5) cm for DCB and control arms, respectively. At 6 months, LLL was –0.01 mm for DCB versus 0.65 mm for PTA ($P = .001$) with fewer binary restenoses (9% vs. 32%) and fewer major adverse events (7% vs. 35%).

In the Invatec/Medtronic In.Pact SFA trial aiming for FDA approval, 331 patients with claudication or rest pain due to superficial femoral lesions were enrolled with a mean lesion length of 8.9 cm (150 subjects

at 13 European centers and 181 subjects at 44 U.S. sites). At 1 year, the DCB group was superior to PTA in terms of primary patency (82% vs. 54%), clinically driven TLR (2.4% vs. 21%), primary sustained clinical improvement (upgrade in Rutherford classification ≥1 class in amputation- and TVR-free surviving patients; 85% vs. 69%), primary safety end point (freedom from 30-day device- and procedure-related death and from target limb major amputation and clinically driven TVR through 12 months; 96% vs. 77%), and MACE (death, clinically driven TVR, target limb major amputation, and thrombosis; 6% vs. 24%).[66]

Although differences in outcomes between these two pivotal femoropopliteal trials are apparent, differences in patient and lesion complexity, end point determination and time point of reporting, effects of evaluator blinding, and so on make direct comparison between trials problematic and should be taken with some circumspection.

Below-the-knee (BTK) intervention in patients with critical limb ischemia has been studied in small, single-center studies with and without randomization, all of which appeared to demonstrate benefit in terms of patency and/or TLR.[70,71] However a well-done large, multicenter, randomized, controlled European effort—the Invatec/Medtronic Study of IN.PACT Amphiron Drug-Eluting Balloon Versus Standard PTA for the Treatment of Below-the-Knee Critical Limb Ischemia (IN.PACT DEEP) trial[72]—failed to show a beneficial drug effect. Although there were some baseline differences in lesion length (favoring DCB), impaired inflow (favoring PTA), and prior target limb revascularization (favoring PTA), the groups appeared to be reasonably similar. The primary efficacy end points of clinically driven TLR (9.2% vs. 13.1%; P = NS) and LLL (0.61± 0.78 vs. 0.62 ± 0.78; P = NS) were no different between DCB and PTA. However, a small difference was reported in the primary safety end point (17.7% vs. 15.8%, P = .021) driven primarily by more frequent major amputations in the DCB arm (8.8% vs. 3.6%; P = .080). As a result of the outcomes in this trial, the In.Pact Deep DCB was voluntarily removed from the market in 2013. There is another trial in this population currently recruiting subjects by Lutonix/Bard in the United States. Until these results are known, the efficacy and safety of DCBs in infrapopliteal disease will remain speculative, as will the causes of the failure of In.Pact Deep.

THE FUTURE OF DRUG-COATED-BALLOON TECHNOLOGY

Although some data support the efficacy of DCBs in both the coronary and peripheral circulations, some of the coronary trial outcomes have been less than robust, and it seems to be becoming clearer that it is not only the specific coating formulation that is important in clinical efficacy but also the interaction of the DCB and newly implanted stents, which is still not well understood. Most of the current efforts in DCB development are focused on addressing the potential limitations of the technology. The safety and efficacy of these technologies in certain applications—such as overlapping balloons, visceral vessel applications, and in use with adjunctive therapies, including atherectomy and stents—will need to be assessed. Notably, the risk of particulate embolization of the coating and any unintended effects will need to be better elucidated, especially in visceral applications. In addition, as the mechanism of action of DCBs becomes better understood, the opportunities to modify various aspects of the technology will increase, including improvements in the antiproliferative agents used, which in combination with different carrier molecules might further extend the tissue residence of the agents and result in more directed deposition of drug into the vessel, with reduced wash-off and distal embolization. Despite the many devices and manufacturers involved with DCBs, a paucity of large-scale clinical datasets on the safety and effectiveness of this technology remains. Fortunately, multiple clinical studies are either underway or are being planned in the near future in Europe that involve coronary, femoropopliteal, and infrapopliteal applications.

SUMMARY

Both the preclinical and clinical data to date, albeit with some mixed results in selected coronary applications, support the early effectiveness and safety of DCBs in several vascular territories and validate the concept that the balloon delivery of a short burst of an antiproliferative agent to a targeted vessel segment is feasible. At the time of this publication, accepted indications for DCB are the treatment of coronary in-stent restenosis and the treatment of de novo and restenotic lesions in the superficial femoral artery.

REFERENCES

1. Grüntzig A: Transluminal dilatation of coronary-artery stenosis. *Lancet* 1(8058):263, 1978.
2. Hwang CW, Wu D, Edelman ER: Physiological transport forces govern drug distribution for stent-based delivery. *Circulation* 104(5):600–605, 2001.
3. Axel DI, Kunert W, Goggelmann C, et al: Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. *Circulation* 96(2):636–645, 1997.
4. Iofina E, Langenberg R, Blindt R, et al: Polymer-based paclitaxel-eluting stents are superior to nonpolymer-based paclitaxel-eluting stents in the treatment of de novo coronary lesions. *Am J Cardiol* 98(8):1022–1027, 2006.
5. Joner M, Finn AV, Farb A, et al: Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 48(1):193–202, 2006.
6. Virmani R, Guagliumi G, Farb A, et al: Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 109(6):701–705, 2004.
7. Scheller B, Speck U, Schmitt A, et al: Acute cardiac tolerance of current contrast media and the new taxane protaxel using iopromide as carrier during porcine coronary angiography and stenting. *Invest Radiol* 37(1):29–34, 2002.
8. Scheller B, Speck U, Romeike B, et al: Contrast media as carriers for local drug delivery. Successful inhibition of neointimal proliferation in the porcine coronary stent model. *Eur Heart J* 24(15):1462–1467, 2003.
9. Scheller B, Speck U, Schmitt A, et al: Addition of paclitaxel to contrast media prevents restenosis after coronary stent implantation. *J Am Coll Cardiol* 42(8):1415–1420, 2003.
10. Speck U, Scheller B, Abramjuk C, et al: Inhibition of restenosis in stented porcine coronary arteries: uptake of paclitaxel from angiographic contrast media. *Invest Radiol* 39(3):182–186, 2004.
11. Scheller B, Speck U, Abramjuk C, et al: Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. *Circulation* 110(7):810–814, 2004.
12. Speck U, Scheller B, Abramjuk C, et al: Neointima inhibition: comparison of effectiveness of non-stent-based local drug delivery and a drug-eluting stent in porcine coronary arteries. *Radiology* 240(2):411–418, 2006.
13. Scheller B, Speck U, Bohm M: Prevention of restenosis: is angioplasty the answer? *Heart* 93(5):539–541, 2007.
13a. Lammer J, Zeller T, Hausegger KA, et al: Heparin-bonded covered stents versus bare-metal stents for complex femoropopliteal artery lesions: the randomized VIASTAR trial (Viabahn endoprosthesis with PROPATEN bioactive surface [VIA] versus bare nitinol stent in the treatment of long lesions in superficial femoral artery occlusive disease). *J Am Coll Cardiol* 62(15):1320–1327, 2013.
14. Albrecht T, Speck U, Baier C, et al: Reduction of stenosis due to intimal hyperplasia after stent supported angioplasty of peripheral arteries by local administration of paclitaxel in swine. *Invest Radiol* 42(8):579–585, 2007.
15. Cremers B, Speck U, Kaufels N, et al: Drug-eluting balloon: very short-term exposure and overlapping. *Thromb Haemost* 101(1):201–206, 2009.
16. Speck U, Cremers B, Kelsch B, et al: Do pharmacokinetics explain persistent restenosis inhibition by a single dose of paclitaxel? *Circ Cardiovasc Interv* 5(3):392–400, 2012.
17. Buszman PP, Tellez A, Afari M, et al: Stent healing response following delivery of paclitaxel via durable polymeric matrix versus iopromide-based balloon coating in the familial hypercholesterolaemic swine model of coronary injury. *EuroIntervention* 9(4):510–516, 2013.
18. Buszman PP, Tellez A, Afari ME, et al: Tissue uptake, distribution, and healing response after delivery of paclitaxel via second-generation iopromide-based balloon coating: a comparison with the first-generation technology in the iliofemoral porcine model. *JACC Cardiovasc Interv* 6(8):883–890, 2013.
19. Kelsch B, Scheller B, Biedermann M, et al: Dose response to paclitaxel-coated balloon catheters in the porcine coronary overstretch and stent implantation model. *Invest Radiol* 46(4):255–263, 2011.
20. Posa A, Hemetsberger R, Petnehazy O, et al: Attainment of local drug delivery with paclitaxel-eluting balloon in porcine coronary arteries. *Coron Artery Dis* 19(4):243–247, 2008.
21. Cremers B, Biedermann M, Mahnkopf D, et al: Comparison of two different paclitaxel-coated balloon catheters in the porcine coronary restenosis model. *Clin Res Cardiol* 98(5):325–330, 2009.
22. Posa A, Nyolczas N, Hemetsberger R, et al: Optimization of drug-eluting balloon use for safety and efficacy: evaluation of the 2nd generation paclitaxel-eluting DIOR-balloon in porcine coronary arteries. *Catheter Cardiovasc Interv* 76(3):395–403, 2010.
23. Yazdani SK, Pacheco E, Nakano M, et al: Vascular, downstream, and pharmacokinetic responses to treatment with a low-dose drug-coated balloon in a swine femoral artery model. *Catheter Cardiovasc Interv* 83(1):132–140, 2014.
24. Joner M, Radke PW, Byrne RA, et al: Preclinical evaluation of a novel drug-eluting balloon in an animal model of in-stent stenosis. *J Biomater Appl* 27(6):717–726, 2013.
25. Herdeg C, Goehring-Frischholz K, Zuern C, et al: Local catheter-based delivery of antithrombotic or antiproliferative drugs: a new concept for prevention of restenosis. *Thromb Res* 123(2):236–243, 2008.
26. Cremers B, Schmitmeier S, Clever YP, et al: Inhibition of neointimal hyperplasia in porcine coronary arteries utilizing a novel paclitaxel-coated scoring balloon catheter. *Catheter Cardiovasc Interv* 84(7):1089–1098, 2014.
27. Cremers B, Toner JL, Schwartz LB, et al: Inhibition of neointimal hyperplasia with a novel zotarolimus coated balloon catheter. *Clin Res Cardiol* 101(6):469–476, 2012.
28. Clever YP, Cremers B, Krauss B, et al: Paclitaxel and sirolimus differentially affect growth and motility of endothelial progenitor cells and coronary artery smooth muscle cells. *EuroIntervention* 7(Suppl K):K32–K42, 2011.
29. Freyhardt P, Zeller T, Kröncke TJ, et al: Plasma levels following application of paclitaxel-coated balloon catheters in patients with stenotic or occluded femoropopliteal arteries. *Rofo* 183(5):448–455, 2011.
30. Scheller B, Hehrlein C, Bocksch W, et al: Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med* 355(20):2113–2124, 2006.

31. Scheller B, Hehrlein C, Bocksch W, et al: Two-year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *Clin Res Cardiol* 97(10):773–781, 2008.
32. Scheller B, Clever YP, Kelsch B, et al: Long-term follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *JACC Cardiovasc Interv* 5(3):323–330, 2012.
33. Unverdorben M, Vallbracht C, Cremers B, et al: Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation* 119(23):2986–2994, 2009.
34. Unverdorben M, Vallbracht C, Cremers B, et al: Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis: the three-year results of the PEPCAD II ISR study. *EuroIntervention* 2014. [Epub ahead of print].
35. RIBS V Study Investigators, under the auspices of the Working Group on Interventional Cardiology of the Spanish Society of Cardiology: a randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent-in-stent restenosis: the RIBS V Clinical Trial (Restenosis Intra-stent of Bare Metal Stents: paclitaxel-eluting balloon vs. everolimus-eluting stent). *J Am Coll Cardiol* 63(14):1378–1386, 2014.
36. Habara S, Mitsudo K, Kadota K, et al: Effectiveness of paclitaxel-eluting balloon catheter in patients with sirolimus-eluting stent restenosis. *JACC Cardiovasc Interv* 4(2):149–154, 2011.
37. Habara S, Iwabuchi M, Inoue N, et al: A multicenter randomized comparison of paclitaxel-coated balloon catheter with conventional balloon angioplasty in patients with bare-metal stent restenosis and drug-eluting stent restenosis. *Am Heart J* 166(3): 527–533, 2013.
38. Rittger H, Brachmann J, Sinha AM, et al: A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study. *J Am Coll Cardiol* 59(15): 1377–1382, 2012.
39. Byrne RA, Neumann FJ, Mehilli J, et al: Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. *Lancet* 381(9865):461–467, 2013.
40. Xu B, Gao R, Wang J, et al: A prospective, multicenter, randomized trial of paclitaxel-coated balloon versus paclitaxel-eluting stent for the treatment of drug-eluting stent in-stent restenosis: results from the PEPCAD China ISR trial. *JACC Cardiovasc Interv* 7(2):204–211, 2014.
41. Authors/Task Force members: 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 35(37):2541–2619, 2014.
42. Cremers B, Clever Y, Schaffner S, et al: Treatment of coronary in-stent restenosis with a novel paclitaxel urea coated balloon. *Minerva Cardioangiol* 58(5):583–588, 2010.
43. Fischer D, Scheller B, Schaefer A, et al: Paclitaxel-coated balloon plus bare metal stent vs. sirolimus-eluting stent in de novo lesions: an IVUS study. *EuroIntervention* 8(4):450–455, 2012.
44. Clever YP, Cremers B, Speck U, et al: Influence of a paclitaxel coated balloon in combination with a bare metal stent on restenosis and endothelial function: comparison with a drug eluting stent and a bare metal stent. *Catheter Cardiovasc Interv* 84(2):323–331, 2014.
45. Cortese B, Micheli A, Picchi A, et al: Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomised clinical trial. The PICCOLETO study. *Heart* 96(16):1291–1296, 2010.
46. Belkacemi A, Agostoni P, Nathoe HM, et al: First results of the DEB-AMI (drug eluting balloon in acute ST-segment elevation myocardial infarction) trial: a multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug-eluting stent in primary percutaneous coronary intervention with 6-month angiographic, intravascular, functional, and clinical outcomes. *J Am Coll Cardiol* 59(25):2327–2337, 2012.
47. Stella PR, Belkacemi A, Dubois C, et al: A multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug-eluting stent in bifurcation lesions treated with a single-stenting technique: six-month angiographic and 12-month clinical results of the drug-eluting balloon in bifurcations trial. *Catheter Cardiovasc Interv* 80(7):1138–1146, 2012.
48. Liistro F, Porto I, Angioli P, et al: Elutax paclitaxel-eluting balloon followed by bare-metal stent compared with Xience V drug-eluting stent in the treatment of de novo coronary stenosis: a randomized trial. *Am Heart J* 166(5):920–926, 2013.
49. Bondesson P, Lagerqvist B, James SK, et al: Comparison of two drug-eluting balloons: a report from the SCAAR registry. *EuroIntervention* 8(4):444–449, 2012.
50. Mathey DG, Wendig I, Boxberger M, et al: Treatment of bifurcation lesions with a drug-eluting balloon: the PEPCAD V (Paclitaxel Eluting PTCA Balloon in Coronary Artery Disease) trial. *EuroIntervention* 7(Suppl K):K61–K65, 2011.
51. Wohrle J, Birkemeyer R, Markovic S, et al: Prospective randomised trial evaluating a paclitaxel-coated balloon in patients treated with endothelial progenitor cell capturing stents for de novo coronary artery disease. *Heart* 97(16):1338–1342, 2011.
52. Unverdorben M, Kleber FX, Heuer H, et al: Treatment of small coronary arteries with a paclitaxel-coated balloon catheter. *Clin Res Cardiol* 99(3):165–174, 2010.
53. Unverdorben M, Kleber FX, Heuer H, et al: Treatment of small coronary arteries with a paclitaxel-coated balloon catheter in the PEPCAD I study: are lesions clinically stable from 12 to 36 months? *EuroIntervention* 9(5):620–628, 2013.
54. German Drug-eluting Balloon Consensus Group: How to use the drug-eluting balloon: recommendations by the German consensus group. *EuroIntervention* 7(Suppl K):K125–K128, 2011.
55. Kleber FX, Rittger H, Bonaventura K, et al: Drug-coated balloons for treatment of coronary artery disease: updated recommendations from a consensus group. *Clin Res Cardiol* 102(11):785–797, 2013.
56. Wohrle J, Zadura M, Mobius-Winkler S, et al: SeQuent Please World Wide Registry: Clinical Results of SeQuent Please Paclitaxel-Coated Balloon Angioplasty in a Large-Scale, Prospective Registry Study. *J Am Coll Cardiol* 60(18):1733–1738, 2012.
57. Zeymer U, Waliszewski M, Spiecker M, et al: Prospective 'real world' registry for the use of the 'PCB only' strategy in small vessel de novo lesions. *Heart* 100(4):311–316, 2014.
58. Latib A, Colombo A, Castriota F, et al: A randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels: the BELLO (Balloon Elution and Late Loss Optimization) study. *J Am Coll Cardiol* 60(24):2473–2480, 2012.
59. Schillinger M, Sabeti S, Loewe C, et al: Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. *N Engl J Med* 354(18):1879–1888, 2006.
60. Schillinger M, Sabeti S, Dick P, et al: Sustained benefit at 2 years of primary femoropopliteal stenting compared with balloon angioplasty with optional stenting. *Circulation* 115(21):2745–2749, 2007.
61. Duda SH, Bosiers M, Lammer J, et al: Sirolimus-eluting versus bare nitinol stent for obstructive superficial femoral artery disease: the SIROCCO II trial. *J Vasc Interv Radiol* 16(3):331–338, 2005.
62. Lammer J, Bosiers M, Zeller T, et al: First clinical trial of nitinol self-expanding everolimus-eluting stent implantation for peripheral arterial occlusive disease. *J Vasc Surg* 54(2):394–401, 2011.
63. Dake MD, Ansel GM, Jaff MR, et al: Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions: 2-year follow-up from the Zilver PTX randomized and single-arm clinical studies. *J Am Coll Cardiol* 61(24):2417–2427, 2013.
64. Scheinert D, Scheinert S, Sax J, et al: Prevalence and clinical impact of stent fractures after femoropopliteal stenting. *J Am Coll Cardiol* 45(2):312–315, 2005.
65. Tepe G, Zeller T, Albrecht T, et al: Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med* 358(7):689–699, 2008.
66. Tepe G, Schnorr B, Albrecht T, et al: Angioplasty of femoral-popliteal arteries with drug-coated balloons: 5-year follow-up of the THUNDER trial. *JACC Cardiovasc Interv* 8(1Pt A):102–108, 2015.
67. Werk M, Langner S, Reinkensmeier B, et al: Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. *Circulation* 118(13):1358–1365, 2008.
68. Scheinert D, Duda S, Zeller T, et al: The LEVANT I (Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis) trial for femoropopliteal revascularization: first-in-human randomized trial of low-dose drug-coated balloon versus uncoated balloon angioplasty. *JACC Cardiovasc Interv* 7(1):10–19, 2014.

68b. FDA Executive Summary prepared for the June 12, 2014, meeting of the Circulatory System Devices Advisory Panel, P13002.

69. Werk M, Albrecht T, Meyer DR, et al: Paclitaxel-coated balloons reduce restenosis after femoro-popliteal angioplasty: evidence from the randomized PACIFIER trial. *Circ Cardiovasc Interv* 5(6):831–840, 2012.
70. Schmidt A, Piorkowski M, Werner M, et al: First experience with drug-eluting balloons in infrapopliteal arteries: restenosis rate and clinical outcome. *J Am Coll Cardiol* 58(11):1105–1109, 2011.
71. Liistro F, Grotti S, Porto I, et al: Drug-eluting balloon in peripheral intervention for the superficial femoral artery: the DEBATE-SFA randomized trial (drug eluting balloon in peripheral intervention for the superficial femoral artery). *JACC Cardiovasc Interv* 6(12):1295–1302, 2013.
72. Zeller T, Baumgartner I, Scheinert D, et al: Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. *J Am Coll Cardiol* 64(15):1568–1576, 2014.

18 Elective Intervention for Stable Angina or Silent Ischemia

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KEY POINTS

- Chronic angina is a growing worldwide problem with significant economic and societal costs.
- By reducing the ischemic burden, percutaneous coronary revascularization provides important clinical benefit in patients with established obstructive coronary artery disease (CAD). The foremost effect is prompt symptom control and improved exercise tolerance. Direct evidence for improvement in survival or definitive reduction of major cardiovascular events is lacking in the broad population of patients with chronic, stable symptomatic CAD.
- Optimal medical therapy (OMT) is an essential component of the successful treatment of patients with established CAD and those at risk.
- Along with OMT, secondary prevention strategies of diet, exercise, and smoking cessation are required elements in the treatment of patients with CAD, and they provide an important and measurable benefit in this population.
- Patients at elevated risk for adverse events—including those with left ventricular dysfunction, chronic kidney disease, diabetes mellitus, and an extensive ischemic burden—have greater potential for measurable prognostic benefit with revascularization in addition to OMT.

Angina pectoris affects approximately 9 million of the 16.3 million people with a diagnosis of CAD in the United States, and the prevalence increases with age for both established and symptomatic coronary disease (Figs. 18-1 and 18-2).[1] In combating this disease, U.S. physicians performed an estimated 6.8 million inpatient cardiovascular procedures in 2007, an increase of 27% over the previous decade, including approximately 622,000 percutaneous coronary revascularization procedures. The mean hospital charge for percutaneous coronary intervention (PCI) was $56,015 in 2008,[1] with average costs near $20,000 for a typical procedure and overnight hospitalization. Although costly, appropriate revascularization in patients with chronic angina renders important prognostic benefits and contributed an estimated 5% to the total observed reduction in coronary heart disease mortality between 1980 and 2002.[2] Despite this measurable success in addressing established disease, the incidence and costs associated with symptomatic CAD continue to grow throughout the world and contribute an ever-increasing proportion to the overall morbidity, mortality, and lost economic productivity in both developed and developing regions. Revascularization is intuitively central to the treatment paradigm for CAD. A mismatch between myocardial oxygen supply and demand is the predominant mechanism implicated in the development of symptoms associated with obstructive CAD. Generally, epicardial coronary lesions that comprise at least a 50% to 79% diameter obstruction (70% to 90% by cross-sectional area measurement) are associated with impaired flow and resultant ischemia. When correlated with clinical or objective evidence of ischemia, such lesions are attractive targets for symptom management. However, the realm of patients with symptoms or signs of ischemia may also include those with abnormal coronary endothelial function, coronary vasospasm, microvascular dysfunction, and even silent, asymptomatic myocardial ischemia. In addition, symptoms reminiscent of ischemic angina may be a manifestation of a noncardiovascular process, such as gastrointestinal, musculoskeletal, or neuropsychiatric pathology—generally, anything from the navel to the nose—whereas other patients, especially women and older adults, may present with symptoms such as fatigue, chronic "soreness," or dyspnea, which may not be immediately recognized as an expression of cardiovascular disease (Tables 18-1 and 18-2).[3] Individuals with significant ischemia may also remain seemingly unaffected by symptoms because of self-regulation of activity, essentially avoiding activities that have previously caused discomfort. Careful attention to individual patient presentation and characteristics, then, is essential for proper diagnostic triage and management. Once recognized, the goals and methods of treatment for this heterogeneous syndrome include

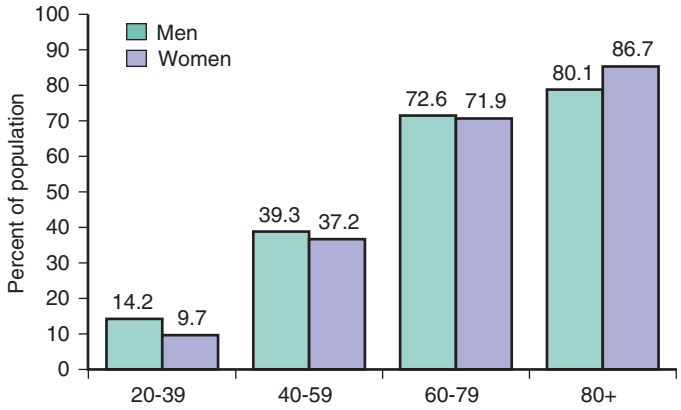


FIGURE 18-1 U.S. prevalence of cardiovascular disease by age and sex. Data include coronary disease, heart failure, stroke, and hypertension. (From Roger VL, Go AS, Lloyd-Jones DM, et al: Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation* 123[4]:e18-e209, 2011.)

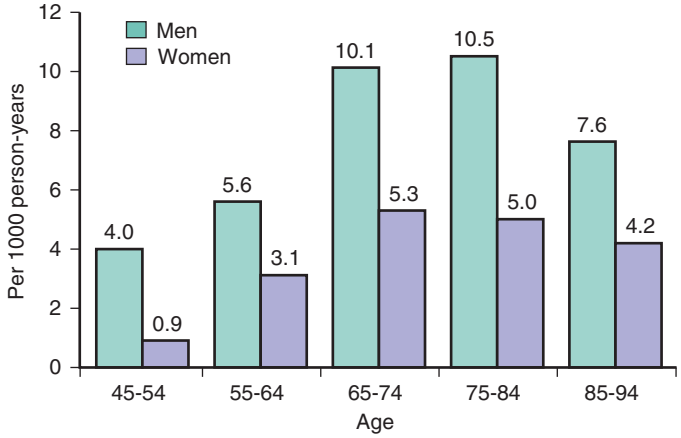


FIGURE 18-2 Incidence of stable angina pectoris from the Framingham Heart Study (1980 to 2003) stratified by age and sex. (From Roger VL, Go AS, Lloyd-Jones DM, et al: Heart Disease and Stroke Statistics—2011 update: a report From the American Heart Association. *Circulation* 123[4]:e18-e209, 2011.)

TABLE 18-1 Potential Nonischemic Diagnoses in Patients with Chest Pain

Nonischemic Cardiovascular
Aortic dissection, pericarditis
Pulmonary
Embolus, pneumothorax, pneumonia, pleuritis
Gastrointestinal
Esophageal, esophagitis, spasm, reflux, cholecystitis, choledocholithiasis, cholangitis, peptic ulcer, pancreatitis
Chest Wall
Costochondritis, fibrositis, rib fracture, sternoclavicular arthritis, biliary herpes zoster
Psychiatric
Anxiety, hyperventilation, panic disorder, affective disorders, somatiform disorder

From Gibbons RJ, Abrams J, Chatterjee K, et al: ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for the Management of Patients with Chronic Stable Angina). *Circulation* 107:149-158, 2003.

TABLE 18-2 Ischemic Provocation or Exacerbating Factors

Increased Oxygen Demand	Decreased Oxygen Supply
NONCARDIAC CONDITIONS	
Hyperthermia	Anemia
Hyperthyroidism	Hypoxemia
Sympathomimetic toxicity (e.g., from cocaine)	Sickle cell disease
Hypertension	Sympathomimetic toxicity
Anxiety	Hyperviscosity
Arteriovenous fistula	Polycythemia
CARDIAC CONDITIONS	
Hypertrophic cardiomyopathy	Hypertrophic cardiomyopathy
Aortic stenosis	Aortic stenosis
Dilated cardiomyopathy	
Tachycardia	

From Gibbons RJ, Abrams J, Chatterjee K, et al: ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for the Management of Patients with Chronic Stable Angina). *Circulation* 107:149-158, 2003.

reduction in both morbidity and mortality, although anticipated benefits depend on patient characteristics and the treatment modality used. Percutaneous revascularization has, as its principal benefit, the relief of angina. Symptom relief is the direct effect of a reduction in ischemic burden, although additional complex factors no doubt play a role, especially in the setting of residual disease or incomplete abrogation of ischemia (Fig. 18-3).[4] Whereas improved survival and reduction of major cardiovascular events are important therapeutic objectives, limited data are available to support a major role for percutaneous revascularization in reducing adverse events in the broader population of patients with stable ischemic coronary disease (Fig. 18-4).[5] In fact, a clear survival advantage for revascularization over medical therapy alone has generally been limited to patients at high clinical or anatomic risk, specifically those high-risk patients undergoing surgical revascularization for severe symptomatic triple-vessel disease, left main CAD, left ventricular (LV) dysfunction, and manifestations of severe ischemia.[6] Numerous advances in the care of patients with established coronary disease have occurred in the interim, however, with the development of advanced medical therapies and surgical and percutaneous revascularization techniques. In the setting of appropriate and optimal medical therapy, percutaneous revascularization remains an important adjunct for symptom relief and for reduction of ischemic burden.

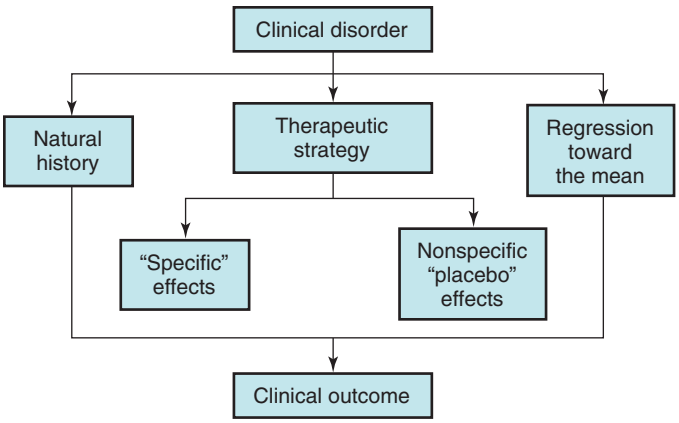


FIGURE 18-3 Factors with potential influence on clinical response to treatment. These include *specific intended effects,* such as ischemia reduction after percutaneous coronary intervention, and *nonspecific effects,* often described as "the placebo effect." These effects occur within the context of the natural history of the clinical condition itself, along with the normal "moderation" of effects, or regression toward the mean outcome, that occurs within populations. (Adapted from Bonetti PO, Holmes DR, Lerman A, Barsness GW: Enhanced external counterpulsation for ischemic heart disease. What's behind the curtain? *J Am Coll Cardiol* 41[11]:1918-1925, 2003.)

REVASCULARIZATION IN PATIENTS WITH CHRONIC STABLE ANGINA

The principles and practice of modern coronary revascularization strategies are rooted in the conduct and results of studies performed in the 1970s and 1980s. These historic investigations set the framework for our current understanding of the role of both surgical and percutaneous coronary revascularization in the treatment armamentarium of chronic symptomatic ischemic CAD. Whereas these studies provided important insight into the outcome of revascularization and medical therapy using the methodology of the time, great strides have subsequently been made in all areas of treatment, thus decreasing the applicability of these trials to guide therapy in the prevailing health care environment. Today, OMT has been clearly established as the cornerstone of treatment for CAD. The impact of medical therapy has grown with the introduction of advanced antiplatelet therapy, statins, and angiotensin-converting enzyme (ACE) and receptor inhibition, among other established and evolving therapies that provide important moderation of the inexorable progression of coronary disease. Indeed, appropriate application of evidence-based therapy has had important societal health implications, with a resultant measurable reduction in adverse cardiac events over the past several decades. Although appropriate revascularization in patients with chronic angina contributed an estimated 5% to this observed reduction in cardiac mortality between 1980 and 2002, a much larger 50% of the total reduction is attributed to improvement in the risk-factor profiles of those populations in jeopardy, largely thanks to improved agents and the greater application of this medical therapy.[2] Whereas PCI is an important adjunct for symptom control and has established value in reducing both subsequent morbidity and mortality after acute coronary syndromes (ACSs), both PCI and surgical revascularization are palliative procedures, and lesion progression accounts for significant recurrent morbidity. Recent studies demonstrate the impact of lesion progression and the need for aggressive concomitant medical therapy in the setting of PCI. Mahn-Won and colleagues[7] retrospectively studied 507 patients who underwent PCI and found that 16% of them underwent clinically driven repeat PCI to treat preexisting nonculprit coronary lesions during the 3-year study period. During the first year after initial PCI, 7.7% of

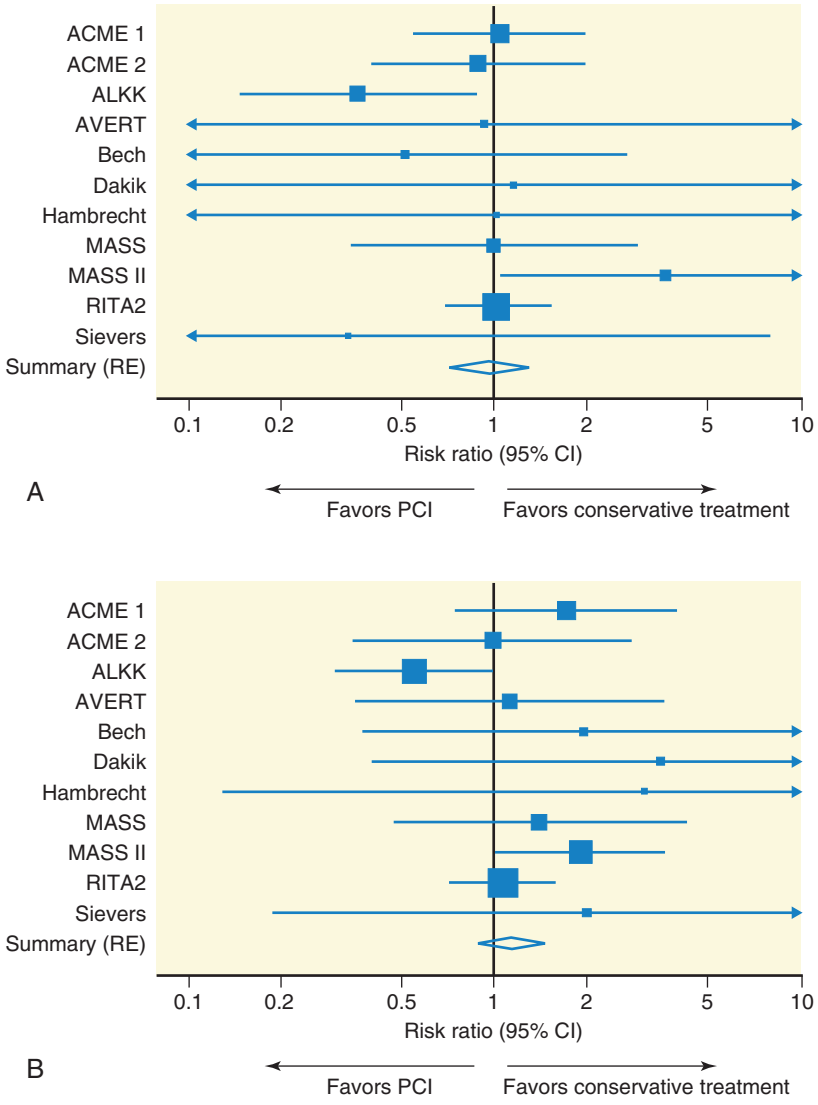


FIGURE 18-4 Point estimates, 95% confidence intervals (CIs), and summary statistics in 11 studies that enrolled patients from 1992 through 2001. **A,** For risk of all-cause death after treatment with percutaneous coronary intervention (PCI) or medical therapy. **B,** For risk of cardiac death or myocardial infarction after PCI or medical therapy. (From Katritsis DG, Ioannidis JPA: Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. *Circulation* 111[22]: 2906-2912, 2005.)

patients in this cohort underwent non–culprit lesion PCI, with the rate increasing to 16% at 3 years. Greater extent of disease, as manifest by a larger baseline number of significant coronary lesions, independently predicted repeat PCI (odds ratio [OR], 2.29; 95% confidence interval [CI], 1.5 to 3.5; $P < .001$), as did the baseline risk factors of low levels of high-density lipoprotein (<40 mg/dL; OR, 2.01; 95% CI, 1.01 to 3.98; $P = .046$), hypercholesterolemia (total cholesterol > 200 mg/dL; OR, 1.46; 95% CI, 1.22 to 1.97; $P = .04$), history of PCI (OR, 1.24; 95% CI, 1.09 to 1.60; $P = .003$), and increased triglyceride levels (OR, 1.003; 95% CI, 1.001 to 1.007; $P = .038$). An additional natural history study[8] of patients who underwent intravascular ultrasound evaluation after PCI for an acute coronary syndrome found that fully one half of major subsequent adverse events at 3 years occurred at nonculprit sites. Adequate medical therapy and risk modification, then, are essential in the periinterventional and postinterventional setting to reduce subsequent mortality and morbidity, including symptom recurrence and need for repeat procedures associated with lesion progression and new lesion development.

ADDITION OF REVASCULARIZATION TO OPTIMAL MEDICAL THERAPY

The selection of treatment strategies in patients with chronic stable angina depends on symptom status, anatomic complexity, clinical comorbidity, and risk. The main indications for revascularization are to improve symptoms that persist despite OMT and to improve prognosis. Although they generally suggest a benefit for revascularization, most randomized trials that compare medical therapy with percutaneous revascularization are limited by their historical nature and entry bias. It is generally agreed that PCI affords rapid and effective symptom relief, a concept borne out in several trials and in a recent meta-analysis[9] of 14 trials that demonstrated a statistically significant benefit in angina relief with PCI compared with medical therapy (OR, 1.69; 95% CI, 1.24 to 2.30). Notably, important heterogeneity was found across the trials, with substantially less benefit noted in more contemporary trials of PCI versus OMT, such as the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial,[10] published in 2007 (OR, 1.10; 95% CI, 0.81 to 1.49), and the Occluded Artery Trial (OAT),[11] published in 2006 (OR, 0.83; 95% CI, 0.47 to 1.47). Using meta-regression analysis of the treatment effects of PCI relative to medical therapy, Wijeysundera and colleagues[9] were able to document an inverse relationship between freedom from angina and the number of "evidence-based" medications utilized during the conduct of a trial (Fig. 18-5). Subgroup analysis of the COURAGE trial[12] confirmed a diminution of angina benefit over time for patients treated with PCI as an initial strategy. Although a statistically significant difference was found in rates of freedom from angina between the OMT-alone and the OMT-plus-PCI groups at 3

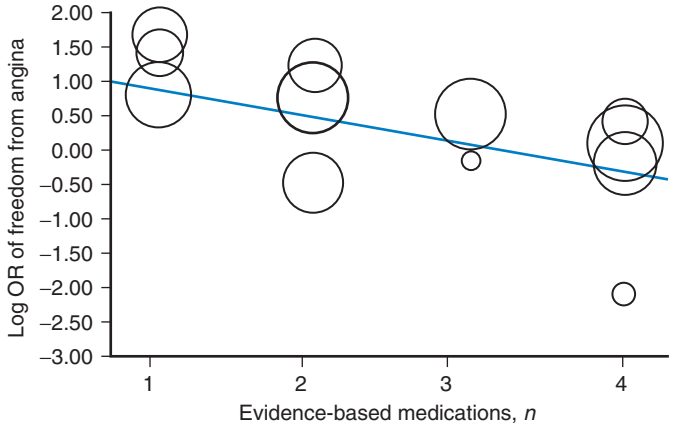
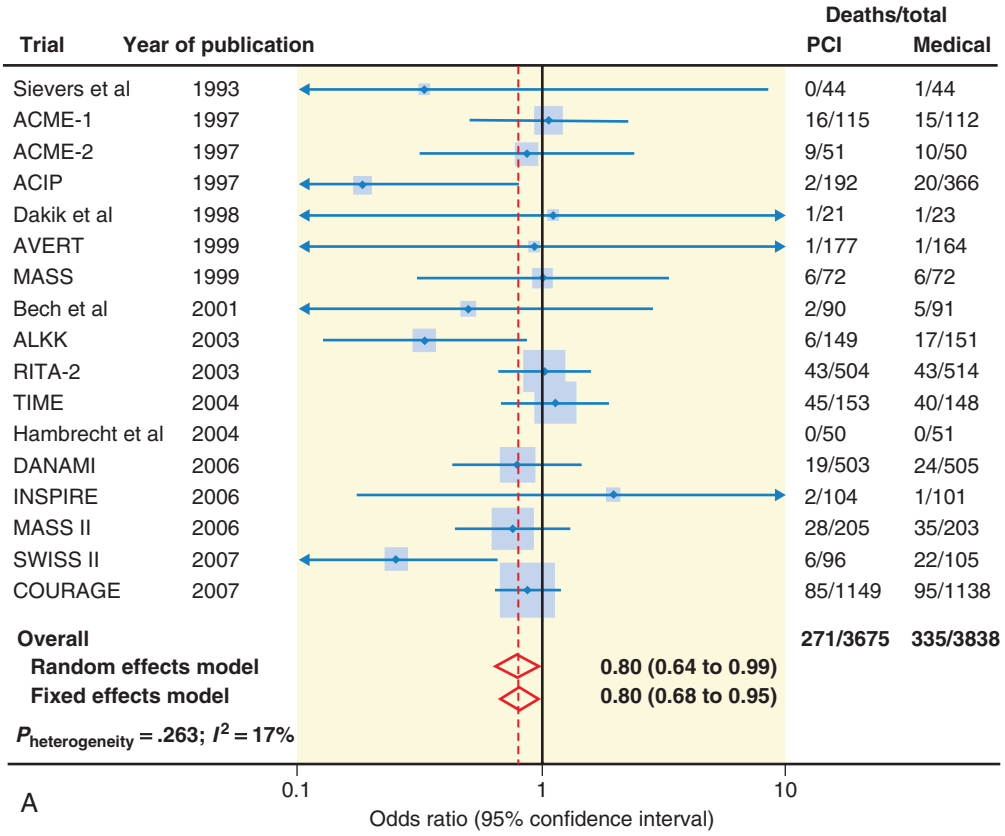


FIGURE 18-5 Meta-regression demonstrates an inverse relationship between freedom from angina and adherence to optimal evidence-based medical regimens within individual trial components of the meta-analysis. In more contemporary trials, evidence-based medication was used more frequently, and the measurable symptom-relief benefit of percutaneous coronary intervention (PCI) was diminished. *OR,* Odds ratio. (From Wijeysundera HC, Nallamothu BK, Krumholz HM, et al: Meta-analysis: effects of percutaneous coronary intervention versus medical therapy on angina relief. *Ann Intern Med* 152[6]:370-379, 2010.)

months (42% vs. 53%, $P < .001$), this difference was no longer evident at 3 years (56% vs. 59%, $P = .30$). Although potential reasons for this convergence of angina rates during follow-up are numerous and include crossover to revascularization from the medical arm, ascertainment bias due to small follow-up populations, and a host of other factors (see Fig. 18-3),[4] an important finding is that in both groups, patients with the most significant anginal burden at baseline obtained the greatest benefit from PCI. In aggregate, these data support a robust, reliable antianginal benefit for PCI in patients with persistent symptoms despite medical therapy.

The benefit of percutaneous revascularization on the hard end points of death and myocardial infarction (MI) is more controversial, and the complexities are greater. The relatively low event rates among stable patients with coronary disease, particularly those healthy enough and eligible to be enrolled in randomized prospective trials, limits the discriminatory ability of individual clinical trials to identify treatment effects. Even large meta-analytic studies, limited by significant heterogeneity of patient groups and inclusion of antiquated therapies (balloon angioplasty and limited medical options), have provided conflicting results. A meta-analysis by Katritsis and colleagues[5] incorporated data from 11 randomized trials of PCI compared with medical therapy in patients with documented CAD in the absence of a recent ACS. With 2950 patients included in the analysis, no significant difference could be identified between PCI and medical therapy in rates of overall death (see Fig. 18-4, *A*), cardiac death and MI (see Fig. 18-4, *B*), or subsequent revascularization. A more recent meta-analysis by Schömig and colleagues[13] of 17 trials involving 7513 patients with chronic stable angina randomized over a 17-year period to PCI or OMT alone again found no significant benefit for PCI over medical therapy with regard to rates of nonfatal MI (Fig. 18-6). However, with selection of cardiac mortality, rather than overall mortality, as an end point, this analysis did suggest a potential advantage for a PCI-based therapeutic strategy for improving long-term outcome (see Fig. 18-6, *B*). Further analysis suggested that this benefit was most pronounced in patients who had suffered a recent MI (<4 weeks prior); they had about a 35% reduction in the odds of death compared with an estimated risk reduction of 17% for patients with truly stable coronary disease. Both of these meta-analyses, however, were limited by several factors that included significant heterogeneity of patient groups and treatments, inclusion of patients with recent ACSs, and significant variability in treatments across studies and time periods. Another meta-analysis[14] that compared revascularization (surgical or percutaneous) with medical therapy over a 30-year period from 1977 to 2007 confirmed a significant reduction in all-cause mortality associated with revascularization (OR, 0.74; 95% CI, 0.63 to 0.88). When this study was stratified by revascularization type, the investigators were also able to show a reduction in mortality with both surgical (OR, 0.62; 95% CI, 0.50 to 0.77) and percutaneous (OR, 0.82; 95% CI, 0.68 to 0.99) revascularization approaches compared with OMT. However, this meta-analysis, like the others, included trials that encompassed a broad array of patient populations, including those with recent ACSs; it was also limited by the historic nature of treatment algorithms spanning the 30-year study period. In a 20-year network analysis that took into account the evolution of interventional approaches over time, Trikalinos and colleagues[15] were unable to document a beneficial effect of PCI-based strategies on rates of death or MI compared with contemporaneous medical therapy. As previously noted, a major hurdle in the assessment of survival benefits associated with revascularization trials is the relatively low overall event rate. Whereas annualized mortality associated with chronic CAD remains approximately 1% to 3% in contemporary series,[14,16,17] the risk of adverse events increases with the degree of LV dysfunction,[18] ischemic burden,[19] and functional limitation (Table 18-3).[20] In addition, risk is increased in the presence of diabetes mellitus, chronic kidney disease, and greater severity of ischemic symptoms[16] and anatomic complexity.[21] It is not surprising then that a gradient of benefit can be observed for revascularization compared with medical therapy, with greater benefit identified in those patients at greatest risk, whether due to anatomic complexity (Fig. 18-7)[21] or severity of ischemic substrate (Fig. 18-8).[22] Note that in the large cohort of patients identified in the Duke database with coronary stenoses of >75% ($n = 18,481$) who were treated with an initial strategy of revascularization (either surgical or percutaneous), significant benefit could be demonstrated across the spectrum of disease complexity compared with those patients treated initially with medical therapy alone.[21]

Recent prospective trials have helped to elucidate the potential benefit of percutaneous revascularization across the spectrum of clinical and anatomic risk, along with the continued importance of OMT. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial[10] is the largest trial yet performed to evaluate whether PCI provides additional clinical benefit over OMT alone. This trial randomized 2287 patients to OMT or OMT with early PCI, utilizing predominantly bare-metal stents. OMT was intended to include antiplatelet therapy, beta-blockade with metoprolol, ACE inhibition or angiotensin receptor blocker (ARB) therapy, and antiischemic measures that included amlodipine and/or nitrate therapy. Diet, exercise, and smoking cessation were also encouraged. All patients underwent entry angiographic evaluation, and those with more than 70% diameter stenosis in at least one epicardial coronary artery with evidence of ischemia or more than 80% stenosis and typical anginal symptoms were eligible for inclusion if coronary anatomy was felt to be suitable for PCI. Exclusion criteria included persistent Canadian Cardiovascular Society (CCS) class IV angina, markedly positive stress evaluation, significant heart failure symptoms, left ventricular ejection fraction (LVEF) below 30%, or revascularization within the previous 6 months. At a mean follow-up of 4.6 years, no significant difference was seen in the primary end point of death or MI between the PCI and medical treatment groups (OR, 1.05; 95% CI, 0.87 to 1.27; $P = .62$), nor was any difference found in overall mortality (7.6% vs. 8.3%, $P = .38$) or freedom from angina (74% vs. 72%, $P = .35$). However, in patients treated with PCI in addition to OMT, freedom from angina was significantly greater up to 3 years, and the medical therapy cohort exhibited a "catch up" pattern only after the initial 2 years of follow-up (Fig. 18-9).[12] Additional early benefits associated with percutaneous intervention included a reduced need for follow-up revascularization during the first year (21% vs. 33%, $P < .001$) with a concomitant reduction in the need for antiischemic drug therapy. These results support



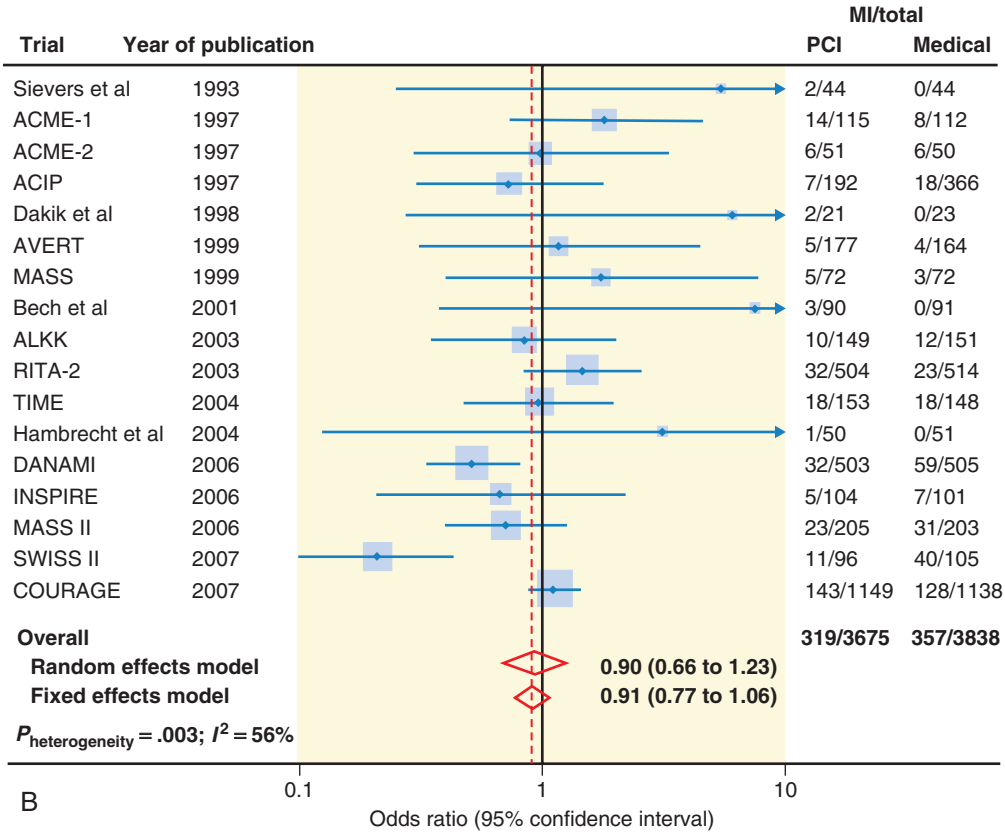


FIGURE 18-6 Odds ratios with 95% confidence intervals among 17 randomized trials of percutaneous coronary intervention (PCI) or medical therapy with an average follow-up period of 51 months, along with summary statistics. **A,** Risk of cardiac death. **B,** Risk of nonfatal myocardial infarction. (From Schömig A, Mehilli J, de Waha A, et al: A meta-analysis of 17 randomized trials of a percutaneous coronary intervention-based strategy in patients with stable coronary artery disease. *J Am Coll Cardiol* 52[11]:894-904, 2008.)

TABLE 18-3 Risk Stratification in Patients with Angina

High Risk (>3% Annual Mortality Rate)

- Severe resting LV dysfunction (LVEF <35%)
- High-risk treadmill score (score ≤–11)
- Severe exercise LV dysfunction (exercise LVEF <35%)
- Stress-induced large perfusion defect (particularly if anterior)
- Stress-induced multiple perfusion defects of moderate size
- Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201)
- Stress-induced moderate perfusion defect with LV dilation or increased lung uptake
- Echocardiographic wall motion abnormality in more than two segments that develops at a low dose of dobutamine (≤10 μg/kg/min) or at a low heart rate (<120 beats/min)
- Stress echocardiographic evidence of extensive ischemia

Intermediate Risk (1% to 3% Annual Mortality Rate)

- Mild/moderate resting LV dysfunction (LVEF 35% to 49%)
- Intermediate-risk treadmill score (–11 to 5)
- Stress-induced moderate perfusion defect without LV dilation or increased lung intake
- Limited stress echocardiographic ischemia that involves two or fewer segments with a wall motion abnormality only at higher doses of dobutamine

Low Risk (<1% Annual Mortality Rate)

- Low-risk treadmill score (score ≥5)
- Normal or small myocardial perfusion defect at rest or with stress
- Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress

From Patel MR, Dehmer GJ, Hirshfeld JW, et al: ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness criteria for coronary revascularization: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology: endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *Circulation* 119(9):1330-1352, 2009.

LV, Left ventricle; *LVEF,* left ventricular ejection fraction.

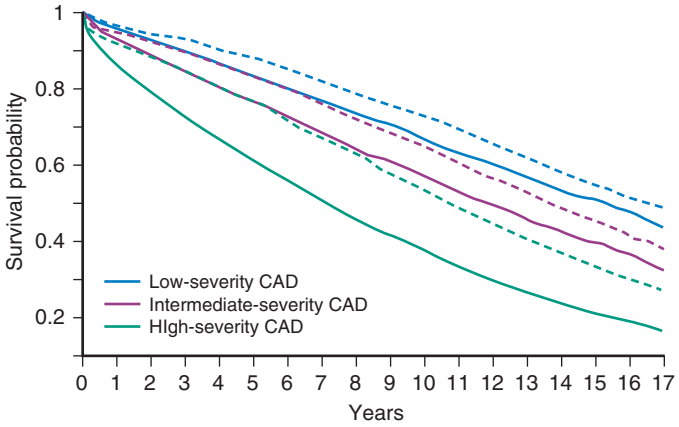


FIGURE 18-7 Adjusted long-term survival estimates for patients treated with an initial medical revascularization (*solid lines*) or surgical or percutaneous revascularization (*dotted lines*) approach, stratified by extent of coronary artery disease (CAD) as defined by tertiles of the Duke Coronary Artery Disease Severity Index. *High-severity* CAD anatomy encompasses those patients with significant (50% to 75% stenosis) left main and/or three-vessel disease; *low-severity* CAD includes patients with single-vessel disease or noncritical (<95% stenosis) two-vessel disease; and *intermediate-severity* CAD comprises patients with critical proximal left anterior descending (LAD) disease and the remaining two-vessel disease anatomic subgroups. (Adapted from Smith PK, Califf RM, Tuttle RH, et al: Selection of surgical or percutaneous coronary intervention provides differential longevity benefit. *Ann Thorac Surg* 82[4]:1420-1429, 2006.)

the widespread use of OMT in patients with established CAD and suggest that in this setting, early PCI is not associated with reduced long-term event rates. Whereas an initial strategy of OMT alone was not associated with increased rates of death or MI, it *was* associated with a significant crossover rate of 30% within the first year of follow-up.[23] In addition, enrolled patients were at relatively low risk, with one-, two-, and three-vessel coronary disease rates of 31%, 39%, and 30%, respectively, and only a 31% incidence of proximal left anterior descending (LAD) disease. Patients also had relatively preserved LV function, and those with left main CAD were not included. Finally, compliance rates with medical therapy at 5 years ranged from 85% for beta-blockade to 95% for aspirin or clopidogrel,[10] rates that far exceeded the less than 40% compliance noted in community-based registry studies such as the 40,000-patient "real world" Reduction of Atherothrombosis for Continued Health (REACH) registry.[24]

The COURAGE nuclear substudy[19] evaluated a small but relatively high-risk patient subset of the overall trial. Based on previous work that demonstrated the prognostic benefit of coronary revascularization in patients with a significant burden of ischemic myocardium,[22,25] the authors initiated an exploratory evaluation that involved 314 consecutive study patients who underwent serial rest/stress myocardial perfusion imaging (MPI) studies. Based on comparisons of pretreatment ischemic burden and studies performed at 6 to 18 months after randomization, patients in the PCI-plus-OMT group experienced a greater degree of ischemia reduction (≥5% reduction in ischemic myocardium) than those treated with OMT alone (33% vs. 19%, $P = .0004$). The degree of ischemia resolution was also greater in patients with more ischemia at baseline. Importantly, low levels of residual ischemia at follow-up were associated with improved symptom status and better unadjusted survival free of MI ($P = .037$), suggesting an important

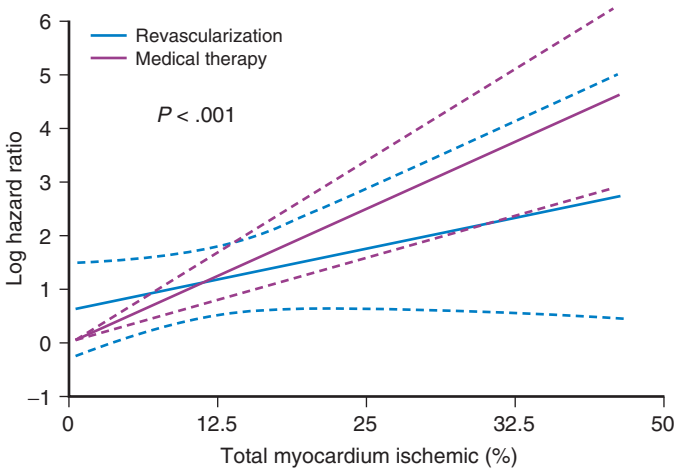


FIGURE 18-8 Log hazard ratio for 10,627 patients undergoing revascularization or medical therapy for ischemic coronary artery disease as a function of extent of myocardial ischemia. The intersection of curves at an approximate point of inducible ischemia of 10% or more of the myocardium represents the retrospectively identified threshold for survival benefit associated with revascularization. (Adapted from Hachamovitch R, Hayes SW, Friedman JD, et al: Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 107[23]:2900-2907, 2003.)

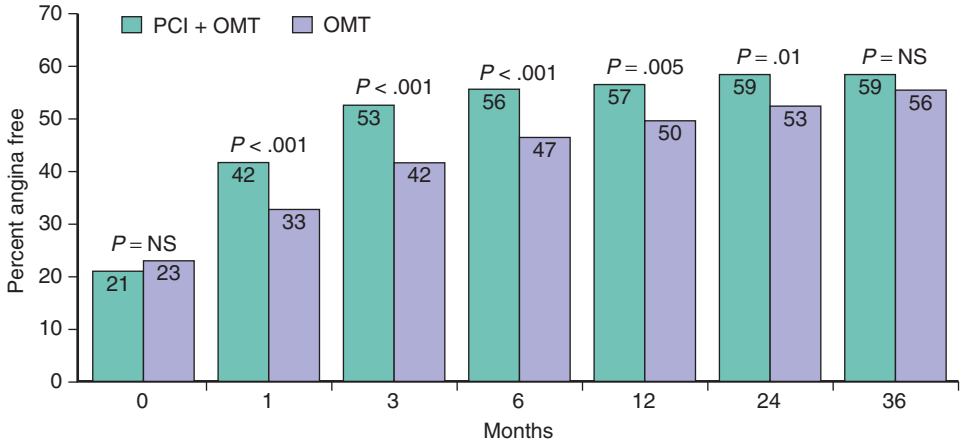


FIGURE 18-9 Changes in the angina frequency scale of the Seattle Angina Questionnaire over time in the COURAGE Trial. Data shown are for the COURAGE trial cohorts of percutaneous revascularization with optimal medical therapy (percutaneous coronary intervention [PCI] plus optimal medical therapy [OMT]) and OMT alone. The early anginal benefit demonstrated with PCI plus OMT is reduced over time because patients in the OMT group experience progressively greater freedom from angina over the initial 3 years of follow-up. (Adapted from Weintraub WS, Spertus JA, Kolm P, et al: Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med* 359[7]:677-687, 2008.)

prognostic role for aggressive ischemia reduction in these patients. As with all large randomized trials, the generalizability of these findings is limited by the type of patients enrolled and the already outmoded forms of therapy provided (drug-eluting stents were largely unavailable during recruitment, as were many novel medical therapeutics, including ranolazine). However, the results of this trial provide additional support for the importance of a foundation of OMT while providing confidence in the benefit of percutaneous revascularization as an adjunctive method of symptom and ischemia control. The Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D)[26] trial addressed a similar question; it enrolled 2368 patients with type 2 diabetes mellitus to early revascularization (coronary bypass surgery or PCI, at the discretion of the treating physician) with OMT and later revascularization as needed for symptom relief. Along with OMT, patients were assigned exercise and risk-factor modification programs with frequent assessment and modification of glycemic control. Patients were included in the trial if they had stable CAD (CCS class I or II in 82%), a positive stress test, and coronary anatomy suitable for revascularization. Exclusion criteria included the need for immediate revascularization, left main CAD, significant heart failure, or prior revascularization within a year of study entry. Like the COURAGE trial, the primary end point of 5-year all-cause mortality was similar between the groups (hazard ratio [HR], 0.5; 95% CI, –2.0 to 3.1; P = .97). Also reminiscent of the COURAGE results, 42% of patients originally assigned to OMT alone crossed over to subsequent revascularization, reinforcing the role of adjunctive revascularization in managing symptoms. Of interest, because the choice of revascularization was left to the discretion of the treating physician and patient, patients with more extensive disease were generally treated with surgical, rather than percutaneous, revascularization. In this group of high-risk patients with diabetes mellitus, surgical revascularization offered a significant reduction in nonfatal infarction, with no such advantage noted in those patients selected for PCI over pharmacologic therapy.[27] Overall, the results of BARI 2D—like those of the COURAGE trial—support the use of OMT for the treatment of CAD, with revascularization providing prompt symptomatic benefit and reduced need for subsequent revascularization, particularly in those patients at greater risk and with symptoms that persist despite aggressive pharmacologic therapy. In addition, exploratory subset analysis of both the COURAGE and BARI 2D studies leaves open the possibility that prompt revascularization may provide important prognostic benefit in patients at increased risk because of complex coronary anatomy or an extensive ischemic substrate. Alternatively, the ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) is designed to randomize approximately 8000 patients with at least moderate ischemia by noninvasive stress imaging to either a routine invasive strategy with revascularization and OMT or to a conservative strategy of OMT with diagnostic angiography and revascularization reserved for failure of OMT (clinicaltrials.gov identifier NCT01471522). The primary end point of the trial is the composite of cardiovascular death and nonfatal MI over 4-year follow-up in addition to secondary end points related to angina status and disease-specific quality of life. Clearly, further study is needed in this area.

SELECTION OF REVASCULARIZATION STRATEGY

In patients who have persistent anginal symptoms despite aggressive medical therapy or high-risk features of CAD, revascularization with coronary artery bypass grafting (CABG) or stent-based PCI is an appropriate consideration. The selection of a specific revascularization strategy depends on numerous factors that include the extent and complexity of the coronary anatomy, presence and severity of comorbidities, patient and physician preference, and available scientific evidence. As technology has advanced in the application of both CABG and PCI, this discussion has evolved dramatically. However, whereas the goals of therapy for both PCI and CABG involve providing symptomatic and prognostic improvement, the methods of achieving these goals continue to be fundamentally different and help to explain the major difference in outcome between the two strategies, that is, the need for more subsequent repeat revascularization in patients undergoing PCI. Because coronary disease is a progressive, incurable condition, both PCI and CABG provide only palliation. Surgical revascularization, however, addresses obstructive coronary disease by providing a perfusion conduit that circumvents a long segment of proximal disease. This allows greater protection from the inexorable development of new and progressive lesions compared with the focal treatment strategy associated with stent placement. In addition, surgical revascularization is associated with more extensive revascularization and a greater likelihood of successful revascularization of all affected territories (full anatomic revascularization),[28] with potential implications for improved survival at follow-up.[28,29] For patients with single-vessel, non–left main CAD and indications for revascularization, few contemporary data are available to suggest the superiority of CABG over PCI. Revascularization in patients with single-vessel disease generally entails less risk of major morbidity or mortality than that in patients with multivessel disease, and outcomes with PCI have been as good

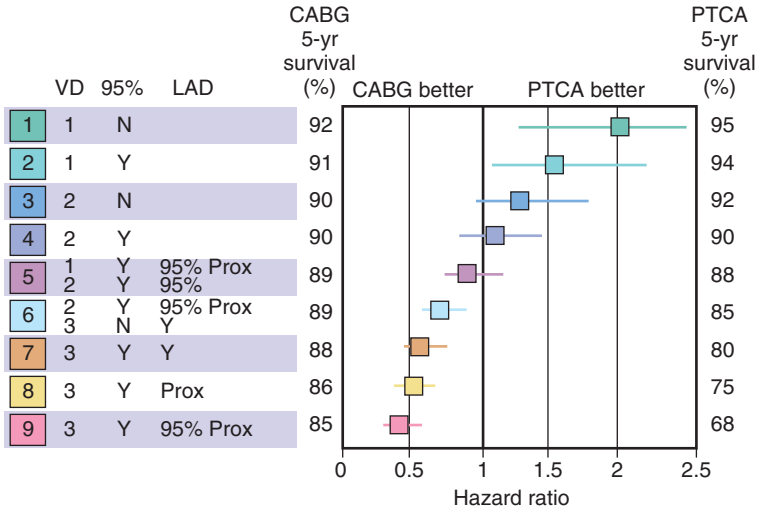


FIGURE 18-10 Relationship of graded coronary anatomy. This includes the number of vessels with at least 75% stenosis (VD), severity of disease (≥95% stenosis), presence of left anterior descending (LAD) coronary artery disease (CAD), and differential mortality hazard after either coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA). A gradient of outcome effect is identified because increased severity of CAD is associated with improved outcome in CABG-treated patients compared with the outcome associated with percutaneous coronary intervention (PCI) in patients with similar high-severity disease. *Y* indicates yes; *N* indicates no. *Prox,* Proximal. (Adapted from Jones RH, Kesler K, Phillips HR 3rd, et al: Long-term survival benefits of coronary artery bypass grafting and percutaneous transluminal angioplasty in patients with coronary artery disease. *J Thorac Cardiovasc Surg* 111[5]: 1013-1025, 1996.)

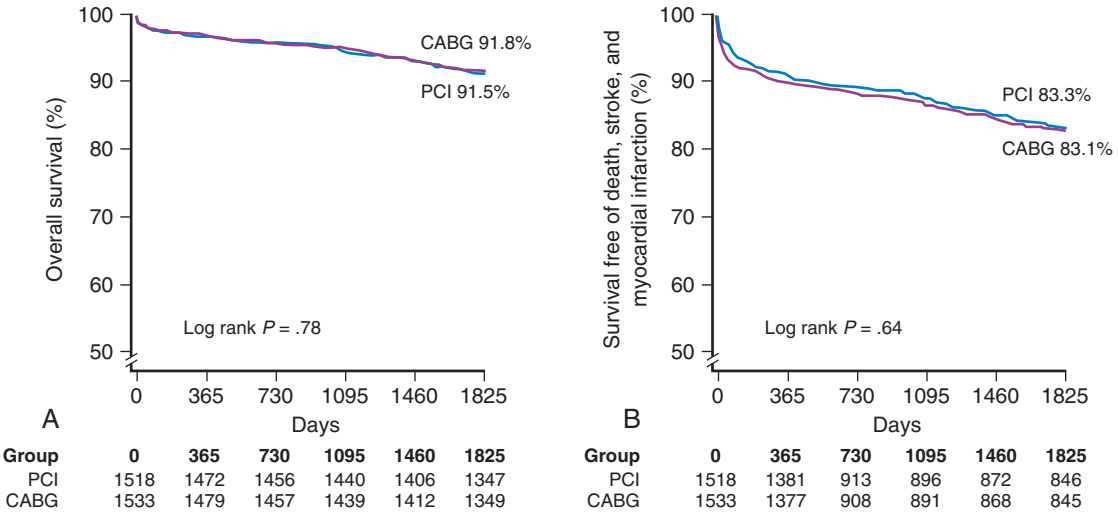
as, or better than, those with surgical revascularization. Historically, however, proximal LAD disease has been considered the purview of the surgeon, with randomized and registry data suggesting a survival advantage with surgery in this group (Fig. 18-10).[30] However, more recent meta-analytic studies[31,32] and 10-year follow-up of one randomized trial[33] have failed to confirm a survival benefit for CABG over PCI for the treatment of LAD disease in the modern era. As with other lesion subsets, a PCI-based strategy is associated with increased subsequent repeat revascularization, even with the routine application of coronary stents.[33]

Now of largely historic interest, the 1980s and 1990s saw the initiation and completion of several multicenter randomized trials to compare percutaneous transluminal coronary angioplasty (PTCA) with CABG in patients with multivessel disease. Among nearly 5000 patients with multivessel coronary disease amenable to either angioplasty or bypass surgery, no difference in death or MI, quality of life, or employment status was demonstrated in these trials; this suggests that the main disadvantage to a primary strategy of angioplasty was the increased need for repeat revascularization. PCI, then, was felt to be a reasonable initial revascularization choice in the setting of preserved ventricular function and technically favorable anatomy.[34] Retrospective database evaluations also confirmed the safety of both modes of revascularization in the majority of patients while documenting a gradient of benefit associated with PTCA or CABG that was dependent on, and correlated directly with, the extent and location of coronary stenoses (see Fig. 18-10).[30]

The evolution of surgical and percutaneous therapies, however, demands recurrent evaluation of comparative outcomes that utilize the best pharmacologic and revascularization practices. Contemporary studies of revascularization in patients with multivessel disease have compared a predominantly stent-based PCI strategy with contemporary surgical techniques, including the judicious use of internal thoracic arterial conduits. The equivalent prognostic impact of bare-metal stent (BMS) placement or CABG for the treatment of multivessel disease was confirmed in a pooled patient-level meta-analysis of 5-year data from 3051 patients enrolled in the Arterial Revascularization Therapies Study (ARTS); the Argentine Randomized Trial of Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients with Multivessel Disease (ERACI-II); the Medicine, Angioplasty, or Surgery Study for Multivessel Coronary Artery Disease (MASS-II); and Stent or Surgery (SoS) trials.[35] In this analysis, the 5-year cumulative incidences of death, MI, and stroke were similar among patients randomized to PCI with BMS compared with CABG (16.7% vs. 16.9%; HR, 1.04; 95% CI, 0.86 to 1.27; $P = .69$). Repeat revascularization, however, occurred significantly more often in patients assigned to PCI (29.0% vs. 7.9%; HR, 0.23; 95% CI, 0.18 to 0.29) compared with CABG, with a persistent separation of the curves over time (Fig. 18-11).

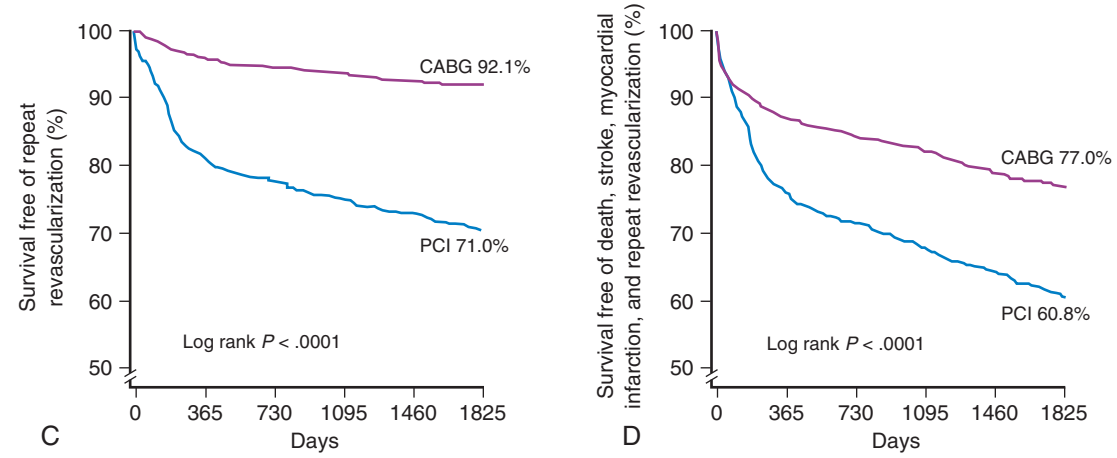
Given the comparable safety of stent-based PCI and CABG in the broad population of patients who present for multivessel revascularization, the further evolution of drug-eluting stent (DES) technology has provided the impetus for further comparative studies. Following the initial positive experience in nonrandomized historical comparisons of outcome after DES, the large Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) trial was initiated.[36] It randomized 1800 patients with three-vessel and/or left main CAD to paclitaxel-eluting stent placement or CABG. The trial was designed as an all-comers noninferiority trial to evaluate long-term outcomes in patients undergoing revascularization for severe CAD. Inclusion criteria comprised patients with previously untreated lesions of 50% or greater diameter stenosis with stable or unstable angina or atypical chest pain. If asymptomatic, patients were required to have positive evidence of myocardial ischemia. Exclusion criteria comprised previous PCI or CABG, acute MI, or the need for concomitant cardiac surgery. At 12 months, the primary end point of major cardiac and cerebrovascular events (MACCEs) was higher in the group of patients who underwent PCI (17.8% vs. 12.4%, $P = .002$), largely the result of an increased rate of repeat revascularization in the PCI arm (13.5% vs. 5.9%, $P < .001$) despite a mean of 4.6 stents (SD ± 2.3) placed per patient. The trial therefore failed to demonstrate noninferiority for paclitaxel stent-based PCI compared with CABG in this high-risk cohort, although the safety end points were reassuringly similar between groups. In fact, no difference was found between the PCI and CABG groups for the composite of all-cause death, MI, and stroke at 12 months (7.6% vs. 7.7%), and no difference was noted in the individual components of death and MI. However, an excess of stroke was noted after CABG compared with PCI (2.2% vs. 0.6%). By 5 years of follow-up, MACCE rates remained higher in patients randomized to PCI (37.3% vs. 26.9%, $P < .0001$) due primarily to a persistent excess of repeat revascularization (25.9% vs. 13.7%, $P < .0001$) but also to a newly apparent excess of MI (9.7% vs. 3.8%, $P < .0001$). Significantly, the differences in all-cause death (13.9% vs. 11.4%) and stroke (2.4% vs. 3.7%) were found to be statistically insignificant between PCI and CABG patients at 5-year follow-up.[37]

Because the SYNTAX trial failed to meet noninferiority for the primary MACCE end point at 1 year, additional analysis must be regarded as exploratory and hypothesis generating. Still, the available information regarding the high-risk subsets of patients with left main CAD and those with diabetes mellitus is of particular interest because both of these groups have historically done poorly with percutaneous revascularization. Among 705 patients with left main CAD in the SYNTAX trial,[38] 1-year MACCE rates were similar among the PCI- and CABG-treated groups (15.8% vs. 13.7%, $P = .44$), including similar rates of death (4.2% vs. 4.4%, $P = .24$) or MI (4.3% vs. 4.1%); however, as in the overall trial, the rate of stroke was higher in the CABG group



Group	0	365	730	1095	1460	1825
PCI	1518	1472	1456	1440	1406	1347
CABG	1533	1479	1457	1439	1412	1349

Group	0	365	730	1095	1460	1825
PCI	1518	1381	913	896	872	846
CABG	1533	1377	908	891	868	845



Group	0	365	730	1095	1460	1825
PCI	1518	1204	772	740	707	665
CABG	1533	1428	927	911	882	855

Group	0	365	730	1095	1460	1825
PCI	1518	1153	729	691	657	616
CABG	1533	1332	867	846	812	785

FIGURE 18-11 Kaplan-Meier 5-year event-free survival estimates from a pooled patient-level meta-analysis of revascularization with coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) with bare-metal stents. **A,** Overall survival. **B,** Survival free of stroke or myocardial infarction. **C,** Survival free of repeat revascularization. **D,** Survival free of major adverse cardiac and cerebrovascular events. (From Daemen J, Boersma E, Flather M, et al: Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation* 118[11]:1146-1154, 2008.)

than in the PCI group (2.7% vs. 0.3%, $P = .009$). When scored for anatomic complexity (see "Tools for Selection of Therapy" section), outcomes for those patients with low or intermediate SYNTAX scores were similar between the PCI and CABG groups. However, in patients in the highest tertile of SYNTAX score, adverse outcomes were significantly higher in those treated with PCI, driven primarily by increased requirements for repeat revascularization. Another exploratory analysis that involved patients with treated diabetes mellitus[39] demonstrated significantly higher event rates in patients undergoing PCI for left main CAD and/or three-vessel disease, related to a marked increase in the need for repeat revascularization in this group (20.3% vs. 6.4%, $P < .001$) at 1 year. Whereas outcomes were similar between treatment groups for both patients with and without diabetes mellitus in the lower tertiles of SYNTAX score, an excess mortality risk was observed in patients with diabetes mellitus in the highest SYNTAX tertile (≥33). The favorable outcomes for both patients with and without diabetes mellitus in the lower SYNTAX tertiles offer an opportunity for further evaluation of the safety and feasibility of PCI in these patient subgroups.

More recently, the Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial[40] has provided further insight into revascularization strategies in diabetic patients with multivessel coronary disease. In this trial, 1900 patients were randomized to PCI or CABG to evaluate the primary end point of all-cause mortality, nonfatal MI, or nonfatal stroke over a median follow-up period of 3.8 years. At 5 years, the primary outcome occurred more frequently in the PCI group compared with the CABG group (26.6% vs. 18.7%, $P = .005$). The benefit of CABG was driven by differences in rates of both MI ($P < .001$) and death from any cause ($P = .049$). Stroke was more frequent in the CABG group, with 5-year rates of 2.4% in the PCI group and 5.2% in the CABG group ($P = .03$). In a secondary analysis, between 6 months and 2 years following index revascularization, CABG provided greater improvements in health status measured by angina relief, physical function, and overall quality of life than treatment with PCI.[41] However, both revascularization strategies resulted in substantial and sustained improvements in quality of life and functional status, and the magnitude of benefit with CABG over PCI was modest. Beyond 2 years, no

difference was seen in health status assessments, in part due to the higher rate of repeat revascularization with PCI.

REVASCULARIZATION IN PATIENTS WITH SILENT ISCHEMIA

A primary goal of percutaneous revascularization is the control of medically refractory symptoms. However, in patients with asymptomatic myocardial ischemia, the only reasonable rationale for proceeding to revascularization is to improve prognosis through amelioration of the ischemic burden. Indeed, substantial evidence supports the prognostic hazard associated with silent myocardial ischemia, which may be present in 2% to 4% of the general population and travels in the company of numerous risk factors and markers of adverse outcome. Patients with diabetes mellitus, prior MI or ACS, chronic renal failure, sudden death episodes, and typical/atypical anginal symptoms may all exhibit evidence of asymptomatic myocardial ischemia on Holter monitor or exercise treadmill testing; prognosis may be impaired in these groups of patients. Unfortunately, it remains unclear when or in whom it is appropriate to screen for silent ischemia. The Detection of Ischemia in Asymptomatic Diabetics (DIAD) trial[42] was a randomized trial to assess the clinical impact of screening for CAD in asymptomatic adults with diabetes mellitus. The study enrolled 1123 patients, of whom 522 were randomly assigned to adenosine-stress radionuclide MPI and 562 to routine care and follow-up. Of the screening group, 22% had documented silent myocardial ischemia, and 6% exhibited a significant degree of ischemia. At 5-year follow-up, the overall cardiac event rate was 2.9% (0.6% per year) and was not significantly different between the screened group and the group that was not screened (2.7% vs. 3.0%, $P = .73$). Among the small group of patients who underwent initial screening and had a significant degree of demonstrable ischemia, event rates were significantly higher than in the overall population (2.4% per year vs. 0.4% per year, $P = .001$). This trial demonstrated the low yield associated with screening asymptomatic patients, even those with high clinical risk profiles. In addition, although this trial was not intended to evaluate the benefit of revascularization for asymptomatic ischemia and did not regulate additional diagnostic or therapeutic measures beyond protocol-specified nuclear stress imaging, the impact of screening was very minor. Perhaps most remarkable was the dynamic nature of the documented ischemia. At 3-year follow-up, 79% of the patients identified as having asymptomatic myocardial ischemia at baseline no longer exhibited evidence of ischemia, but 10% of patients without previously documented ischemia had an abnormal study during that time. Although the potential benefit of diagnostic strategies to evaluate for silent ischemia is unclear, very few data remain regarding the role of revascularization in patients with documented silent ischemia. The best inferential data for the potential prognostic benefit of revascularization in this clinical setting involve the documentation of an association between degree of myocardial ischemia and poor outcome. Zellweger and colleagues[43] identified just such an association among 3664 consecutive asymptomatic patients undergoing MPI. During an average of 1.9 years of follow-up, 38 patients suffered death or MI. Patients with greater degrees of ischemia at baseline had statistically greater event rates: patients who exhibited more than 7.5% ischemic myocardium suffered event rates in excess of 3% per year. Hachamovitch and colleagues[22] similarly followed 10,627 patients without a history of coronary disease who had undergone MPI. At a mean follow-up of nearly 2 years, cardiac death was observed in 1.4% of patients. These investigators discovered a statistically significant benefit associated with revascularization compared with OMT in patients with an ischemic burden approaching 10% or more of the myocardium, whereas OMT held the edge with lower levels of ischemia (see Fig. 18-8). The nuclear substudy of the COURAGE trial, discussed earlier,[19] also provides fascinating insight into the potential for amelioration of myocardial ischemia to affect outcome.

The most direct evidence of a potential role for revascularization in patients with asymptomatic ischemia was documented in the Asymptomatic Cardiac Ischemic Pilot (ACIP) trial.[44] In ACIP, 558 patients with coronary disease suitable for revascularization, silent ischemia on Holter monitor, and ischemia on exercise testing were randomized to medical treatment of angina, medical treatment of angina and ambulatory ischemic episodes, or revascularization. At both 1- and 2-year[25] follow-up, survival was best in the routine revascularization arm and was worst in the angina-guided arm, suggesting that amelioration of silent ischemia through prompt revascularization may provide important clinical benefit (Fig. 18-12). Unfortunately, further data in this regard have not been forthcoming, leaving physicians with as many questions as answers for the appropriate diagnostic and therapeutic strategies in patients suspected to suffer from silent ischemia.

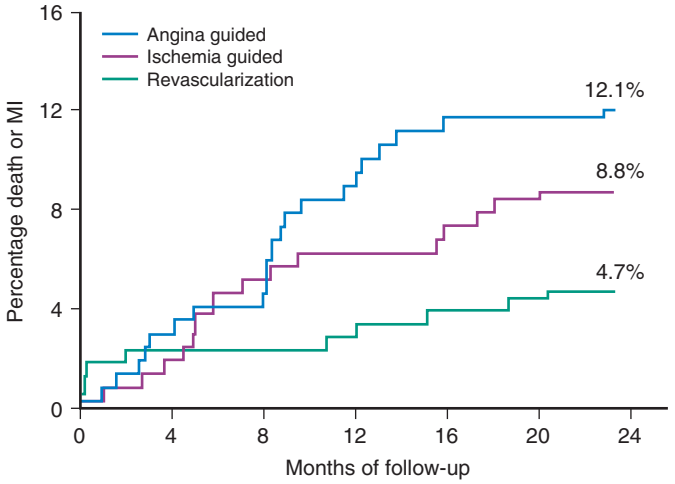


FIGURE 18-12 Two-year cumulative rates of death or myocardial infarction. Data are from 558 patients with ischemia on ambulatory monitoring and stress testing treated with revascularization, revascularization in the presence of documented ischemia, or angina-guided revascularization. The outcome of the planned revascularization strategy was significantly different from that of the angina-guided strategy, with a 61% relative risk reduction ($P < .01$). The 27% relative risk reduction between the angina-guided and ischemia-guided arms was not significant, nor was the difference between the revascularization and ischemia-guided strategies. (From Davies RF, Goldberg AD, Forman S, et al: Asymptomatic Cardiac Ischemia Pilot [ACIP] study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. *Circulation* 95[8]:2037-2043, 1997.)

TOOLS FOR SELECTION OF THERAPY

The growing number and scope of prospective trials on revascularization has provided an important objective structure to guide general discussion of treatment algorithms. However, revascularization decisions for individual patients continue to rely on the subjective "read" by practicing physicians of what is best for the patient. Beyond the essential institution of OMT and risk-factor modification programs for all patients, determination of whether to offer revascularization—and if so, what type—is often based on the subjective compilation of baseline clinical characteristics and presentation features. Factors such as anginal status, age, sex, and risk-factor profile provide important clues regarding the selection of optimal treatment. In addition, individual patient desires and experience, as well as the bias of treating physicians, play a significant role in shading discussions and ultimate treatment choice. Several comparative tools are now available to assist physicians and patients in discussing revascularization options. These tools provide guidance through the integration of certain anatomic,

functional, and/or baseline clinical components. Some scores, such as the Mayo Clinic risk score[45] and the National Cardiovascular Data Registry (NCDR) risk score,[46] were developed to aid in risk assessment after PCI, whereas others—such as the Society of Thoracic Surgeons (STS) score (see the online risk calculator at http://riskcalc.sts.org/STSWebRiskCalc273),[47] the EuroSCORE[48] (see the online risk calculator at www.euroscore.org/calc.html), and the age, creatinine, and ejection fraction (ACEF)[49] score—have been validated as independent predictors of adverse events in patients undergoing CABG. Although several of these scores have subsequently been evaluated for prognostic ability in patients who present for either PCI or CABG,[38,49,50] they have not proved useful in determining optimal treatment selection. The SYNTAX score,[51] on the other hand, was developed to provide prognostic information regarding outcome after either PCI or CABG in patients with multivessel disease based on the functional impact of angiographically documented coronary disease. The SYNTAX score is a quantitative score that provides a cumulative measure of the extent and complexity of angiographically evident CAD, taking into account the number, location, and characteristics of lesions identified angiographically, as well as the extent of myocardium subserved. Among patients with three-vessel and/or left main CAD randomized in the SYNTAX trial,[36] those who were treated with paclitaxel-eluting stent PCI exhibited increasing MACCE rates at 2 years in direct relationship to increased disease complexity as defined by the baseline SYNTAX score. This effect was not identified in patients treated with an initial strategy of CABG. Although MACCE rates were not statistically different between patients treated in the PCI or CABG arms when the baseline SYNTAX score was low (0 to 22) or intermediate (23 to 32), patients with high SYNTAX scores (>32) experienced lower MACCE rates when treated with CABG compared with those who underwent PCI.[52] Because the SYNTAX score has not shown discriminative ability for risk prognostication among patients undergoing CABG, a mode of revascularization less affected by the complexity of disease, the primary impact of this score is to aid in the identification of patients at undue risk for MACCE after PCI who might therefore benefit from treatment with CABG. Whether incorporation of additional clinical demographics into the SYNTAX model enhances the discriminative value and risk prediction is a focus of ongoing study.[53]

Risk scores can provide statistical insight into the population-based risks associated with percutaneous or surgical revascularization, but they are unable to identify specific risks for an individual patient. To provide additional assistance in risk stratification and treatment selection, some national bodies have recently undertaken an initiative to provide guidance through the publication of appropriateness criteria. These documents are essentially an extension of evidence-based guideline documents and serve to fill the gap between known scientific findings and individual patient variability. In the case of the American College of Cardiology Foundation (ACCF)/Society for Cardiovascular Angiography and Interventions (SCAI)/Society of Thoracic Surgeons (STS)/American Association for Thoracic Surgery (AATS)/American Heart Association (AHA)/and American Society of Nuclear Cardiology (ASNC) 2009 Appropriateness Criteria for Coronary Revascularization,[20,54] nominated technical panelists use a compendium of currently available evidence and current consensus to evaluate the likely benefit and risk associated with revascularization across a broad range of specific patient subtypes. These scenarios are rated on a scale of 1 to 9, first by individual panelists and then collectively. After final review, each scenario is scored as either *appropriate* (scores 7 to 9: revascularization is generally acceptable and reasonable and is likely to improve the patient's outcome), *uncertain* (scores 4 to 6: revascularization may be acceptable or reasonable, but further research is necessary for this patient scenario), or *inappropriate* (scores 1 to 3: revascularization is not generally accepted or reasonable in this situation and is unlikely to provide prognostic or clinical benefit). In this way, recommendations found in the appropriateness criteria can facilitate discussions with patients, family, and members of the medical team regarding the likely benefits of revascularization strategies (Figs. 18-13 through 18-16).

Low-Risk Findings on Noninvasive Study							Asymptomatic					
Symptoms **Med. Rx**							**Stress Test** **Med. Rx**					
Class III or IV Max Rx	U	A	A	A	A		High Risk Max Rx	U	A	A	A	A
Class I or II Max Rx	U	U	A	A	A		High Risk No/min Rx	U	U	A	A	A
Asymptomatic Max Rx	I	I	U	U	U		Int. Risk Max Rx	U	U	U	U	A
Class III or IV No/min Rx	I	U	A	A	A		Int. Risk No/min Rx	I	I	U	U	A
Class I or II No/min Rx	I	I	U	U	U		Low Risk Max Rx	I	I	U	U	U
Asymptomatic No/min Rx	I	I	U	U	U		Low Risk No/min Rx	I	I	U	U	U
Coronary Anatomy	CTO of 1 vz.; no other disease	1-2 vz. disease; no prox. LAD	1 vz. disease of prox. LAD	2 vz. disease with prox. LAD	3 vz. disease; no left main		**Coronary Anatomy**	CTO of 1 vz.; no other disease	1-2 vz. disease; no prox. LAD	1 vz. disease of prox. LAD	2 vz. disease with prox. LAD	3 vz. disease; no left main

FIGURE 18-13 Appropriateness ratings for asymptomatic patients without prior coronary bypass with low-risk findings on noninvasive imaging study. *A,* Appropriate; *CTO,* chronic total occlusion; *I,* inappropriate; *Int.,* intermediate; *Max,* maximum; *Med.,* medical; *min,* minimum; *prox. LAD,* proximal left anterior descending artery; *Rx,* treatment; *U,* uncertain; *vz.,* vessel. (From Patel MR, Dehmer GJ, Hirshfeld JW, et al: ACCF/SCAI/STS/AATS/AHA/ASNC 2009 appropriateness criteria for coronary revascularization: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology: endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *Circulation* 119[9]:1330-1352, 2009.)

Intermediate-Risk Findings on Noninvasive Study							CCS Class I or II Angina						
Symptoms **Med. Rx**							**Stress Test** **Med. Rx**						
Class III or IV Max Rx	A	A	A	A	A		High Risk Max Rx	A	A	A	A	A	
Class I or II Max Rx	U	A	A	A	A		High Risk No/min Rx	U	A	A	A	A	
Asymptomatic Max Rx	U	U	U	U	A		Int. Risk Max Rx	U	A	A	A	A	
Class III or IV No/min Rx	U	U	A	A	A		Int. Risk No/min Rx	U	U	U	A	A	
Class I or II No/min Rx	U	U	U	A	A		Low Risk Max Rx	U	U	A	A	A	
Asymptomatic No/min Rx	I	I	U	U	A		Low Risk No/min Rx	I	I	U	U	U	
Coronary Anatomy	CTO of 1 vz.; no other disease	1-2 vz. disease; no prox. LAD	1 vz. disease of prox. LAD	2 vz. disease with prox. LAD	3 vz. disease; no left main		**Coronary Anatomy**	CTO of 1 vz.; no other disease	1-2 vz. disease; no prox. LAD	1 vz. disease of prox. LAD	2 vz. disease with prox. LAD	3 vz. disease; no left main	

FIGURE 18-14 Appropriateness ratings for patients without prior coronary bypass with intermediate-risk findings on noninvasive imaging study and Canadian Cardiovascular Society (CCS) class I or II angina. *A,* Appropriate; *CTO,* chronic total occlusion; *I,* inappropriate; *Int.,* intermediate; *Max,* maximum; *Med.,* medical; *min,* minimum; *prox. LAD,* proximal left anterior descending artery; *Rx,* treatment; *U,* uncertain; *vz.,* vessel. (From Patel MR, Dehmer GJ, Hirshfeld JW, et al: ACCF/SCAI/STS/AATS/AHA/ASNC 2009 appropriateness criteria for coronary revascularization: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology: endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *Circulation* 119[9]:1330-1352, 2009.)

High-Risk Findings on Noninvasive Study							CCS Class III or IV Angina						
Symptoms **Med. Rx**							**Stress Test** **Med. Rx**						
Class III or IV Max Rx	A	A	A	A	A		High Risk Max Rx	A	A	A	A	A	
Class I or II Max Rx	A	A	A	A	A		High Risk No/min Rx	A	A	A	A	A	
Asymptomatic Max Rx	U	A	A	A	A		Int. Risk Max Rx	A	A	A	A	A	
Class III or IV No/min Rx	A	A	A	A	A		Int. Risk No/min Rx	U	U	A	A	A	
Class I or II No/min Rx	U	A	A	A	A		Low Risk Max Rx	U	A	A	A	A	
Asymptomatic No/min Rx	U	U	A	A	A		Low Risk No/min Rx	I	U	A	A	A	
Coronary Anatomy	CTO of 1 vz.; no other disease	1-2 vz. disease; no prox. LAD	1 vz. disease of prox. LAD	2 vz. disease with prox. LAD	3 vz. disease; no left main		**Coronary Anatomy**	CTO of 1 vz.; no other disease	1-2 vz. disease; no prox. LAD	1 vz. disease of prox. LAD	2 vz. disease with prox. LAD	3 vz. disease; no left main	

FIGURE 18-15 Appropriateness ratings for patients without prior coronary bypass with high-risk findings on noninvasive imaging study and Canadian Cardiovascular Society (CCS) class III or IV angina. *A,* Appropriate; *CTO,* chronic total occlusion; *I,* inappropriate; *Int.,* intermediate; *Max,* maximum; *Med.,* medical; *min,* minimum; *prox. LAD,* proximal left anterior descending artery; *Rx,* treatment; *U,* uncertain; *vz.,* vessel. (From Patel MR, Dehmer GJ, Hirshfeld JW, et al: ACCF/SCAI/STS/AATS/AHA/ASNC 2009 appropriateness criteria for coronary revascularization: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology: Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *Circulation* 119[9]:1330-1352, 2009.)

	CABG			PCI		
	No diabetes and normal LVEF	Diabetes	Depressed LVEF	No diabetes and normal LVEF	Diabetes	Depressed LVEF
Two-vessel coronary artery disease with proximal LAD stenosis	A	A	A	A	A	A
Three-vessel coronary artery disease	A	A	A	U	U	U
Isolated left main stenosis	A	A	A	I	I	I
Left main stenosis and additional coronary artery disease	A	A	A	I	I	I

FIGURE 18-16 Appropriateness rating of specific method of revascularization in patients with advanced coronary artery disease deemed to be revascularization candidates. *A,* Appropriate; *CABG,* coronary artery bypass grafting; *I,* inappropriate; *LAD,* left anterior descending artery; *LVEF,* left ventricular ejection fraction; *PCI,* percutaneous coronary intervention; *U,* uncertain. (From Patel MR, Dehmer GJ, Hirshfeld JW, et al: ACCF/SCAI/STS/AATS/AHA/ASNC 2009 appropriateness criteria for coronary revascularization: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology: Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *Circulation* 119[9]:1330-1352, 2009.)

SUMMARY

Symptomatic CAD is a growing problem throughout the world, with significant associated economic and societal costs. Although there is presently no cure for ischemic CAD, it is increasingly possible to alter the course of the disease through judicious utilization of the rapidly evolving medical, surgical, and percutaneous therapies currently available. Successful disease management and symptom palliation can be achieved by a robust regimen based on optimal medical management and risk-factor modification through diet and exercise. Percutaneous revascularization also plays an important role in achieving improved quality of life and, ultimately, prognosis. Indeed, percutaneous revascularization can effectively modulate long-term outcome directly through a reduction of ischemic burden, as well as indirectly through symptom control and improved exercise tolerance. As percutaneous technology continues to evolve, which it surely will, promising new indications will be discovered and added to the ever-expanding list of beneficial effects. In the setting of rising health care costs and the economic realities of delivering a finite resource, however, efforts to establish and clarify the most appropriate revascularization strategies and candidates will ensure the continued availability of these techniques to an ever-growing population of those who may benefit.

REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, et al: Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation* 123(4):e18–e209, 2011.
2. Ford ES, Ajani UA, Croft JB, et al: Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med* 356(23): 2388–2398, 2007.
3. Gibbons RJ, Abrams J, Chatterjee K, et al: ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *Circulation* 107:149–158, 2003.
4. Bonetti PO, Holmes DR, Lerman A, et al: Enhanced external counterpulsation for ischemic heart disease. What's behind the curtain? *J Am Coll Cardiol* 41(11):1918–1925, 2003.
5. Katritsis DG, Ioannidis JPA: Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. *Circulation* 111(22):2906–2912, 2005.
6. Barsness GW, Gersh BJ, Brooks MM, et al: Rationale for the revascularization arm of the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. *Am J Cardiol* 97(12, Suppl 1):31–40, 2006.
7. Mahn-Won P, Ki-Bae S, Pum-Joon K, et al: Long-term percutaneous coronary intervention rates and associated independent predictors for progression of nonintervened nonculprit coronary lesions. *Am J Cardiol* 104(5):648–652, 2009.
8. Stone GW, Maehara A, Lansky AJ, et al: A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 364(3): 226–235, 2011.
9. Wijeysundera HC, Nallamothu BK, Krumholz HM, et al: Meta-analysis: effects of percutaneous coronary intervention versus medical therapy on angina relief. *Ann Intern Med* 152(6):370–379, 2010.
10. Boden WE, O'Rourke RA, Teo KK, et al: Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 356(15):1503–1516, 2007.
11. Hochman JS, Lamas GA, Buller CE, et al: Coronary intervention for persistent occlusion after myocardial infarction. *N Engl J Med* 355(23):2395–2407, 2006.
12. Weintraub WS, Spertus JA, Kolm P, et al: Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med* 359(7):677–687, 2008.
13. Schömig A, Mehilli J, de Waha A, et al: A meta-analysis of 17 randomized trials of a percutaneous coronary intervention-based strategy in patients with stable coronary artery disease. *J Am Coll Cardiol* 52(11):894–904, 2008.
14. Jeremias A, Kaul S, Rosengart TK, et al: The impact of revascularization on mortality in patients with nonacute coronary artery disease. *Am J Med* 122(2):152–161, 2009.
15. Trikalinos TA, Alsheikh-Ali AA, Tatsioni A, et al: Percutaneous coronary interventions for non-acute coronary artery disease: a quantitative 20-year synopsis and a network meta-analysis. *Lancet* 373(9667):911–918, 2009.
16. Daly CA, De Stavola B, Sendon JL, et al: Predicting prognosis in stable angina—results from the Euro heart survey of stable angina: prospective observational study. *BMJ* 332(7536):262–267, 2006.
17. Hjemdahl P, Eriksson SV, Held C, et al: Favourable long term prognosis in stable angina pectoris: an extended follow up of the angina prognosis study in Stockholm (APSIS). *Heart* 92(2):177–182, 2006.
18. Barsness GW: Managing the patient with severe left ventricular dysfunction. In Ellis SG, Holmes DR, Jr, editors: *Strategic approaches in coronary intervention*, ed 3, Philadelphia, 2006, Lippincott, Williams & Wilkins, pp 407–423.
19. Shaw LJ, Berman DS, Maron DJ, et al: Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 117(10):1283–1291, 2008.
20. Patel MR, Dehmer GJ, Hirshfeld JW, et al: ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: A report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology: endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *Circulation* 119(9):1330–1352, 2009.
21. Smith PK, Califf RM, Tuttle RH, et al: Selection of surgical or percutaneous coronary intervention provides differential longevity benefit. *Ann Thorac Surg* 82(4):1420–1429, 2006.
22. Hachamovitch R, Hayes SW, Friedman JD, et al: Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 107(23): 2900–2907, 2003.
23. Maron DJ, Boden WE, O'Rourke RA, et al: Intensive multifactorial intervention for stable coronary artery disease: optimal medical therapy in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial. *J Am Coll Cardiol* 55(13):1348–1358, 2010.
24. Steinberg BA, Steg PG, Bhatt DL, et al: Comparisons of guideline-recommended therapies in patients with documented coronary artery disease having percutaneous coronary intervention versus coronary artery bypass grafting versus medical therapy only (from the REACH International Registry). *Am J Cardiol* 99(9): 1212–1215, 2007.
25. Davies RF, Goldberg AD, Forman S, et al: Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. *Circulation* 95(8):2037–2043, 1997.
26. The BARI 2D Study Group: A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 360(24): 2503–2515, 2009.
27. Chaitman BR, Hardison RM, Adler D, et al: The Bypass Angioplasty Revascularization Investigation 2 Diabetes randomized trial of different treatment strategies in type 2 diabetes mellitus with stable ischemic heart disease: impact of treatment strategy on cardiac mortality and myocardial infarction. *Circulation* 120(25):2529–2540, 2009.
28. Sarno G, Garg S, Onuma Y, et al: Impact of completeness of revascularization on the five-year outcome in percutaneous

coronary intervention and coronary artery bypass graft patients (from the ARTS-II Study). *Am J Cardiol* 106(10):1369–1375, 2010.
29. Hannan EL, Racz M, Holmes DR, et al: Impact of completeness of percutaneous coronary intervention revascularization on long-term outcomes in the stent era. *Circulation* 113(20):2406–2412, 2006.
30. Jones RH, Kesler K, Phillips HR, 3rd, et al: Long-term survival benefits of coronary artery bypass grafting and percutaneous transluminal angioplasty in patients with coronary artery disease. *J Thorac Cardiovasc Surg* 111(5):1013–1025, 1996.
31. Aziz O, Rao C, Panesar SS, et al: Meta-analysis of minimally invasive internal thoracic artery bypass versus percutaneous revascularisation for isolated lesions of the left anterior descending artery. *BMJ* 334(7594):617, 2007.
32. Kapoor JR, Gienger AL, Ardehali R, et al: Isolated disease of the proximal left anterior descending artery: comparing the effectiveness of percutaneous coronary interventions and coronary artery bypass surgery. *JACC Cardiovasc Interv* 1(5):483–491, 2008.
33. Goy J-J, Kaufmann U, Hurni M, et al: 10-year follow-up of a prospective randomized trial comparing bare-metal stenting with internal mammary artery grafting for proximal, isolated de novo left anterior coronary artery stenosis: the SIMA (Stenting versus Internal Mammary Artery grafting) Trial. *J Am Coll Cardiol* 52(10):815–817, 2008.
34. Barsness GW, Holmes DR, Jr, Gersh BJ: Integrated management of patients with diabetes mellitus and ischemic heart disease: PCI, CABG, and medical therapy. *Curr Probl Cardiol* 30(11):583–617, 2005.
35. Daemen J, Boersma E, Flather M, et al: Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation* 118(11): 1146–1154, 2008.
36. Serruys PW, Morice M-C, Kappetein AP, et al: Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 360(10):961–972, 2009.
37. Mohr FW, Morice M-C, Kappetein AP, et al: Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical Syntax trial. *Lancet* 381(9867):629–638, 2013.
38. Morice MC, Serruys PW, Kappetein AP, et al: Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation* 121(24):2645–2653, 2010.
39. Banning AP, Westaby S, Morice M-C, et al: Diabetic and nondiabetic patients with left main and/or 3-vessel coronary artery disease: comparison of outcomes with cardiac surgery and paclitaxel-eluting stents. *J Am Coll Cardiol* 55(11):1067–1075, 2010.
40. FREEDOM Trial Investigators: Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 367(25):2375–2384, 2012.
41. Abdallah MS, Wang K, Magnuson EA, et al: Quality of life after PCI vs CABG among patients with diabetes and multivessel coronary artery disease: a randomized clinical trial. *JAMA* 310(15): 1581–1590, 2013.
42. Young LH, Wackers FJ, Chyun DA, et al: Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes. *JAMA* 301(15):1547–1555, 2009.
43. Zellweger M, Hachamovitch R, Kang X, et al: Threshold, incidence, and predictors of prognostically high-risk silent ischemia in asymptomatic patients without prior diagnosis of coronary artery disease. *J Nucl Cardiol* 16(2):193–200, 2009.
44. Rogers WJ, Bourassa MG, Andrews TC, et al: Asymptomatic Cardiac Ischemia Pilot (ACIP) study: outcome at 1 year for patients with asymptomatic cardiac ischemia randomized to medical therapy or revascularization. *J Am Coll Cardiol* 26(3): 594–605, 1995.
45. Singh M, Rihal CS, Lennon RJ, et al: Bedside estimation of risk from percutaneous coronary intervention: the New Mayo Clinic risk scores. *Mayo Clin Proc* 82(6):701–708, 2007.
46. Peterson ED, Dai D, DeLong ER, et al: Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. *J Am Coll Cardiol* 55(18):1923–1932, 2010.
47. Edwards F, Clark R, Schwartz M: Coronary artery bypass grafting: the Society of Thoracic Surgeons National Database experience. *Ann Thorac Surg* 57(1):12–19, 1994.
48. Nashef SA, Roques F, Michel P, et al: European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 16(1):9–13, 1999.
49. Ranucci M, Castelvecchio S, Menicanti L, et al: Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. *Circulation* 119(24):3053–3061, 2009.
50. Singh M, Gersh BJ, Li S, et al: Mayo Clinic risk score for percutaneous coronary intervention predicts in-hospital mortality in patients undergoing coronary artery bypass graft surgery. *Circulation* 117(3):356–362, 2008.
51. Sianos G, Morel MA, Kappetein AP, et al: The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 1(2):219–227, 2005.
52. Mohr FW, Rastan AJ, Serruys PW, et al: Complex coronary anatomy in coronary artery bypass graft surgery: Impact of complex coronary anatomy in modern bypass surgery? Lessons learned from the SYNTAX trial after two years. *J Thorac Cardiovasc Surg* 141(1):130–140, 2011.
53. Farooq V, van Klaveren D, Steyerberg EW, et al: Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 381(9867):639–650, 2013.
54. Patel MR, Dehmer GJ, Hirshfeld JW, et al: ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 59(9):857–881, 2012.

19 Percutaneous Intervention for Non–ST-Segment Elevation Acute Coronary Syndromes

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KEY POINTS

- Risk assessment at admission is vitally important and should be repeated during hospitalization.
- Patients presenting with hemodynamic instability, severe left ventricular dysfunction or overt heart failure, recurrent or persistent rest angina despite intensive medical therapy, mechanical complications, and those with significant electrical instability are deemed to be at extremely high risk for death or a complicated myocardial infarction and should undergo urgent coronary angiography.
- Stable patients are managed by one of two strategies: an early invasive strategy and an ischemia-guided strategy.
- An early invasive strategy is recommended for high-risk patients. This includes intensive medical therapy followed by coronary angiography and revascularization as appropriate.
- An ischemia-guided strategy is recommended for low- or intermediate-risk patients. Patients are treated with medical therapy unless they develop refractory or recurrent ischemia or hemodynamic instability.
- When drug-eluting stents are used for revascularization in non–ST-elevation acute coronary syndrome (NSTE-ACS), aspirin should be continued indefinitely. In addition, dual antiplatelet therapy consisting of clopidogrel, prasugrel, or ticagrelor should be continued for 1 year.

Over the past 33 years, percutaneous coronary intervention (PCI) has evolved from a somewhat tenuous and experimental procedure to a durable and mainstream therapy, and as a result, the clinical indications for PCI have broadened to include patients with both stable angina pectoris and acute coronary syndrome (ACS).[1-3]

Acute coronary syndrome refers to the spectrum of clinical signs and symptoms that occur as a result of acute myocardial ischemia, and it is classified as an NSTE-ACS or as an ST-segment–elevation ACS (STE-ACS). NSTE-ACS includes patients with unstable angina (UA, negative cardiac biomarkers) or non–ST-segment elevation myocardial infarction (NSTEMI, positive cardiac biomarkers), and STE-ACS includes patients with ST-segment–elevation myocardial infarction (STEMI).[4] Over the last 10 years, the incidence rates of STEMI have decreased significantly, and STEMI now makes up less than one third of all MIs in the United States. Thus NSTE-ACS currently accounts for over two-thirds of all acute coronary syndromes.[5] Various strategies have been proposed for the management of NSTE-ACS patients, and more recent guidelines and clinical trials increasingly support an invasive strategy for high-risk ACS patients and a less invasive, more conservative strategy for patients deemed to be at lower risk.[6]

In this chapter, we discuss PCI for patients with NSTE-ACS and focus on the pathophysiology, risk stratification, adjunctive treatment during PCI, early invasive versus ischemia-guided strategy, and the most recent American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of patients with NSTE-ACS.[7]

BACKGROUND AND RATIONALE FOR PERCUTANEOUS CORONARY INTERVENTION IN PATIENTS WITH NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

Coronary atherosclerosis is a chronic disease in which atheromatous material generally evolves silently over time and may eventually result in the development of a high-risk (i.e., vulnerable) plaque (Fig. 19-1).[8] Rupture or erosion of this high-risk plaque triggers the formation of intracoronary thrombosis, which can lead to a critical stenosis or occlusion of the coronary artery, as well as associated vasospasm. Although the initial stenosis may evolve silently, healing of a ruptured or eroded plaque may lead to more rapid progression of the stenosis; this may remain clinically silent or may cause angina pectoris. Thus ACS may present with different clinical presentations: UA, NSTEMI, STEMI, and sudden death. All ACS clinical manifestations share a common pathophysiologic pathway—plaque rupture/erosion and some degree of thrombosis and vasoconstriction—but the duration (i.e., transient or permanent) and severity (i.e., subtotal or total coronary occlusion) are different and are either associated with myocardial necrosis (STEMI and NSTEMI) or without myocardial necrosis (UA) as manifest by negative cardiac biomarkers. It is important to note that within the first few months after an initial episode of coronary instability, the tendency is strong for repeat instability caused by progression in the severity of the culprit stenosis or by progression of remote lesions.

Although plaque rupture or erosion with associated thrombosis is the most common cause of ACS, it may also be caused by dynamic obstruction (i.e., Prinzmetal's angina or vasospasm secondary to drug abuse), spontaneous coronary artery dissection (most commonly occurring in peripartum women), severe coronary narrowing without thrombus or spasm (i.e., advanced progressive atherosclerosis or severe restenosis from prior PCI), or a precipitating condition extrinsic to the coronary circulation (i.e., fever, sepsis, tachycardia, hypotension, anemia, hypoxemia, etc.).[6] Thus when evaluating individual patients with ACS, it is important to consider the most likely etiology, especially if an invasive strategy is being considered, given that PCI is not necessarily an appropriate therapy for all causes of ACS.

Patients with NSTE-ACS have long-term outcomes similar to patients with STE-ACS and worse than patients with UA.[9] NSTE-ACS patients have a similar prognosis to STE-ACS patients likely due to a high prevalence of multivessel disease as well as a higher incidence of recurrent ischemia (35% vs. 23% at 1 year in the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes [GUSTO-IIb] trial).[9] The optimal management of UA or NSTEMI, therefore, is twofold: immediate relief of ischemia and the prevention of progression to acute MI or cardiac death. This can be achieved by a combination of antiischemic, antiplatelet, and antithrombotic therapies with or without PCI (see Fig. 19-1).

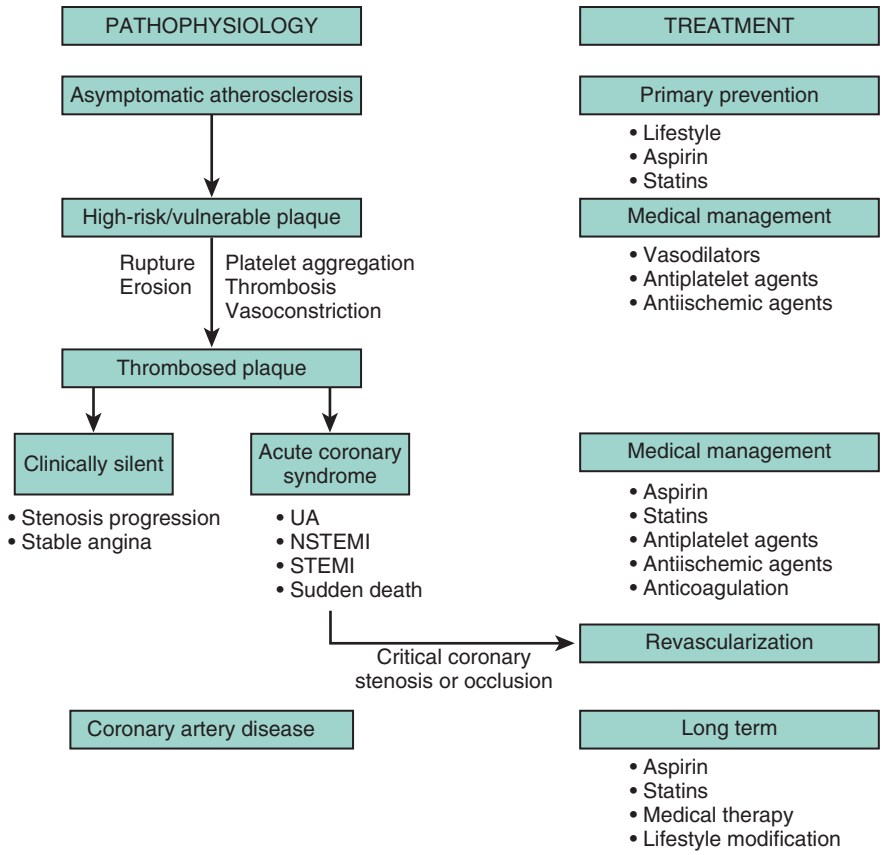


FIGURE 19-1 Physiopathologic mechanisms underlying acute coronary syndromes. *ACE,* Angiotensin-converting enzyme; *CABG,* coronary artery bypass grafting; *NSTEMI,* non–ST-segment elevation myocardial infarction; *PCI,* percutaneous coronary intervention; *STEMI,* ST-segment–elevation myocardial infarction; *UA,* unstable angina.

Risk Stratification

Although risks of individual patients who present with NSTE-ACS vary widely, several risk scores have been devised to risk-stratify patients, and help identify those who may benefit from an early invasive strategy. The Thrombolysis in Myocardial Infarction (TIMI) risk score, which predicts the risk of 14-day all-cause mortality and new or recurrent MI, is a validated risk-prediction model based on data from the TIMI-IIB and Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) trials and is the system most commonly used. Seven variables at presentation were independently predictive of outcome (Fig. 19-2):[10]

1. Age 65 years or older
2. At least two anginal events over the previous 24 hours
3. ST-segment deviation
4. Elevated serum cardiac markers
5. Three or more risk factors for coronary artery disease
6. Aspirin use within the previous week
7. Known history of CAD (stenosis >50%)

The Global Registry of Acute Coronary Events (GRACE) developed a risk calculator for bedside risk estimation of 6-month mortality for patients after hospitalization for ACS.[11] The overall 6-month mortality rate was 4.8%, and nine predictive variables were identified (Fig. 19-3, *A* and *B*):

1. Older age
2. Previous MI
3. History of heart failure
4. Increased heart rate
5. Lower systolic blood pressure

- Age ≥65 yr
- ≥2 anginal events in 24 hours
- ST-segment deviation
- Elevated serum cardiac markers
- ≥3 risk factors for CAD
- Aspirin use (prior 7 days)
- Prior coronary stenosis (>50%)

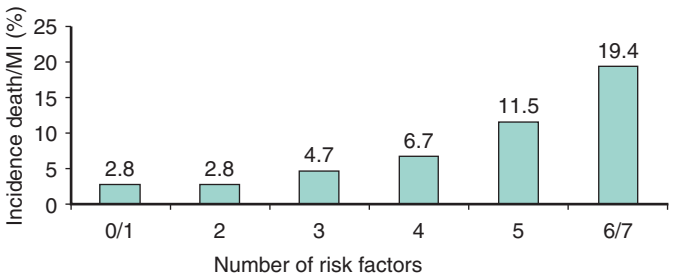


FIGURE 19-2 The Thrombolysis in Myocardial Infarction (TIMI) risk score for death or myocardial infarction (MI) at 14 days, derived by assigning a value of 0 when a factor is absent and 1 when a factor is present. *CAD,* Coronary artery disease.

1. Age
Years
30–39 0
40–49 18
50–59 36
60–69 55
70–79 73
80–89 91
≥90 100

2. History of congestive heart failure 24

3. History of myocardial infarction 12

4. Resting heart rate
Beats/min
50–70 3
70–90 9
90–110 14
110–150 23
150–200 35
≥200 43

5. Systolic blood pressure
mm Hg
≤79.9 24
80–99.9 22
100–120 18
120–140 14
140–160 10
160–200 4
≥200 0

6. ST-segment
Depression 11

7. Initial serum creatinine
mg/dL
0–0.39 1
0.4–0.79 3
0.8–1.19 5
1.2–1.59 7
1.6–1.99 9
2.3–3.99 15
≥4 20

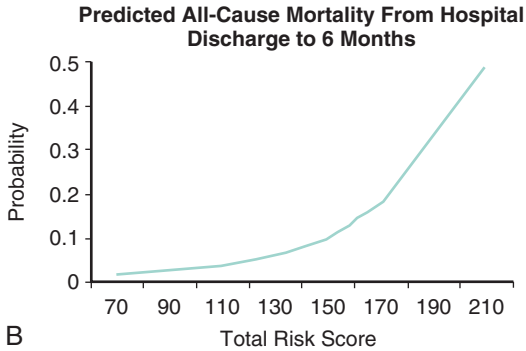
8. Elevated cardiac enzymes 15

9. No in-hospital percutaneous coronary intervention 14

A

Points
1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____

Total risk score _____ (Sum of points)
Mortality risk _____ (From plot)



B

FIGURE 19-3 **A,** The Grace Registry developed a risk calculator for bedside risk estimation of 6-month mortality in patients after hospitalization for acute coronary syndrome. Points assigned for each of the nine criteria are in the right-hand column. **B,** Plot of predicted all-cause mortality.

6. Serum creatinine level
7. Elevated levels of cardiac biomarkers
8. ST-segment depression
9. No PCI

The presence of elevated cardiac biomarkers is a particularly important prognostic indicator that has been associated with an increased risk for reinfarction and death (discussed further below). It is important to note that although determination of patient risk is vitally important upon initial presentation with NSTE-ACS, individual patient risk often changes during hospitalization; therefore it should be frequently reassessed.

PREDICTING A LATE POSITIVE SERUM TROPONIN LEVEL IN INITIALLY TROPONIN-NEGATIVE PATIENTS WITH NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

A limitation of the use of the TIMI risk score in identifying patients at higher risk who present with NSTE-ACS is that some patients may initially present with negative cardiac biomarkers, only to demonstrate elevation in these markers 12 hours later. Of 1342 patients who were enrolled in the TIMI-IIIB trial, 200 (14.9%) were troponin negative at baseline but developed an elevated troponin I level (≥0.4 ng/mL) at 12 hours.[12] Six independent predictors were identified (Table 19-1), and a score was derived to identify patients with the highest likelihood to become troponin positive later during hospital admission (Fig. 19-4). The derived score was tested in 855 patients in the GUSTO IIa study and similarly predicted a late rise in troponin T levels. This score, therefore, may be useful to further assist in risk stratification of patients who present with NSTE-ACS and initially unremarkable troponin levels.

TABLE 19-1 Predictors of Late Troponin Level Rise in Initially Troponin-Negative Patients

Predictor*	Odds Ratio	95% Confidence Interval	*P* Value
ST-segment deviation	3.52	2.38 to 5.23	<.001
Presentation within 8 hours from symptom onset	2.91	1.92 to 4.40	<.001
No prior percutaneous coronary intervention	2.88	1.54 to 5.39	.001
No prior beta-blockade	1.74	1.15 to 2.63	.008
Unheralded angina	1.65	1.12 to 2.42	.01
History of myocardial infarction	1.59	1.06 to 2.37	.02

From Januzzi J, Newby L, Murphy S, et al: Predicting a late positive serum troponin in initially troponin-negative patients with non-ST-elevation acute coronary syndrome: clinical predictors and validated risk score results from the TIMI IIIB and GUSTO IIA studies. *Am Heart J* 151(2):360-366, 2006.
*Late is defined as 12 hours or more.

ADJUNCTIVE TREATMENT DURING PERCUTANEOUS CORONARY INTERVENTION FOR NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

Antiplatelet Treatment

Aspirin

The activation and aggregation of platelets after the rupture of a vulnerable plaque are key components in the pathophysiology of ACS. Aspirin inhibits the cyclooxygenase (COX) pathway in platelets and in the

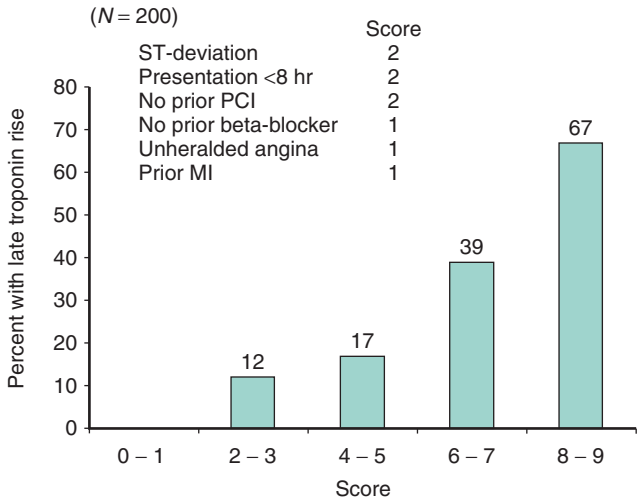


FIGURE 19-4 The TIMI-IIIB score used to identify patients who become troponin-positive later during hospital admission. *MI,* Myocardial infarction; *PCI,* percutaneous coronary intervention.

endothelium, which prevents thromboxane A2 (TXA_2) production and therefore inhibits platelet aggregation.[13,14] Because COX-1 inhibition is irreversible, the antiplatelet effects of aspirin last through the entire lifetime of the platelets (7 to 10 days). Multiple studies have shown the benefit of aspirin therapy in CAD with reduction in angina, death, and MI by 30%.[15,16] In the setting of NSTE-ACS, the ACC/AHA guidelines recommend an initial loading dose of at least 162 mg in order to achieve an immediate clinical antithrombotic effect; thereafter a maintenance dose of 81 mg aspirin daily is sufficient for cardioprotection. Higher doses of aspirin have not been shown to have added cardiovascular benefit and are associated with higher risks of bleeding.[15,16]

The Seventh Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-7) trial randomized 25,086 patients with ACS undergoing an early invasive strategy (70.8% with UA/NSTE-ACS) to low-dose (75 to 100 mg) versus high-dose (300 to 325 mg) aspirin and found no significant difference in cardiovascular death, MI, or stroke at 30 days.[17] In OASIS-7, no significant difference in bleeding was reported with higher doses of aspirin; however, an analysis of 192,036 patients in 31 clinical trials showed that higher doses of aspirin (>200 mg) were associated with substantially higher rates of major and minor gastrointestinal bleeding.[18] Although aspirin is certainly an important pharmacologic therapy in ACS patients, it does not prevent all thrombotic events.

Thienopyridines

Thienopyridines—such as ticlopidine, clopidogrel, and prasugrel—exert their antiplatelet effects by irreversibly blocking the $P2Y_{12}$ receptor and its associated signaling pathway, thereby inhibiting platelet activation for the entire lifespan of the platelet. Thienopyridines are administered as an initial loading dose followed by a maintenance dose because they take several hours to exhibit their irreversible antiplatelet effect. It is important to note that their mechanism of action is entirely independent of and complementary to that of aspirin, and the combination of aspirin and a thienopyridine is superior to the use of aspirin alone.[19,20]

Clopidogrel

Clopidogrel is the most widely studied of the thienopyridine class. The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial[21] studied 19,185 patients with atherosclerotic vascular disease and revealed a 9% relative risk reduction in vascular death, MI, or ischemic stroke without a significant increase in bleeding. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial[19] enrolled 12,562 patients and demonstrated a 20% reduction in cardiovascular death, MI, and stroke. A subset of this population that underwent PCI was studied in the PCI-CURE trial,[22] and this showed that pretreatment with clopidogrel for a median of 6 days before PCI was associated with a 31% reduction in cardiovascular death or MI. A loading dose of 600 mg achieves maximal platelet inhibition faster than 150 mg or 300 mg and has lasting benefit of up to 30 days in low- to intermediate-risk patients undergoing elective PCI.[23] In higher-risk patients, use of glycoprotein (GP) IIb/IIIa inhibitors may have an added benefit.

An important consideration for the use of clopidogrel in ACS patients is the substantial variability in individual patient response to clopidogrel. Multiple potential hypotheses have been proposed to explain this "clopidogrel resistance," such as differences in clopidogrel dosing, intestinal absorption problems, and varying availability and clearance of the active metabolite.[24] Genetic factors such as polymorphisms of the hepatic CYP pathway, which is responsible for metabolizing clopidogrel's prodrug into an active metabolite, are becoming increasingly well understood, and at least three major genetic polymorphisms of the CYP2C19 isoenzyme—CYP2C19*1, CYP2C19*2, and CYP2C19*3—have been attributed with loss of function and diminished responsiveness to clopidogrel.[25,26] However, considerable debate persists regarding management strategies for clopidogrel resistance. Though platelet function testing is available to direct individual patient care, genetic testing thus far has not been shown to improve clinical outcomes in patients with clopidogrel resistance.[27] The Gauging Responsiveness With a VerifyNow Assay–Impact on Thrombosis and Safety (GRAVITAS) trial[28] randomized patients with clopidogrel resistance to high-dose versus standard-dose clopidogrel but found no differences in cardiovascular outcomes between the two groups. The absorption of clopidogrel may also be affected by other medications that utilize the CYP pathway. Proton pump inhibitors (PPIs) such as omeprazole and esomeprazole may also interact with and decrease the effectiveness of clopidogrel. The Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT)[29] randomized patients taking aspirin and clopidogrel to omeprazole versus placebo. Although this trial found no clinical difference in cardiovascular outcomes between patients taking omeprazole and those taking placebo, the U.S. Food and Drug Administration (FDA) has nevertheless issued a warning against the concomitant use of clopidogrel with the PPIs esomeprazole and omeprazole.

Prasugrel

Prasugrel is a second-generation irreversible $P2Y_{12}$ inhibitor that is more potent and more consistent with respect to platelet inhibition. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON–TIMI 38) trial[30] evaluated 13,608 patients with moderate- to high-risk ACS (NSTE-ACS and STE-ACS) after randomly receiving either prasugrel or clopidogrel during PCI. In this study, prasugrel significantly reduced the composite end point of cardiovascular death, nonfatal MI, or nonfatal stroke by 19% compared with clopidogrel (Fig. 19-5). A subgroup analysis showed that prasugrel was associated with a 24% reduction in MI, a 34% reduction in the need for urgent revascularization, and a 52% reduction in stent thrombosis.[31] These benefits, however, were also associated with a 0.5% absolute increase in non–coronary artery bypass graft surgery (CABG)–related TIMI major bleeding and a 0.3% absolute increase in fatal bleeding. A landmark analysis of this trial revealed that patients with a previous transient ischemic attack (TIA) or stroke, those who were 75 years of age or older, or those who weighed less than 60 kg were at especially high risk of bleeding. These patient subgroups are therefore relatively contraindicated for treatment with prasugrel.[31] In the setting of NSTE-ACS, prasugrel can be given at the time of PCI but should not be given upstream of PCI. In A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients With Non–ST-Elevation

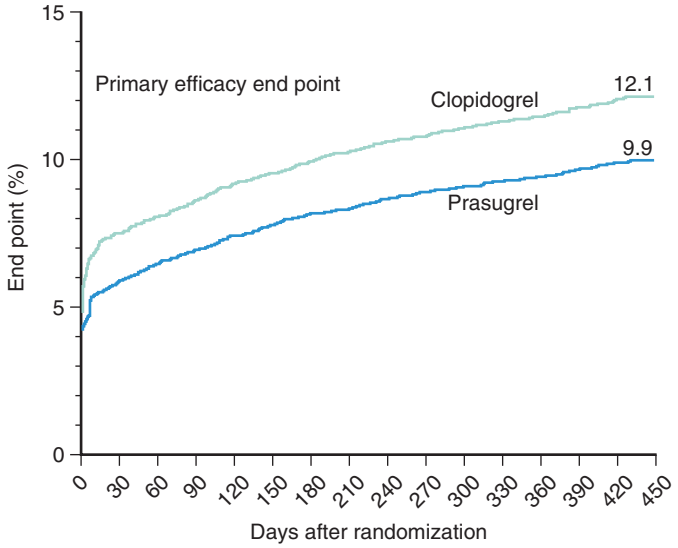


FIGURE 19-5 Results of TRITON-TIMI 38 trial. Primary efficacy end point was defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. (From Wiviott SD, Braunwald E, McCabe CH, et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 35[20]:2001-2015, 2007.)

Myocardial Infarction (ACCOAST), upstream therapy with prasugrel increased bleeding complications but did not improve cardiovascular outcomes.[32]

Ticagrelor

Ticagrelor is the newest $P2Y_{12}$ inhibitor on the market, and it has several distinct characteristics compared with previous $P2Y_{12}$ inhibitors. First, it is a non–thienopyridine, a cyclopentyltriazolopyrimidine that is a noncompetitive inhibitor of the $P2Y_{12}$ receptor.[33] Second, it is a reversible platelet inhibitor with a short half-life of 7.2 hours and therefore requires twice-daily dosing. Ticagrelor was compared with clopidogrel in the Study of Platelet Inhibition and Platelet Outcomes (PLATO),[34] which randomized 18,624 patients with ACS to either ticagrelor or clopidogrel. Of these, 11,598 had UA/NSTE-ACS. The primary end point was a composite of cardiovascular death, MI, or stroke. Ticagrelor was found to have a 1.9% absolute reduction and 16% relative reduction in the primary end point (9.8% vs. 11.7%). The absolute risk reduction of cardiovascular mortality for ticagrelor was 1.1%. Subgroup analysis showed that the significant reduction in the primary end point held true for NSTE-ACS patients but not among UA patients. Rates of all-cause major bleeding were similar between groups, but non–CABG-related TIMI major bleeding was significantly higher with ticagrelor. This multicenter study was notable for significant geographic variances in outcome; surprisingly, patients in North America randomized to ticagrelor were not found to have the same benefit. Compared with clopidogrel, no significant difference was found in the primary end point. Subsequent analyses attributed this variation to a dose-related aspirin effect on ticagrelor, because patients in North America were found to be taking significantly higher maintenance doses of aspirin (>300 mg) during the study. Doses of aspirin greater than 100 mg may attenuate the effects of ticagrelor; for this reason, patients receiving ticagrelor should only take low-dose aspirin (81 mg daily).

Dual-antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) is considered standard pretreatment of patients with NSTE-ACS undergoing PCI with or without stent implantation (ACC/AHA guidelines class IIb recommendation, level of evidence [LOE] A).[6] The preference for ticagrelor instead of clopidogrel is a class IIa recommendation.[7] However, the optimal timing for initiation of a $P2Y_{12}$ inhibitor may still pose a dilemma in actual clinical practice. The frequency of adverse cardiac events is reduced within the first hours of treatment with a $P2Y_{12}$ inhibitor, but if the patient is referred for urgent or emergent surgery, this approach may be associated with more perioperative blood loss.[18] However, given the fact that CABG is less likely to be necessary in the contemporary stent era even for high-risk NSTE-ACS patients, early $P2Y_{12}$ inhibition is recommended unless urgent CABG is deemed to be very likely.

Anticoagulant Treatment

Heparin

Since the beginning of PCI, unfractionated heparin (UFH) has been given to prevent thrombosis during intracoronary instrumentation and to minimize thrombosis at the site of the plaque, which is damaged by balloon angioplasty and/or stent implantation. Treatment with UFH in addition to aspirin usually is given based on the data from a meta-analysis that demonstrated a reduction of the combined death and MI rate of 7.9% for those treated with UFH compared with 10.3% for those treated with aspirin alone.[35] UFH is given as an initial intravenous (IV) bolus of 60 IU/kg followed by a 12 IU/kg/h infusion, and guided by an activated clotting time (ACT) in the range of 250 to 300 seconds. If combined with a GP IIb/IIIa inhibitor, the dose of UFH should be lower: an initial IV bolus of 50 to 60 IU/kg and ACT in the range of 200 to 250 seconds to prevent excessive bleeding complications.

Low-Molecular-Weight Heparin

Low-molecular-weight heparin (LMWH) has also been used in the setting of PCI for NSTE-ACS. In the Fast Revascularization During Instability in Coronary Artery Disease (FRISC) trial,[36] 1506 patients were randomly assigned to receive dalteparin (120 IU/kg twice daily, with a maximal dose of 10,000 IU) or UFH during the first 5 to 7 days of hospitalization followed by dalteparin (7500 IU subcutaneously, daily) or placebo for 35 to 45 days. Dalteparin was associated with a 63% relative risk reduction in death or MI during the first 6 days (1.8% in the treatment group vs. 4.8% in the placebo group), with persistence of these differences at 40 days. The ESSENCE trial[37] evaluated 3171 UA/NSTE-ACS patients who were randomly assigned to receive enoxaparin (1 mg/kg subcutaneously (SC) twice daily) or continuous infusion of UFH (minimum of 48 hours to a maximum of 8 days). The dose of enoxaparin should be reduced to 1 mg/kg SC daily in patients with a creatinine clearance (CrCl) < 30 mL/min. The risk of recurrent angina, MI, or death was significantly lower in the enoxaparin patients than in the UFH patients at 14 days (16.6% vs. 19.8%). The benefit persisted at 30 days, but at the cost of increased minor bleeding with no significant difference in major bleeding (6.5% vs. 7%).[37]

The TIMI-IIB trial[38] randomized 3910 patients with UA/NSTE-ACS to receive either enoxaparin or UFH for 3 to 8 days while hospitalized followed by either enoxaparin or placebo through day 43 as an outpatient. At 8 days, a 14.6% risk reduction in the composite end point of MI, death, and need for urgent revascularization was noted, and at 43 days, a 12.3% risk reduction in the same end point was reported. Bleeding was similar in both groups during initial hospitalization, but the risk of major bleeding during the outpatient phase of the study was doubled in the enoxaparin group compared with placebo. These data suggest that enoxaparin may be more effective than UFH at reducing the risk of ischemic events during the acute management of NSTE-ACS patients without an important increase in major bleeding events. A metaanalysis of nearly 22,000 patients with UA/NSTE-ACS enrolled in six randomized trials reported a relative risk reduction of 9% in the composite end point of death or MI at 30 days for patients treated with enoxaparin compared with those treated with UFH and found no significant difference in major bleeding at 7 days.[39] These results demonstrate that use of enoxaparin was beneficial when an ischemia-guided strategy was utilized for patient management.

Subsequent trials compared UFH and enoxaparin when an early invasive strategy is implemented. The Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial[40] studied 10,027 patients with high-risk

UA/NSTE-ACS who were treated using an early invasive strategy. In this study, no significant difference was found in the primary end point of all-cause mortality or nonfatal MI at 30 days, but patients who received enoxaparin exhibited a 20% increase in TIMI major bleeding in association with invasive procedures, especially CABG.[40] When considered as a whole, the data presented above support the notion that treatment with enoxaparin, compared with UFH, appears to be more efficacious at reducing ischemic events in UA/NSTE-ACS patients who are treated with an ischemia-guided strategy. However, interpretation of data from the SYNERGY trial, and from others (such as the Aggrastat to Zocor [A-to-Z] trial) comparing UFH and enoxaparin in UA/NSTE-ACS patients treated with an early invasive strategy, must be interpreted carefully. Many of the patients in these trials had already received other antithrombotic agents before being randomized to a given treatment arm. Thus the high rate of patient crossover is an important confounding factor. The most recent ACC/AHA guidelines consider enoxaparin to be a reliable alternative to UFH for patients treated both with an early invasive and an ischemia-guided strategy (class I, LOE A).[7]

Bivalirudin

Bivalirudin is a direct thrombin inhibitor and a synthetic analogue of hirudin that reversibly binds thrombin and inhibits clot-bound thrombin. The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events 2 (REPLACE-2)[41] trial demonstrated that bivalirudin could be used as an alternative to UFH plus GP IIb/IIIa blockade in low-risk patients who undergo PCI. The efficacy of bivalirudin was further evaluated in the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial.[42] It randomized 13,800 patients with moderate- to high-risk UA/NSTE-ACS undergoing an invasive strategy into three treatment groups: group I received UFH or enoxaparin plus GP IIb/IIIa inhibitor, group II received bivalirudin plus GP IIb/IIIa inhibitor, and group III received bivalirudin alone. The primary end point at 30 days was a net clinical outcome based on an ischemic composite (i.e., death from any cause, MI, or unplanned revascularization for ischemia) or major bleeding. The net outcome was lower with the bivalirudin-alone strategy, which could be ascribed to a significant reduction in major bleeding in the bivalirudin group (Table 19-2).

Fondaparinux

Fondaparinux is a synthetic polysaccharide that leads to indirect inhibition of activated factor X (FXa), and it was evaluated in the Fifth Organization to Assess Strategies for Ischemic Syndromes (OASIS-5) trial.[43] In this study 20,078 patients were randomized to treatment with either fondaparinux (2.5 mg/day) or enoxaparin (1 mg/kg twice daily) for a mean of 6 days. Approximately 40% of patients underwent PCI and 15% underwent CABG in both groups. Fondaparinux was equivalent to enoxaparin in terms of the primary efficacy end point at 9 days—composite of death, MI, or refractory ischemia—and major bleeding at 9 days was significantly lower with fondaparinux than with enoxaparin (2.2% vs. 4.1%; $P < .001$). However, fondaparinux was associated with an increased rate of guide catheter thrombosis; therefore it should be administered concurrently with an additional anticoagulant that has anti-IIa activity.[7]

Glycoprotein IIb/IIIa Inhibitors

The final common pathway of platelet activation and aggregation is mediated by a conformational change in the GP IIb/IIIa receptor from an inactive to an active state. GP IIb/IIIa inhibitors interfere with the ability of the GP IIb/IIIa receptor to bind with target ligands, and thus they are potent inhibitors of platelet aggregation.[44] All three currently used GP IIb/IIIa inhibitors—abciximab, eptifibatide, and tirofiban—exhibit different pharmacodynamic and pharmacokinetic properties, different clinical trial outcomes, and as a result have different recommendations for clinical use.

Abciximab

Abciximab (formerly c7E3) was the first of the three currently used GP IIb/IIIa inhibitors to be subjected to large-scale clinical trial testing and was first evaluated in the prestent era of the early 1990s. The Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial[45] studied high-risk patients with UA, evolving MI, or complex coronary lesion anatomy and showed a 35% reduction in the composite end point of death, MI, or recurrent ischemia compared with placebo. The c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial[46] studied 1265 patients with UA who underwent PCI. In this study, a 30% relative reduction in the primary end point of all-cause mortality, MI, or recurrent ischemia requiring urgent revascularization was reported at 30 days. The rate of MI was noted to be lower before, during, and after PCI in patients treated with abciximab, and a subgroup analysis revealed that abciximab facilitated thrombus resolution and prevented recurrent ischemia. Abciximab therefore has clearly been shown to be efficacious in the setting of UA/NSTE-ACS patients undergoing PCI. The Global Use of Strategies to Open Occluded Coronary Arteries IV–Acute Coronary Syndrome (GUSTO-IV–ACS) trial,[47] however, studied 7800 patients with UA/NSTE-ACS who were not scheduled to undergo an early invasive strategy. Patients in this study were randomized to receive an abciximab bolus followed by infusion for either 24 or 48 hours, or placebo. In this trial abciximab provided no benefit as it relates to the primary composite end point of death or MI at 30 days, even in a subgroup of patients with elevated troponin levels. The current ACC/AHA guidelines reflect these results; abciximab is not recommended for the treatment of patients with UA/NSTE-ACS for whom an ischemia-guided strategy is planned.[6]

Tirofiban

Tirofiban was studied in the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial,[48] in which 3232 patients with UA were randomized to receive either UFH or tirofiban for 48 hours. A 32% reduction in the rate of death, MI, or refractory ischemia was noted at 48 hours, but no significant difference was noted at 30 days. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial[49] randomized UA and NSTE-ACS patients to receive aspirin plus either heparin, tirofiban, or both. The tirofiban-only arm was stopped early because of excess death at 7 days (4.6% vs. 1.1% in the heparin-only arm). Patients who received both heparin and tirofiban exhibited

TABLE 19-2 ACUITY Trial Results

End Point (30 Days)	UFH/Enox + GPI ($n = 4603$)	Bivalirudin + GPI ($n = 4604$)	Bivalirudin Alone ($n = 4612$)	*P* Value
Net outcome (%)	11.7	11.8	10.1	.0014
Ischemic composite (%)	7.3	7.7	7.8	NS
Major bleeding (%)	5.7	5.3	3.0	<.0001

From Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes, *N Engl J Med* 355:2203-2216, 2006.
ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; *Enox,* enoxaparin; *GPI,* glycoprotein IIb/IIIa inhibitor; *NS,* not significant; *UFH,* unfractionated heparin.

the greatest benefit in terms of a reduction in the composite end point at 7 days of death, MI, or refractory ischemia. This benefit was sustained at 30 days and at 6 months (27.2% vs. 32% in the heparin-only arm).

Eptifibatide

Eptifibatide was studied in 9461 patients with NSTE-ACS in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy (PURSUIT) trial.[50] In this study, treatment with eptifibatide was associated with a 10% reduction in the relative risk of death and MI at 30 days. A meta-analysis[51] confirmed the utility of GP IIb/IIIa inhibitors in the management of patients with moderate to high-risk UA/NSTE-ACS. This analysis pooled 31,402 patients from six different GP IIb/IIIa trials involving ACS patients and showed a 9% reduction in the odds ratio of death or MI for patients treated with a GP IIb/IIIa inhibitor compared with those who received a placebo. Subgroup analysis revealed a 15% reduction in the odds ratio of death or MI for troponin-positive patients and showed no such reduction in troponin-negative patients. Reduction in the odds ratio of death or MI was also noted to be greater in patients who underwent PCI within 5 days.[51] The Do Tirofiban and Reopro Give Similar Efficacy Outcomes Trial (TARGET)[52] was a direct comparison between abciximab and tirofiban. It demonstrated that the primary end point—a composite of death, nonfatal MI, or urgent revascularization at 30 days—was significantly higher in the tirofiban group compared with those receiving abciximab (7.6% vs. 6.0%), but at 6 months, this difference was no longer statistically significant.[52]

The Early Versus Delayed Provisional Eptifibatide in Acute Coronary Syndromes (EARLY-ACS) trial[53] compared early routine versus delayed provisional administration of eptifibatide in 9492 patients with NSTE-ACS who were randomly assigned to an invasive strategy. The primary end point was the composite of death, MI, recurrent ischemia requiring urgent revascularization, or thrombotic bailout at 96 hours. No difference in the primary end point was observed between the two groups at 96 hours; however, use of early routine eptifibatide was associated with higher rates of non–life-threatening bleeding and transfusions.

With the multitude of antiplatelet therapies being administered to ACS patients, some had concerns that the efficacy of GP IIb/IIIa inhibitors might be reduced in patients pretreated with clopidogrel. The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 (ISAR–REACT-2) trial[54] addressed this issue. ISAR–REACT-2 was a randomized, double-blind trial that compared treatment with abciximab ($n = 1012$) or placebo ($n = 1010$) in patients with NSTE-ACS who were treated with a 600-mg loading dose of clopidogrel. The primary end point was a composite of death, MI, and urgent target-vessel revascularization (TVR) due to myocardial ischemia at 30 days. The reduction in the primary end point was significant in favor of abciximab in all patients with NSTE-ACS (8.9% vs. 11.9%), and this was achieved with no difference in TIMI-defined major bleeding (Fig. 19-6). As seen in several other trials, abciximab was highly effective in high-risk NSTE-ACS patients (i.e., troponin-positive patients) but was not effective in troponin-negative patients.

Despite the demonstrated advantages of GP IIb/IIIa inhibitors in the treatment of patients with UA/NSTE-ACS undergoing PCI, most of these studies were done before the benefits of clopidogrel were clearly established. The optimal timing of GP IIb/IIIa initiation is therefore still being clarified. Early routine use of GP IIb/IIIa inhibitors has been associated with a significantly higher risk of major bleeding.[42,53] Contemporary trials are therefore needed to define the role and timing of GP IIb/IIIa inhibitors in NSTE-ACS and to assess whether the benefits of triple-antiplatelet therapy outweigh the risks of bleeding in this setting. Several trials are currently ongoing that will help address this question. The most recent ACC/AHA guidelines recommend the use of GP IIb/IIIa inhibitors in patients with NSTE-ACS and high-risk features such as an elevated troponin. It is a class I recommendation in patients not adequately pretreated with clopidogrel or ticagrelor and a class IIa recommendation in patients who have been pretreated.

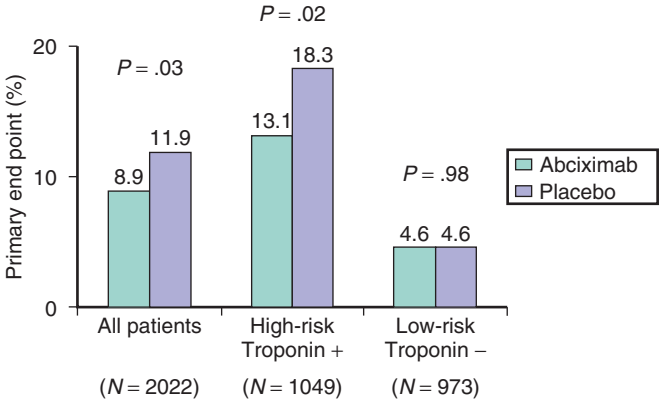


FIGURE 19-6 Results of ISAR-REACT-2 Trial, comparing abciximab with placebo. Primary end point was defined as composite of death, myocardial infarction, and urgent TVR at 30 days. (From ISAR-REACT-2 Trial Investigators: Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA* 295:1531–1538, 2006.)

EARLY INVASIVE STRATEGY VERSUS ISCHEMIA-GUIDED STRATEGY FOR PATIENTS WITH NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

ACS patients who present with hemodynamic instability, severe left ventricular dysfunction or overt heart failure, recurrent or persistent rest angina despite intensive medical therapy, mechanical complications (e.g., acute mitral regurgitation and ventricular septal defect), or sustained ventricular tachycardia are at extremely high risk for death or a complicated MI. For this reason, unless they have been deemed inappropriate for revascularization, these patients should undergo urgent coronary angiography.[6] For the management of other less overtly ill patients who present with NSTE-ACS, two strategies have emerged: an ischemia-guided strategy (previously called an *initial conservative strategy*) and an early invasive strategy. The *ischemia-guided strategy* entails the use of intensive medical therapy, which includes aspirin, antiplatelet therapy (clopidogrel, ticagrelor), anticoagulation (UFH, LMWH, or fondaparinux), beta-blockers, statins, and/or nitroglycerin (if not contraindicated; Fig. 19-7). Patients who become asymptomatic on this regimen are typically observed for 48 to 72 hours and then undergo cardiac stress testing, usually with some form of myocardial imaging (nuclear imaging or echocardiography). Patients who manifest signs or symptoms of ongoing ischemia at any time during observation or who demonstrate high- or intermediate-risk findings on stress testing are then referred for coronary angiography and subsequent revascularization as appropriate. Patients with low-risk stress test findings are treated medically with aspirin indefinitely, clopidogrel or ticagrelor for up to 12 months, statins, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors.[6] Prior to coronary angiography and revascularization, patients managed with an *early invasive strategy* are also treated with intensive medical therapy that includes aspirin, anticoagulation (UFH, LMWH, bivalirudin, or fondaparinux), and a $P2Y_{12}$ inhibitor. GP IIb/IIIa inhibitors can be considered if high-risk features are present.

Initial studies—TIMI IIIB, Veterans Affairs Non-Q-Wave Myocardial Infarction Strategies In Hospital (VANQWISH), and Medicine Versus Angiography in Thrombolytic Exclusion (MATE)—did not show superiority for either an early invasive or an ischemia-guided strategy.[55-57] However, these trials were done before the advent of stents, adjunctive anticoagulation, and antiplatelet therapy, which have all significantly improved PCI outcomes. Five important randomized trials have been done in the contemporary PCI era: Fast Revascularization During Instability in Coronary Artery Disease (FRISC-II);[58] Treat

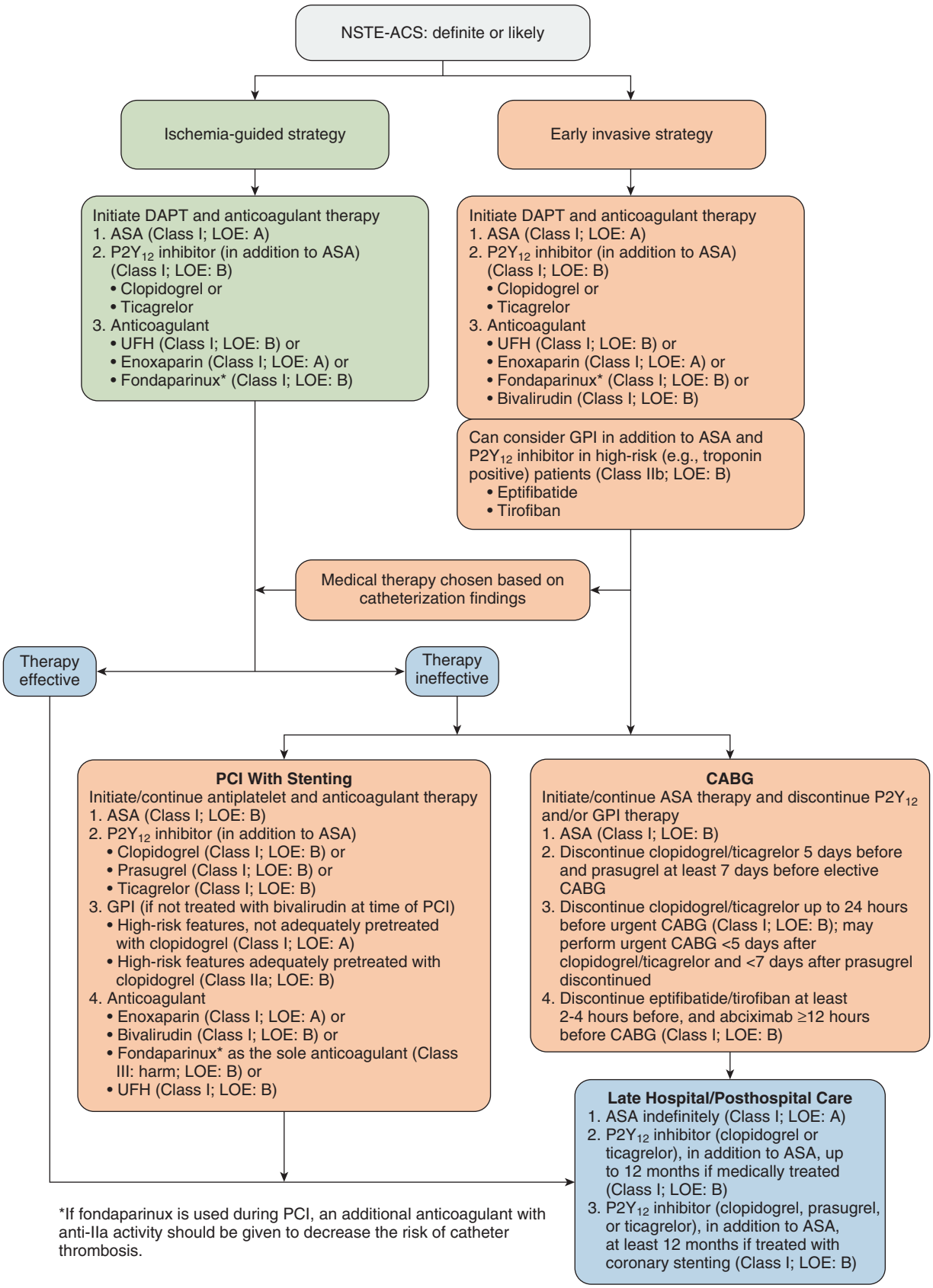


FIGURE 19-7 American College of Cardiology/American Heart Association guidelines: algorithm for patients with NSTE-ACS. *ASA,* Aspirin; *DAPT,* dual-antiplatelet therapy; *GPI,* glycoprotein IIb/IIIa inhibitor; *NSTE-ACS,* non–ST-elevation acute coronary syndrome. (From Amsterdam EA, Wegner NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 64[24]:e139-e228, 2014.)

Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction (TACTICS–TIMI 18)[59]; Value of First-Day Angiography/Angioplasty in Evolving Non–ST-Segment Elevation Myocardial Infarction (VINO)[60]; Randomized Intervention Trial of Unstable Angina 3 (RITA-3)[61]; and Invasive Versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS).[62]

With an early invasive strategy, early revascularization (in hospital) was achieved in 44% to 76% of patients (Fig. 19-8). Even with an ischemia-guided strategy, the need to cross over with early revascularization ranged from 9% to 40%. The contrast in the frequencies of early revascularization between the early invasive and ischemia-guided strategies varied from as low as 24% (TACTICS-TIMI 18) to as high as 62% (FRISC-II). Revascularization after hospital discharge was predominantly performed in the patients randomized to an ischemia-guided strategy. The primary end point of these trials was defined as a composite of death and MI with or without rehospitalization. All trials with the exception of RITA-3 and ICTUS found a statistically significant advantage with an early invasive strategy (Table 19-3). The in-hospital mortality rates are shown in Figure 19-9. The mortality rates at the end of follow-up are presented in Figure 19-10. Although there was no initial difference in death and nonfatal MI at 1 year in the RITA-3 trial, there was a significant mortality benefit at 5 years, with a 24% reduction in all-cause mortality in the early invasive group. This benefit was seen mainly in high-risk patients. The RITA-3 trial was unique in that patients were ultimately followed over a long-term period of 10 years, and this data was recently published. At 10 years, there was no longer a mortality benefit. Reasons for this may be multifactoral and include treatment crossover over the long follow-up period or improved medical therapies over the years (Table 19-4 and Fig. 19-11).[63]

Optimal Timing of Intervention

In patients with NSTE-ACS who are undergoing an early invasive strategy, the optimal timing of intervention has not yet been defined.[6] During an NSTE-ACS, early or immediate revascularization of the culprit lesion may decrease the time for recurrent ischemic events. On the other hand, allowing these patients to be treated first with aggressive antithrombotic therapy prior to angiography may help stabilize the lesion and may thereby reduce periprocedural complications during revascularization. The Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) study[64] investigated whether the outcomes of early catheterization and later catheterization

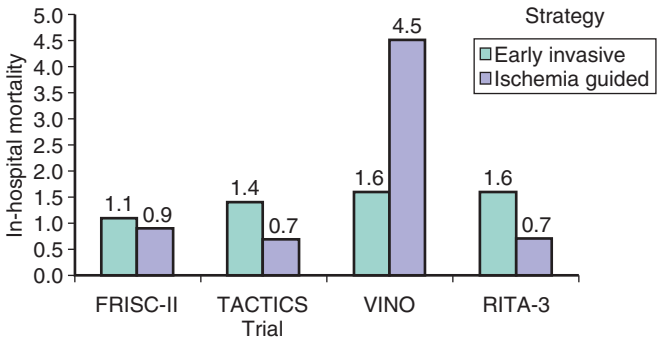


FIGURE 19-9 Incidence of in-hospital mortality in several trials.

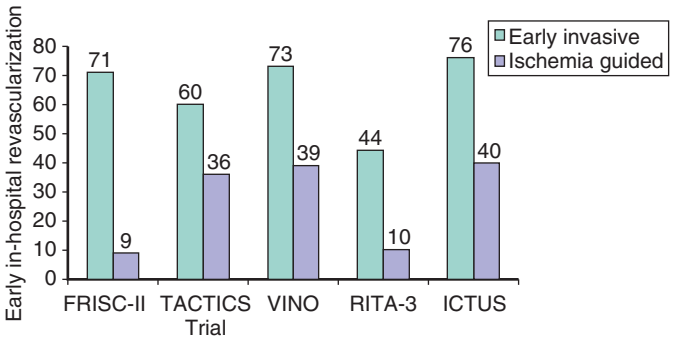


FIGURE 19-8 Incidence of early (in-hospital) revascularization in several trials.

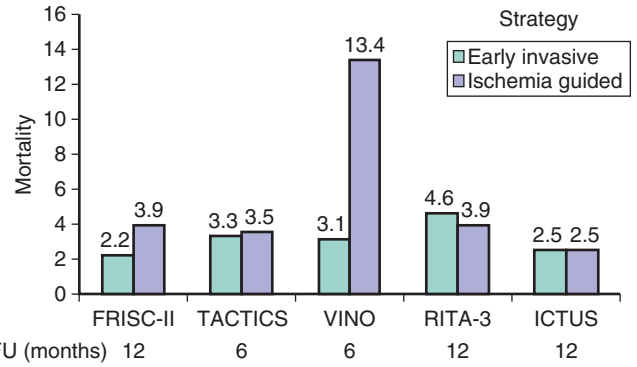


FIGURE 19-10 Incidence of mortality at the end of follow-up (FU) in several trials.

TABLE 19-3 Early Invasive Versus Ischemia-Guided Strategies in Five Trials

Trial	Primary End Point	Early Invasive	Ischemia Guided	RR or OR	CI 95%, *P* Value
FRISC-II[58]	Death/MI at 1 yr	10.4%	14.1%	RR = 0.74	0.60 to 0.92, *P* = .005
TACTICS[59]	Death/MI/rehosp. for ACS at 6 mo	15.9%	19.4%	OR = 0.78	0.62 to 0.97, *P* = .025
VINO[60]	Death/MI at 6 mo	6.2%	22.3%		*P* < .001
RITA-3[61]	Death/MI at 1 yr	7.6%	8.3%	RR = 0.91	0.67 to 1.25, *P* = .58
ICTUS[62]	Death/MI/rehosp. <1 yr	22.7%	21.2%	RR = 1.07	0.87 to 0.133, *P* = .33

ACS, Acute coronary syndrome; *CI,* confidence interval; *FRISC-II,* Fast Revascularization During Instability of Coronary Artery Disease; *ICTUS,* Invasive Conservative Treatment in Unstable Coronary Syndromes; *MI,* myocardial infarction; *OR,* odds ratio; *PCI,* percutaneous coronary intervention; *RITA-3,* Randomized Intervention Trial of Unstable Angina; *RR,* relative risk; *TACTICS,* Treat Angina With Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy; *VINO,* Value of First-Day Angiography/Angioplasty In Evolving Non–ST-Segment Elevation Myocardial Infarction: An Open Multicenter Randomized Trial.

were different. A total of 56,352 patients were treated at 310 U.S. hospitals and were entered into the CRUSADE registry. The patients were retrospectively classified as having very early (23.4-hr) or later (46.3-hr) catheterization. The in-hospital adverse cardiac events that occurred in the two groups are presented in Table 19-5. No difference was found between the two groups, but the investigators warned cautiously that they could not exclude an important risk reduction, particularly for early catheterization within 12 hours of presentation.

This issue was addressed in the Intracoronary Stenting With Antithrombotic Regimen Cooling-Off (ISAR-COOL) trial,[65] which randomized 410 patients who had symptoms of UA plus ST-segment depression or elevated cardiac troponin T levels. Patients were randomized to antithrombotic pretreatment for 3 to 5 days (the cooling-off strategy) or very early intervention after pretreatment for less than 6 hours. Antithrombotic pretreatment consisted of heparin, aspirin, clopidogrel, and tirofiban. The outcome is presented in Table 19-6. The reduction was significant in the combined death and MI rate in favor of the very early intervention strategy. This favorable outcome was predominantly attributable to adverse events occurring before catheterization.

The Early or Late Intervention in Unstable Angina (ELISA) pilot study[66] investigated whether pretreatment with a GP IIb/IIIa inhibitor, tirofiban, was beneficial compared with no pretreatment. A total of 220 patients with NSTE-ACS were randomized to an early strategy (i.e., early angiography without tirofiban pretreatment) or to a late strategy (i.e., delayed angiography after pretreatment with tirofiban). The primary end point was enzymatic infarct size (LDHQ48) as assessed by the area under the lactate dehydrogenase release curve up to 48 hours after symptom onset (LDHQ48). The infarct size and clinical outcome at 30 days are presented (Table 19-7). The study showed that delayed angiography with pretreatment with tirofiban was associated with a smaller enzymatic infarct size. No differences in clinical outcome were reported at 30 days.

The CRUSADE quality improvement initiative investigated the use of an early invasive management within 48 hours in 17,926 high-risk NSTEMI patients (Table 19-8).[67] A total of 8037 patients (44.8%) underwent early cardiac catheterization, and of these, 75% were revascularized: 4733 (58.9%) underwent PCI, and 1296 (16.1%) underwent CABG. The unadjusted incidence of in-hospital mortality and postadmission MI was significantly lower for patients who underwent early invasive management than for those who did not, and patients who underwent early invasive management were younger and had less comorbidity (Table 19-7). The adjusted risks for death and MI were therefore lower for patients who underwent early invasive management, and in a propensity-matched pair analysis, the mortality rate remained lower for patients who underwent early invasive management (2.5% vs. 3.7%, $P < .01$).

The Optimal Timing of Coronary Angiography and Potential Intervention in Non–ST-Elevation Acute Coronary Syndromes (OPTIMA) trial[68] randomized patients with NSTE-ACS undergoing PCI to either immediate PCI or PCI within 24 to 48 hours. Medical therapy was the

TABLE 19-4 RITA-3 Trial Outcomes at 1-, 5-, and 10-Year Follow-Up

Outcome	Early Intervention ($n = 895$)	Ischemia Guided ($n = 915$)	*P* Value
Follow-up years			
1-year death/MI	7.6%	8.3%	.58
5-year death/MI	16.6%	20.0%	.04
10-year death	25.1%	25.4%	.94
10-year cardiovascular death	15.1%	16.1%	.65

From Henderson RA, Jarvis C, Clayton T, et al: 10-Year mortality outcome of a routine invasive versus a selective invasive strategy in non-ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol* 66:511-520, 2015.
MI, Myocardial infarction.

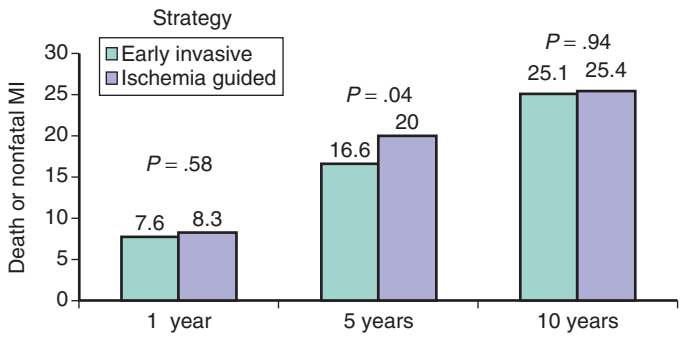


FIGURE 19-11 Incidence of death or nonfatal myocardial infarction at 10-year follow-up, from the RITA-3 trial. (From Henderson RA, Jarvis C, Clayton T, et al: 10-year mortality outcome of a routine invasive strategy versus a selective invasive strategy in non-ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol* 66:511-520, 2015.)

TABLE 19-5 Timing of Intervention in Patients with Non–ST-Elevation Myocardial Infarction and Acute Coronary Syndrome in the CRUSADE Registry

	TIMING OF CATHETERIZATION		
	46.3 hours	23.4 hours	
In-Hospital Events	($n = 10,804$)	($n = 45, 548$)	*P* Value
Death (%)	4.4	4.1	.23
Recurrent MI (%)	2.	3.0	.36
Death/MI (%)	6.6	6.6	.86

From CRUSADE Investigators: Optimal timing of intervention in non-ST-segment elevation acute coronary syndromes: insights from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Registry. *Circulation* 112:3049-3057, 2005.
CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA guidelines [National Quality Improvement Initiative and Registry]; *MI,* myocardial infarction.

TABLE 19-6 Outcomes of the ISAR-COOL Trial

Outcome Characteristic	Prolonged Antithrombotic Pretreatment (%) ($n = 207$)	Early Intervention (%) ($n = 203$)	*P* Value
Definitive Treatment			
Conservative	28.0	21.7	
CABG	7.7	7.9	
PCI (stents)	64.3	70.4	
30 days			
Death/MI	11.6	5.9	.04
Death	1.4	0	.25
Nonfatal MI	10.1	5.9	.12
Q-wave	3.4	2.0	
Non–Q-wave	6.8	3.9	
Major bleeding event	3.9	3.0	.61

From Neumann FJ, Kastrati A, Pogatsa-Murray G, et al: Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. *JAMA* 290:1593-1599, 2003.
CABG, Coronary artery bypass grafting; *ISAR-COOL,* Intracoronary Stenting With Antithrombotic Regimen Cooling Off; *MI,* myocardial infarction; *PCI,* percutaneous intervention.

TABLE 19-7 Outcomes of the ELISA Pilot Study

Outcome Characteristic	Early Strategy* ($n = 109$)	Delayed Strategy† ($n = 111$)
Median time to angiography	6 hr	50 hr
Treatment		
PCI (%)	61	58
CABG (%)	14	19
Conservative (%)	25	23
30-Day clinical outcome of death/MI (%)	9.2	9.0
Enzymatic infarct size (LDHQ48)	629 ± 503	432 ± 441 ($P = .02$)

From van't Hof AW, de Vries ST, Dambrink JH, et al: A comparison of two invasive strategies in patients with non-ST elevation acute coronary syndromes: results of the Early or Late Intervention in unStable Angina (ELISA) pilot study: 2b/3a upstream therapy and acute coronary syndromes. *Eur Heart J* 24:1401-1405, 2003.
*Early angiography and no pretreatment.
†Delayed angiography (24 to 48 hr) and pretreatment with tirofiban.
CABG, Coronary artery bypass grafting; *ELISA,* Early or Late Intervention in Unstable Angina; *LDHQ48,* cumulative enzyme release up to 48 hours after symptom onset as assessed by the area under the lactate dehydrogenase release curve; *MI,* myocardial infarction; *PCI,* percutaneous intervention.

TABLE 19-8 Outcomes of the CRUSADE Trial: In-Hospital Death or Myocardial Infarction

Outcome	No Early Invasive Management ($n = 9889$)	Early Invasive Management ($n = 8037$)	Adjusted Odds Ratio (95% CI)
Mortality (%)	6.2	2.0	0.63 (0.52 to 0.77)
Postadmission MI (%)	3.7	3.1	0.95 (0.79 to 1.14)
Death or MI (%)	8.9	4.7	0.79 (0.69 to 0.90)

From CRUSADE Investigators: Optimal timing of intervention in non-ST-segment elevation acute coronary syndromes: insights from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Registry. *Circulation* 112:3049-3057, 2005.
CI, Confidence interval; *CRUSADE,* Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes With Early implementation of the ACC/AHA guidelines; *MI,* myocardial infarction.

TABLE 19-9 TIMACS Trial 6-Month End Points

	Early Intervention (%)	Delayed Intervention (%)	RR/OR	CI 95%, *P* value
6-Month End Points				
Death	4.8	5.9	0.81	CI (0.6 to 1.11), $P = .19$
Myocardial infarction	4.8	5.7	0.83	CI (0.61 to 1.14), $P = .25$
Stroke	1.3	1.4	0.9	CI (0.49 to 1.68), $P = .74$
Refractory ischemia	1	3.3	0.3	CI (0.17 to 0.54), $P < .001$
Repeat intervention	8.7	8.5	1.04	CI (0.82 to 1.34), $P = .73$
Composite End Points				
Death, MI, stroke	9.6	11.3	0.85	CI (0.68 to 1.06), $P = .15$
Death, MI, refractory ischemia	9.5	12.9	0.72	CI (0.58 to 0.89), $P = .003$
Death, MI, stroke, refractory ischemia, repeat intervention	8.7	8.5	0.84	CI (0.71 to 0.99), $P = .04$

From Mehta SR, Grangar CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 360:2165-2175, 2009.
CI, Confidence interval; *MI,* myocardial infarction; *OR,* odds ratio; *RR,* relative risk; *TIMACS,* Timing of Intervention in Acute Coronary Syndromes.

same for both groups and consisted of triple-antiplatelet therapy with aspirin, clopidogrel, and a GP IIb/IIIa inhibitor. The primary end point was a composite of death, nonfatal MI, and revascularization at 30 days. This small study ($n = 142$) was terminated early because of poor enrollment. However, it demonstrated that the primary end point was significantly higher in the immediate PCI group, and this was driven by significantly higher rates of MI in the immediate PCI group.

In a similar fashion, the Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes (ABOARD) trial[69] randomly assigned 352 patients with high-risk NSTE-ACS (TIMI risk >3) to receive immediate versus delayed coronary angiography (between 8 and 60 hr post randomization). Over 96% of patients received aspirin and clopidogrel; GP IIb/IIIa inhibition was used in 65% in the immediate intervention group and in 57% in the delayed intervention group. In this study, the difference was not significant in either the primary outcome of peak hospital troponin I value or the secondary combined outcome of death, MI, or urgent revascularization at 1 month.

The Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial[70] was a larger study that randomized 3031 patients with NSTE-ACS to early PCI (within 24 hr) or delayed PCI (at least 36 hr). In this trial, aspirin and clopidogrel was used in over 85% of patients, and GP IIb/IIIa inhibitors were used in 23% of patients. The primary end point was a composite of death, MI, and stroke at 6 months. In this trial, no significant difference was found between the two groups. However, when stratified by risk according to the GRACE score, the highest risk patients in the trial (highest tertile, GRACE risk score >140) did have a substantial and significant reduction in the primary end point with an early intervention strategy (13.9% vs. 21.0%, HR 0.65, $P = .006$). This difference was not seen in patients in the lower two risk tertiles (Table 19-9, Fig. 19-12).

The secondary end point of the TIMACS trial was a composite of death, MI, and refractory ischemia, and here there was significant benefit in early intervention across the entire study population, including in low-risk patients (9.5% vs. 12.9%, $P = .003$). A 28% relative reduction in the secondary end point in the early intervention group was driven mainly by a significant reduction in refractory ischemia (1.0% vs. 3.3% in the early vs. delayed groups, $P < .001$; Table 19-10).[70]

Patients Who Derive Benefit From an Early Invasive Strategy

Patients with elevated troponin levels (data from FRISC-II and TACTICS–TIMI 18), ST-segment depression (data from FRISC-II, TACTICS–TIMI 18, and TIMI IIIB), the degree of and number of ECG leads with ST-segment depression (data from FRISC-II), and age greater than 65 years (data from TIMI IIIB and TACTICS–TIMI 18) have been clearly shown to benefit from an early invasive strategy. The TIMI risk score applied to TACTICS–TIMI 18 showed that patients at low risk (TIMI risk score 0 to 2) demonstrated no difference in

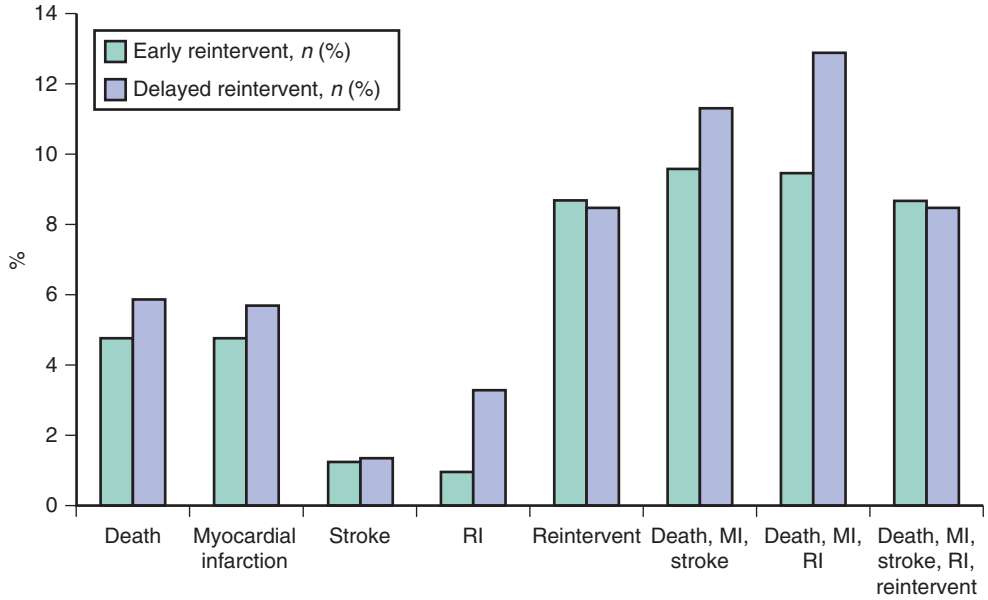


FIGURE 19-12 TIMACS trial results. *MI,* Myocardial infarction; *RI,* refractory ischemia.

TABLE 19-10 Early Versus Delayed Invasive Strategy

Trial	End Point	Early Invasive, *n* (%)	Conservative, *n* (%)	RR or OR	CI 95% *P* Value
ISAR- COOL	30-day death/ MI	12 (5.9%)	24 (11.6%)	1.96	CI (1.01–3.82) *P* = .04
ELISA	30-day death/ MI	10 (9.2%)	10 (9.0%)		*P* = .97
ABOARD	30-day death/ MI/ revascularization	24 (13.7%)	18 (10.2%)		*P* = .31
TIMACS	30-day death/ MI/ refractory ischemia/ revascularization	191 (12%)	187 (13%)	0.91	CI (0.75–1.12) *P* = .37

ABOARD, Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes; *CI,* Confidence interval; *ELISA,* Early or Late Intervention in Unstable Angina; *ISAR-COOL,* Intracoronary Stenting With Antithrombotic Regimen Cooling-Off; *MI,* myocardial infarction; *MI,* myocardial infarction; *OR,* odds ratio; *RR,* relative risk; *TIMACS,* Timing of Intervention in Acute Coronary Syndromes.

TABLE 19-11 Rates of Death, Myocardial Infarction, or Rehospitalization for Acute Coronary Syndrome Stratified by TIMI Risk Score

TIMI Risk Score	EVENT RATE (%)		Odds Ratio	95% CI
	Invasive	Conservative		
Low (0 to 2)	19.8	15.1	1.39	1.02 to 1.88
Intermediate (3 to 4)	18.2	21.8	0.80	0.64 to 0.99
High (5 to 7)	22.7	34	0.57	0.38 to 0.87

Data from TIMI IIIB (Antiplatelet Trialists' Collaboration: Collaborative overview of randomized trials of antiplatelet therapy: I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 308[6921]:81-106, 1994) and TACTICS–TIMI 18 (Serebrauny VL, Steinhubl SR, Berger PB, et al: Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. *Am J Cardiol* 95[10]:1218-1222, 2005).
CI, Confidence interval; *TIMI,* thrombolysis in myocardial infarction.

outcome—that is, a composite of death, MI, or rehospitalization for ACS at 6 months—whether they were treated with an early invasive or an ischemia-guided strategy.[59] Patients at intermediate risk (TIMI risk score 3 to 4), however, showed better outcomes when treated with an early invasive strategy; these were manifested by a significant reduction in the composite of death, MI, or rehospitalization for ACS at 6 months. Patients at highest risk (TIMI risk score 5 to 7) showed an even greater improvement in outcomes with an invasive strategy (Table 19-11).[70a]

Although the presence of elevated cardiac biomarkers and ST-segment depression are each variables in the TIMI risk score, further analysis from the TACTICS–TIMI 18 trial data revealed that the degree of cardiac biomarker elevation and magnitude of ST-segment depression were each independent predictors of poorer outcomes and that these patients benefited from an early invasive strategy.[71] A metaanalysis using 5-year outcomes from the FRISC-II, ICTUS, and RITA-3 trials showed that an early invasive strategy was associated with significantly lower rates of cardiovascular death or nonfatal MI (14.7% vs. 17.9%, *P* = .002). The absolute risk reduction in the highest-risk patients with an early invasive strategy was 11.1%.[72]

Based on the evidence, it appears that use of an early invasive strategy for high-risk patients with NSTE-ACS is superior to reduce major adverse cardiac events (MACEs) than use of an ischemia-guided strategy. An early invasive strategy with cardiac catheterization within 72 hours of symptoms is now an AHA/ACC Practice Guidelines Class 1B recommendation for NSTE-ACS and a Level 1A recommendation from the European Society of Cardiology.[73] Patients with elevated troponin levels or with high-risk indicators stand to derive the most benefit.

SPECIAL POPULATIONS

Diabetes

Insulin resistance is associated with a prothrombotic and proinflammatory state, and cardiovascular disease remains the leading cause of death among diabetics. With rates of obesity across the globe rising

to epidemic proportions, the prevalence of diabetes is expected to double by the year 2030.[74,75] Diabetic patients who have acute coronary syndrome have significantly worse outcomes compared with the general population. Mortality rates for diabetic patients are significantly higher across the board for both UA/NSTE-ACS and STE-ACS. The mortality difference is seen at 30 days for both UA/NSTE-ACS (2.1% vs. 1.1%, diabetics vs. nondiabetics, $P < .001$) and STE-ACS (8.5% vs. 5.4%, diabetics vs. nondiabetics, $P < .001$). At 1 year, diabetic patients continue to have a significantly higher mortality risk (HR 1.65 for UA/NSTE-ACS, HR 1.22 for STE-ACS). In particular, at 1 year, diabetic patients who present with UA/NSTE-ACS have mortality rates that are almost as high as nondiabetics who present with STE-ACS (7.2% vs. 8.1%).[76]

Diabetic patients who present with an ACS are therefore a high-risk population. As such, in the 2012 American College of Cardiology Foundation (ACCF)/AHA Focused Update, diabetic patients who present with UA/NSTE-ACS were designated as a subgroup for whom an early invasive strategy would be preferred. Subgroup analysis of diabetic patients in both the FRISC-II and TACTICS–TIMI 18 trial showed a significant risk reduction in MI and death with an invasive strategy.[6] In addition to an early invasive strategy, current guidelines recommend maintaining glucose levels below 180 mg/dL, but this must be done with caution to avoid hypoglycemia.[6]

Chronic Kidney Disease

Patients with chronic kidney disease (CKD) have worse outcomes after MI than the general population. In patients with end-stage renal disease, the 2-year mortality rate after an MI is 50%—twice that of the general population.[77] However, even mild CKD carries a worse prognosis after acute MI.[78] In addition, patients with CKD who undergo PCI for ACS have a higher mortality risk compared with those who have normal renal function.[79] However, few data are available regarding early invasive therapy in this high-risk group. The Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) study[80] was an observational, nonrandomized study that found a 36% lower mortality rate with early revascularization in patients with mild to moderate CKD who presented with NSTE-ACS but not with severe CKD (stage 4). A subsequent meta-analysis of randomized controlled trials in patients with CKD did not find a significant benefit in mortality or MI with an invasive strategy, although an invasive strategy was associated with significantly lower rates of rehospitalization compared with an ischemia-guided strategy.[81] Currently, the 2012 ACCF/AHA focused update considers an early invasive strategy reasonable in patients with mild and moderate CKD but recommends that physicians exercise judgement in this population.[6]

Women

The benefit of using an early invasive strategy for treating women is achieved primarily in women with high-risk features such as ST-segment changes or elevated troponin levels. Women who were managed with very early aggressive revascularization had a better long-term outcome than men.[82] The combined end point of death and nonfatal MI was significantly reduced at a follow-up of 20 months for women compared with men (OR 0.65; 95% CI, 0.28 to 0.92).

RADIAL PERCUTANEOUS CORONARY INTERVENTION

Patients undergoing an invasive approach for ACS are concurrently treated with antithrombotic and antiplatelet therapy and are therefore at higher risk for bleeding than those undergoing elective PCI. These bleeding complications are associated with a significant mortality risk.[83,84] PCI via radial arterial access is associated with significantly lower rates of bleeding compared with femoral arterial access, and increasingly more operators are utilizing radial artery PCI during ACS, including STEMI. The Trial of Trans-Radial Versus Trans-Femoral Percutaneous Coronary Intervention (PCI) Access Site Approach in Patients With Unstable Angina or Myocardial Infarction Managed With an Invasive Strategy (RIVAL)[85] randomized 7021 patients with STEMI ($n = 1958$) or NSTE-ACS ($n = 5063$) to radial versus femoral PCI. The primary end point was a composite of death, MI, stroke, and non–CABG-related major bleeding. A significant reduction was seen in mortality (1.3% vs. 3.2%, radial vs. femoral, $P = .006$) and in the primary end point (3.1% vs. 5.2%, radial vs. femoral, $P = .026$) with radial PCI in patients with STEMI. However, in NSTE-ACS patients, the difference was not significant in either mortality or the primary end point. Preliminary data from the Radial Versus Femoral Access in Mortality Reduction in Non–ST-Elevation Myocardial Infarction (REALITY-NSTEMI) study was presented at the Transcatheter Cardiovascular Therapeutics (TCT) 2013 Scientific Sessions. This observational cohort study enrolled 10,095 patients who presented with NSTE-ACS and found that transradial access was associated with significantly lower rates of bleeding (0.23% vs. 0.97%, radial vs. femoral, $P = .001$) and access-site complications (0.35% vs. 1.00%, radial vs. femoral, $P = .003$). Preliminary data also found a mortality benefit with transradial access in patients with NSTE-ACS at 30 days (HR 0.55; 95% CI, 0.31 to 0.97; $P = .041$), at 6 months (HR 0.59; 95% CI, 0.41 to 0.87; $P = .007$), and at 1 year (HR 0.74; 95% CI, 0.55 to 0.99; $P = .042$). Full details of REALITY-NSTEMI had not been published at the time of printing.[86]

REVASCULARIZATION OF MULTIVESSEL DISEASE IN NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

When patients undergo coronary angiography for NSTE-ACS and are found to have multivessel disease, the interventionalist must decide on an appropriate strategy for revascularization: PCI versus CABG and multivessel PCI versus culprit-vessel PCI. CABG was compared with PCI in patients who were candidates for either procedure based on angiographic findings in the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME)[87] trial and in the Argentine Randomized Trial of Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple-Vessel Disease (ERACI-II).[88] It is important to note that both trials were performed before the advent of drug-eluting stents, which are known to substantially reduce the rate of repeat revascularization, and both trials excluded patients who had clear indications for CABG over PCI (such as left main CAD). In the AWESOME trial,[87] 454 patients with medically refractory angina or provocable ischemia after stabilization with medical therapy who were at high risk for increased 30-day postoperative mortality after CABG were randomly assigned to undergo PCI (54% with stenting and 11% with a GP IIb/IIIa inhibitor) or CABG. PCI and CABG were associated with similar mortality rates at 30 days, 3 years, and 5 years; however, survival free of UA or repeat revascularization was lower in the PCI group. A registry of 1650 patients who were eligible for the AWESOME trial but were not randomized showed similar results (AWESOME registry).[89] In ERACI-II, 450 patients with multivessel disease were randomly assigned to CABG or PCI with bare-metal stents. Unlike the AWESOME trial, ERACI-II showed a significantly lower rate of major adverse events (death, MI, repeat revascularization, and stroke) at 30 days in the PCI group, primarily driven by a reduction in death. At 18 months, mortality remained lower in the PCI group; however, it was noted that the excess deaths seen in the CABG group had all occurred within the first 30 days. PCI was associated with a significant increase in new revascularization procedures at 18 months[88] and 5 years,[90] and a difference in mortality between the PCI and CABG groups was no longer apparent at 5 years.[90]

When NSTE-ACS patients are found to have significant multivessel disease by coronary angiography and there are no clear advantages for CABG, the interventionalist is next faced with the decision of whether to perform PCI on the culprit vessel only or to undertake multivessel

PCI. In making this decision, it is always important to consider from a practical standpoint that it may not always be overtly obvious which lesion is the clear culprit for the ACS event. This is especially the case when a patient has been treated with anticoagulant and antiplatelet therapy for many hours prior to angiography, which may decrease the intracoronary thrombus burden associated with a recently ruptured plaque and may make it difficult or impossible to identify. A retrospective analysis of the safety and efficacy of multivessel stenting versus culprit vessel–only stenting utilizing bare-metal stents in 1240 patients with NSTE-ACS revealed that multivessel stenting was associated with a significant reduction in the composite end point of death, MI, or revascularization during a mean follow-up period of 2.3 years.[91] This benefit, however, was entirely attributable to a lower subsequent revascularization rate in the patients who had undergone multivessel stenting compared with those who did not, and no differences in safety end points were found between the two groups.[91] The decision to proceed with multivessel PCI versus culprit vessel–only PCI may be influenced by several factors, including but not limited to angiographic severity/complexity of the lesions present, amount of myocardium supplied by the lesions in question, amount of fluoroscopy time used, and amount of contrast used, which leads to concerns over renal toxicity. In many cases, because of one or more of the previously mentioned factors, an interventionalist may choose to bring a patient back for a staged PCI procedure, either during the same hospitalization or at a later time, in order to complete the task of total revascularization.

DRUG-ELUTING STENTS FOR PATIENTS WITH NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

The primary limitation of PCI using bare-metal stents (BMSs) has been the higher rate of repeat revascularization. Drug-eluting stents (DESs) are associated with substantially reduced rates of target-lesion revascularization (TLR) in patients undergoing PCI and are being increasingly used in those with NSTE-ACS. In various randomized trials comparing the efficacy of DESs with that of BMSs to reduce the restenosis and target-vessel revascularization (TVR) rates, the reported proportions of patients with unstable CAD were between 30% and 50%.[92-95] Although many variables were studied that predicted early in-hospital complications or TVR, the presence of unstable CAD was not reported as a predictive factor. In a subanalysis of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry, investigating the safety and efficacy of sirolimus-eluting stents, it was shown that sirolimus stenting in patients with UA and in those with stable angina was associated with an almost similar risk reduction in the need for TVR compared with bare-metal stenting.[96] The hazard ratio at 1 year of clinically driven TVR for DES use was 0.30 (95% CI, 0.13 to 0.71; $P < .0006$) compared with bare-metal stenting. The Basel Stent Kosten Effektivitäts Trial (BASKET)[97] demonstrated that there were fewer adverse cardiac events for patients ($N = 301$) with NSTE-ACS who received a DES than for those given a BMS.

A subgroup analysis of the One-Year Clinical Results With the Slow-Release, Polymer-Based Paclitaxel-Eluting TAXUS Stent (TAXUS IV) trial,[98] which examined 450 patients with ACS (80% UA and 20% NSTE-ACS), revealed a significant reduction in MACEs for patients treated with paclitaxel-eluting stents compared with bare-metal stenting, with a benefit due entirely to a lower rate of TLR. An analysis of the mandated Massachusetts State PCI Registry showed that in 1228 matched pairs, the 2-year risk of death or recurrent MI was significantly lower in patients who received DESs, as was the rate of revascularization.[99] It may be concluded, then, that the safety and efficacy of DES implantation are similar in patients who present with stable or unstable CAD. However, because of delayed healing after DES and the effects of stent implantation in a highly unstable thrombotic milieu, the use of DAPT should be continued for at least 1 year after DES implantation.

STATINS AND PERCUTANEOUS CORONARY INTERVENTION FOR NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

Early and post-PCI statin therapy is beneficial to reduce adverse coronary events after ACS. The Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering (MIRACL) trial[100] randomized 3086 patients with unstable CAD to early treatment with 80 mg of atorvastatin ($n = 1355$) or placebo ($n = 1384$). At 16 weeks, the primary end point—a composite of death, nonfatal MI, cardiac arrest, and recurrent ischemia—occurred in 14.8% in the atorvastatin group and 17.4% in the placebo group ($P = .048$). Only 16% of these patients underwent revascularization.

In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial,[101] intensive statin treatment in patients hospitalized for an ACS was compared with standard statin therapy. The combined primary end point was death from any cause, MI, documented UA, rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. The trial randomized 4162 patients to intensive statin treatment (80 mg of atorvastatin daily, $n = 2099$) or to pravastatin (40 mg, $n = 2063$). Of these patients, 69% underwent PCI for the treatment of their index ACS before randomization, and 75% underwent an early invasive strategy. The low-density lipoprotein (LDL) cholesterol levels were 106 mg/dL before treatment in each group. The primary end point at the end of follow-up (mean, 24 months) was reached in 22.4% of the intensive atorvastatin group and in 26.3% of the standard-dose pravastatin group ($P = .005$). The difference in treatment effect started at 30 days, which confirmed the results with statin treatment in the MIRACL trial.

In the Lescol Intervention Prevention Study (LIPS),[102] 1669 patients were randomized to receive 80 mg of fluvastatin or placebo, with treatment starting 2 days after successful PCI. The LIPS study showed that the statin-treated group had a significantly lower incidence of adverse clinical events (24.1%) than the placebo group (26.7%, $P = .01$).

The most recently published AHA/ACC guidelines regarding statin therapy are notable for a dramatic departure from recommendations established during previous years. Patients with a history of ACS are at higher risk for recurrent atherosclerotic cardiovascular disease and death. For years, previous guideline recommendations had advocated secondary prevention with statins titrated to a goal LDL less than 100 mg/dL, with an option to titrate to a goal less than 70 mg/dL. With the newest guidelines, target LDL levels have been eliminated. Statin therapy is now categorized as (1) low intensity (lowers LDL-C by less than 30%), (2) moderate intensity (lowers LDL-C by 30% to 50%), and (3) high intensity (lowers LDL-C by 50% or more). The newest guidelines now recommend that all patients with a history of atherosclerotic cardiovascular disease receive statin therapy. In patients with an established history of CAD, those 75 years of age or younger without contraindications to statins should receive high-intensity statin therapy. Patients older than 75 years or those who may be at risk for drug interactions should receive moderate-intensity statin therapy. *High-intensity statin therapy* is defined as atorvastatin 40 or 80 mg or rosuvastatin 20 mg. *Moderate-intensity statin therapy* consists of the following options: (1) atorvastatin 10 to 20 mg, (2) rosuvastatin 5 to 10 mg, (3) simvastatin 20 to 40 mg, (4) pravastatin 40 to 80 mg, (5) lovastatin 40 mg, or (6) fluvastatin 40 mg twice daily. Once the appropriate intensity of statin therapy has been initiated, the current guidelines no longer recommend treating to a target LDL.[103]

MANAGEMENT OF PATIENTS WITH NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

Outlined here is a pragmatic approach consistent with the most recent ACC/AHA and European Society of Cardiology (ESC) guidelines.[6,104-106] Patients with NSTE-ACS should receive antiischemic, antiplatelet, and anticoagulant treatment. An early risk assessment is vitally important

TABLE 19-12 American College of Cardiology/American Heart Association Risk Stratification: Short-Term Risk Stratification of Death or Nonfatal Myocardial Infarction in Patients With Non–ST-Elevation Myocardial Infarction and Acute Coronary Syndrome

Feature	High Risk (At Least One of These Must Be Present)	Intermediate Risk (No High-Risk Features, Must Have One of These)	Low Risk (No Intermediate- or High-Risk Feature, May Have These)
History	Accelerating tempo of ischemic symptoms in preceding 48 hr	Prior MI, peripheral or cerebrovascular disease, or CABG; prior aspirin use	
Character of pain	Prolonged ongoing rest pain (>20 min)	Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of CAD rest angina (<20 min or relieved with rest or sublingual nitroglycerin)	New-onset or progressive CCS class III or IV angina in the past 2 weeks with moderate or high likelihood of CAD
Clinical findings	Pulmonary edema, most likely related to ischemia New or worsening MR murmur S_3 or new or worsening rale, Hypotension, bradycardia, tachycardia Age >75 yr	Age >70 yr	
ECG findings	Angina at rest with transient ST-segment changes >0.05 mV BBB, new or presumed new Sustained ventricular tachycardia	T-wave inversions >0.2 mV Pathologic Q waves	Normal or unchanged ECG pattern during an episode of chest discomfort
Cardiac markers	Elevated (e.g., TnT or TnI >0.1 ng/mL)	Slightly elevated (e.g., TnT >0.01 but <0.1 ng/mL)	Normal

From Amsterdam EA, Wenger NK, Brindis RG, et al: 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 64:e139-e228, 2014.
CABG, coronary artery bypass grafting; *BBB,* bundle branch block; *CAD,* coronary artery disease; *CCS,* Canadian Cardiovascular Society; *ECG,* electrocardiography; *MI,* myocardial infarction; *MR,* mitral regurgitation; *Tn,* troponin (I and T forms).

TABLE 19-13 American College of Cardiology/American Heart Association High-Risk Indicators for Non–ST-Segment Elevation Acute Coronary Syndrome

Recurrent angina or ischemia at rest or with low-level activities despite intensive antiischemic treatment
- Elevated troponin levels
- New or presumably new ST-segment depression

Recurrent angina or ischemia with congestive heart failure symptoms, S_3 gallop, pulmonary edema, worsening rales, or new or worsening mitral regurgitation
- High-risk findings on noninvasive stress testing
- Depressed left ventricular systolic function
- Hemodynamic instability
- Sustained ventricular tachycardia
- Percutaneous coronary intervention within 6 months
- Prior coronary artery bypass grafting

From Amsterdam EA, Wenger NK, Brindis RG, et al: 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 64:e139-e228, 2014.

TABLE 19-14 European Society of Cardiology Guidelines for Risk

High-Risk Indicators	Low-Risk Indicators
Elevated troponin levels	Normal troponin levels
Recurrent ischemia	No recurrent ischemia
ST-segment depression	No release of creatine kinase MB fraction
Early unstable angina after myocardial infarction	Presence of negative or flat T waves
Hemodynamic instability	Normal electrocardiogram
Major arrhythmias: ventricular fibrillation, ventricular tachycardia	

From Hamm C, Bassand J, Agewall S, et al: ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 32(23):2999-3054, 2011.

in order to identify those who may benefit from an early aggressive approach. This assessment should be based on clinical presentation, age, electrocardiographic (ECG) changes, cardiac enzymes and biomarkers, and clinical course. The risk level is classified as high, intermediate, or low (Tables 19-12 through 19-14); further management is guided by risk classification. Patients who present with NSTE-ACS and evidence of hemodynamic instability or cardiogenic shock, severe left ventricular dysfunction or overt heart failure, recurrent or persistent angina at rest despite intensive medical therapy, acute mitral regurgitation or ventricular septal defect, or sustained ventricular arrhythmias should undergo urgent coronary angiography and appropriate revascularization. Patients who are stable but have a history of prior CABG or PCI within 6 months, new ST-segment depression, elevated cardiac biomarkers, angina with minimal activity despite intensive medical therapy, left ventricular ejection fraction below 40%, or a TIMI risk score greater than 2 should be managed with an early invasive strategy. Patients with a low TIMI risk score (<2) and no high-risk features should be managed with an ischemia-guided strategy. The findings of coronary angiography largely determine whether patients should be referred for PCI or CABG (see Fig. 19-7). If PCI is the chosen revascularization modality, it may be performed in the same sitting or in a staged fashion as deemed appropriate by the treating physician. Patients undergoing PCI should receive adjunctive treatment with aspirin, a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor), and an anticoagulant (UFH, LMWH, bivalirudin, or fondaparinux) with or without a GP IIb/IIIa antagonist. Lifestyle changes and secondary prevention using aspirin, beta-blockers, statins, and ACE inhibitors should be implemented for all survivors of NSTE-ACS as appropriate.

REFERENCES

1. Grüntzig AR, Senning A, Siegenthaler WE: Non-operative dilatation of coronary artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med* 301:61–68, 1979.
2. de Feyter PJ, Serruys PW, van den Brand M, et al: Emergency coronary angioplasty in refractory unstable angina. *N Engl J Med* 313:342–346, 1985.
3. Sigwart U, Puel J, Mirkovitch V, et al: Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med* 316:701–706, 1987.
4. Thygesen K, Alpert JS, Jaffe AS, et al: Third universal definition of myocardial infarction—expert consensus document. *J Am Coll Cardiol* 60:1–18, 2012.
5. Yeh RW, Sidney S, Chandra M, et al: Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med* 362:2155–2165, 2010.
6. Jneid H, Anderson JL, Wright RS, et al: 2012 ACCF/AHA focused update of the Guideline for the Management of Patients with Unstable Angina/Non-ST myocardial Infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 60:645–681, 2012.
7. Amsterdam EA, Wenger NK, Brindis RG, et al: 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 64:e139–e228, 2014.
8. Fuster V, Moreno PR, Fayad ZA, et al: Atherothrombosis and high-risk plaque. Part I. Evolving concepts. *J Am Coll Cardiol* 46:937–945, 2005.
9. Armstrong PW, Fu Y, Chang WC, et al: Acute coronary syndromes in the GUSTO-IIb trial: prognostic insights and impact of recurrent ischemia. The GUSTO-IIb Investigators. *Circulation* 98:1860–1868, 1998.
10. Antman EM, Cohen M, Bernink PJ, et al: The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA* 284:835–842, 2000.
11. Eagle KA, Lim MJ, Dabbous OH, et al: A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 291:2727–2733, 2004.
12. Januzzi JL, Jr, Newby LK, Murphy SA, et al: Predicting a late positive serum troponin in initially troponin-negative patients with non-ST-elevation acute coronary syndrome: clinical predictors and validated risk score results from the TIMI IIIB and GUSTO IIA studies. *Am Heart J* 151:360–366, 2006.
13. Patrono C, Coller B, FitzGerald GA, et al: Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 126(3 Suppl):234S–264S, 2004.
14. Loll PJ, Picot D, Garavito RM, et al: The structural basis of aspirin activity inferred from the crystal structure of inactivated prostaglandin H2 synthase. *Nat Struct Biol* 2(8):637–643, 1995.
15. Collaborative overview of randomized trials of antiplatelet therapy: I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *BMJ* 308(6921):81–106, 1994.
16. Antithrombotic Trialists' Collaboration: Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 324:71–86, 2002.
17. CURRENT–OASIS 7 Investigators: Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med* 363(10):930–942, 2010.
18. Serebrauny VL, Steinhubl SR, Berger PB, et al: Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. *Am J Cardiol* 95(10):1218–1222, 2005.
19. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators: Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 345:494–502, 2001.
20. Bhatt DL, Fox KA, Hacke W, et al: Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 354(16):1706–1717, 2006.
21. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 348(9038):1329–1339, 1996.
22. Mehta SR, Yusuf S, Peters RJ, et al: Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 358(9281):527–533, 2001.
23. Kandzari DE, Berger PB, Kastrati A, et al: Influence of treatment duration with a 600 mg dose of clopidogrel before percutaneous coronary revascularization. *J Am Coll Cardiol* 44(11):2133–2136, 2004.
24. Oqueli E, Hiscock M, Dick R: Clopidogrel resistance. *Heart Lung Circ* 16(Suppl 3):S17–S28, 2007.
25. Frere C, Cuisset T, Morange PE, et al: Effect of cytochrome p450 polymorphisms on platelet reactivity after treatment with clopidogrel in acute coronary syndrome. *Am J Cardiol* 101(8):1088–1093, 2008.
26. Holmes DR, Jr, Dehmer GJ, Kaul L, et al: ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Task Force on clinical expert consensus documents and the American Heart Association endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 56:321–341, 2010.
27. Price MJ: The evidence base for platelet function testing in patients undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv* 3(3):277–283, 2010.
28. Price MJ, Berger PB, Teirstein PS, et al: Standard- vs. high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS Randomized trial. *JAMA* 305(11):1097–1105, 2011.
29. COGENT Investigators: Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 363:1909–1917, 2010.
30. Wiviott SD, Braunwald E, McCabe CH, et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 357(20):2001–2015, 2007.
31. Wiviott SD, Braunwald E, McCabe CH, et al: Intensive oral antiplatelet therapy for reduction of ischemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomized trial. *Lancet* 371(9621):1353–1363, 2008.
32. Montalescot G, Bolognese L, Dudek D, et al: Pretreatment with prasugrel in non-ST- segment elevation acute coronary syndromes. *N Engl J Med* 369:999–1010, 2013.
33. Van Giezen J, Nilsson L, Berntsson P, et al: Ticagrelor binds to human P2Y12 independently from ADP but antagonizes ADP-induced receptor signaling and platelet aggregation. *J Thromb Haemost* 7:1353–1363, 2009.
34. Wallentin L, Becker RC, Judaj A, et al: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 361(11):1045–1057, 2009.
35. Oler A, Whooley MA, Oler J, Grady D: Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *JAMA* 276:811–815, 1996.
36. Swahn E, Wallentin L: Low-molecular-weight heparin (Fragmin) during instability in coronary artery disease (FRISC). FRISC study Group. *Am J Cardiol* 80(5A):25E–29E, 1997.
37. Cohen M, Demers C, Gurfinkel EP, et al: A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* 337(7):447–452, 1997.
38. Antman EM, McCabe CH, Gurfinkel EP, et al: Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation* 100(15):1593–1601, 1999.
39. Peterson JL, Mahaffey KW, Hasselblad V, et al: Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-segment elevation acute coronary syndromes: a systematic overview. *JAMA* 292(1):89–96, 2004.
40. Furguson JJ, Califf RM, Antman EM, et al: Enoxaparin vs. unfractionated heparin in high- risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. *JAMA* 292(1):45–54, 2004.
41. Lincoff AM, Bittl JA, Harrington RA, et al: Bivalirudin and provisional glycoprotein IIb/IIIa blockage compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 289:853–863, 2003.
42. Stone GW, McLaurin BT, Cox DA, et al: Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 355:2203–2216, 2006.
43. Yusuf S, Mehta SR, Chrolavicius S, et al: Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 354:1464–1476, 2006.
44. Topol EJ, Byzova TV, Plow EF: Platelet GPIIb-IIIa blockers. *Lancet* 353(9148):227–231, 1999.
45. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. *N Engl J Med* 330(14):956–961, 1994.
46. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. *Lancet* 349(9063):1429–1435, 1997.
47. GUSTO IV-ACS Investigators: Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomized trial. *Lancet* 357(9272):1915–1924, 2001.
48. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. *N Engl J Med* 338:1498–1505, 1998.
49. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. *N Engl J Med* 338(21):1488–1497, 1998.
50. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med* 339(7):436–443, 1998.
51. Boersma E, Harrington RA, Moliterno DJ, et al: Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomized clinical trials. *Lancet* 359(9302):189–198, 2002.
52. TARGET Investigators: Outcomes at 6 months for the direct comparison of tirofiban and abciximab during percutaneous coronary revascularisation with stent placement: the TARGET follow-up study. *Lancet* 360:355–360, 2002.
53. Giugliano RP, White JA, Bode C, et al: Early vs. delayed, provisional eptifibatide in acute coronary syndromes. *N Engl J Med* 360:2176–2190, 2009.
54. Intracoronary Stenting and Antithrombotic Regimen Rapid Early Action for Coronary Treatment 2 (ISAR-REACT 2) Trial Investigators: Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA* 295:1531–1538, 2006.
55. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation* 89:1545–1556, 1994.
56. Boden WE, O'Rourke RA, Crawford MH, et al: Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med* 338:1785–1792, 1998.
57. McCullough PA, O'Neill WW, Graham M, et al: A prospective randomized trial of triage angiography in acute coronary syndromes ineligible for thrombolytic therapy. Results of the medicine versus angiography in thrombolytic exclusion (MATE) trial. *J Am Coll Cardiol* 32:596–605, 1998.
58. Wallentin L, Lagerqvist B, Husted S, et al: Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. FRISC II Investigators. Fast Revascularisation during Instability in Coronary artery disease. *Lancet* 356:9–16, 2000.
59. Cannon CP, Weintraub WS, Demopoulos LA, et al: Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 344:1879–1887, 2001.
60. Spacek R, Widimsky P, Straka Z, et al: Value of first day angiography/angioplasty in evolving Non-ST segment elevation myocardial infarction: an open multicenter randomized trial. The VINO Study. *Eur Heart J* 23:230–238, 2002.
61. Fox KA, Poole-Wilson PA, Henderson RA, et al: Randomized Intervention Trial of unstable Angina Investigators. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: The British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. *Lancet* 360:743–751, 2002.
62. The Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) Investigators: Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med* 353:1095–1104, 2005.
63. Henderson RA, Jarvis C, Clayton T, et al: 10-year mortality outcome of a routine invasive strategy versus a selective invasive strategy in non-ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol* 66:511–520, 2015.
64. CRUSADE Investigators: Optimal timing of intervention in non-ST-segment elevation acute coronary syndromes: insights from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Registry. *Circulation* 112:3049–3057, 2005.
65. Neumann FJ, Kastrati A, Pogatsa-Murray G, et al: Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. *JAMA* 290:1593–1599, 2003.
66. van't Hof AW, de Vries ST, Dambrink JH, et al: A comparison of two invasive strategies in patients with non-ST elevation acute coronary syndromes: Results of the Early or Late Intervention in unStable Angina (ELISA) pilot study: 2b/3a upstream therapy and acute coronary syndromes. *Eur Heart J* 24:1401–1405, 2003.
67. Bhatt DL, Roe MT, Peterson ED, et al: Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: Results from the CRUSADE Quality Improvement Initiative. *JAMA* 292:2096–2104, 2004.
68. Riezebos RK, Ronner E, Ter Bals E, et al: Immediate versus deferred coronary angioplasty in non-ST-segment elevation acute coronary syndromes. *Heart* 95(10):807–812, 2009.

69. Montalescot G, Cayla G, Collet JP, et al: Immediate vs. delayed intervention for acute coronary syndromes: a randomized controlled trial. *JAMA* 302:947–954, 2009.
70. Mehta SR, Grangar CB, Boden WE, et al: Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 360:2165–2175, 2009.
70a. Fox KA, Poole-Wilson P, Clayton TC, et al: 5-Year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: The British Heart Foundation RITA 3 randomised trial. *Lancet* 366:914–920, 2005.
71. Sabatine MS, Morrow DA, McCabe CH, et al: Combination of quantitative ST deviation and troponin elevation provides independent prognostic and therapeutic information in unstable angina and non-ST-elevation myocardial infarction. *Am Heart J* 151:25, 2006.
72. Fox KA, Clayton TC, Damman P, et al: Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome. *J Am Coll Cardiol* 55:2435–2445, 2010.
73. Hamm CW, Bassand JP, Agewall S: ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 32:2999–3054, 2011.
74. Danaei G, Lawes CM, Vander Hoorn S, et al: Global and regional mortality from ischemic heart disease and stroke attributable to higher-than-optimum blood glucose concentration: comparative risk assessment. *Lancet* 368(9548):1651–1659, 2006.
75. Wild S, Roglic G, Green A, et al: Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27(5):1047–1053, 2004.
76. Donahoe SM, Stewart GC, McCabe CH: Diabetes and mortality following acute coronary syndromes. *JAMA* 298(7):765–775, 2007.
77. Sarnak MJ, Levey AS, Schoolwerth AC, et al: Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension* 42:1050–1065, 2003.
78. Anavekar NS, McMurray JJ, Velazquez EJ, et al: Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 351:1285–1295, 2004.
79. Best PJ, Lennon R, Ting HH, et al: The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol* 39:1113–1119, 2002.
80. Szummer K, Lundman P, Jacobson SH, et al: Influence of renal function on the effects of early revascularization in non-ST-elevation myocardial infarction: data from the Swedish WebSystem for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). *Circulation* 120:851–858, 2009.
81. Charytan DM, Wallentin L, Lagerqvist B, et al: Early angiography in patients with chronic kidney disease: a collaborative systematic review. *Clin J Am Soc Nephrol* 4:1032–1043, 2009.
82. Mueller C, Neumann FJ, Roskamm H, et al: Women do have an improved long-term outcome after non-ST-elevation acute coronary syndromes treated very early and predominantly with percutaneous coronary intervention: a prospective study in 1,450 consecutive patients. *J Am Coll Cardiol* 40:245–250, 2002.
83. Moscucci M, Fox KA, Cannon CP, et al: Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 24:1815–1823, 2003.
84. Eikelboom JW, Mehta SR, Anand SS, et al: Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* 114:774–782, 2006.
85. Mehta SR, Jolly SS, Cairns J: Effects of radial versus femoral artery access in patients with acute coronary syndromes with or without ST-segment elevation. *J Am Coll Cardiol* 60:2490–2499, 2012.
86. Iqbal MB, Arujuna A, Archbold A, et al: Superior outcomes associated with radial versus femoral access in non-ST elevation myocardial infarction: an observational cohort study of 10,095 patients. Results of the Radial Versus Femoral Access in Mortality Reduction in Non-ST Elevation Myocardial Infarction (REALITY-NSTEMI) Study. *J Am Coll Cardiol* 62(18_S1):B14–B14, 2013.
87. Morrison DA, Sethi G, Sacks J, et al: Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. Investigators of the Department of Veterans Affairs Cooperative Study #385, the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). *J Am Coll Cardiol* 38:143–149, 2001.
88. Rodriguez A, Bernardi V, Navia J, et al: Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in patients with Multiple-Vessel Disease (ERACI II): 30-day and one-year follow-up results. ERACI II Investigators. *J Am Coll Cardiol* 37:51–58, 2001.
89. Morrison DA, Sethi G, Sacks J, et al: Percutaneous coronary intervention versus coronary artery bypass surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: the VA AWESOME multicenter registry: comparison with the randomized control trial. *J Am Coll Cardiol* 26:266, 2002.
90. ERACI II Investigators: Five-year follow-up of the Argentine randomized trial of coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple vessel disease (ERACI II). *J Am Coll Cardiol* 46:582–588, 2005.
91. Shishehbor MH, Lauer MS, Singh IM, et al: In unstable angina or non-ST-segment acute coronary syndrome, should patients with multivessel coronary artery disease undergo multivessel or culprit-only stenting? *J Am Coll Cardiol* 49:849–854, 2007.
92. Morice MC, Serruys PW, Sousa JE, et al: A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 346:1773–1780, 2002.
93. Moses JW, Leon MB, Popma JJ, et al: Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 349:1315–1323, 2003.
94. Colombo A, Drzewiecki J, Banning A, et al: Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 108:788–794, 2003.
95. TAXUS-IV Investigators: A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 350:221–231, 2004.
96. Lemos PA, Serruys PW, van Domburg RT, et al: Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *Circulation* 109:190–195, 2004.
97. BASKET Investigators: Incremental cost-effectiveness of drug-eluting stents compared with a third-generation bare-metal stent in a real-world setting: Randomised Basel Stent Kosten Effektivitäts Trial (BASKET). *Lancet* 366:921–929, 2005.
98. Moses JW, Mehran R, Nikolsky E, et al: Outcomes with the paclitaxel-eluting stent in patients with acute coronary syndromes: analysis from the TAXUS-IV trial. *J Am Coll Cardiol* 45:1165–1171, 2005.
99. Mauri L, Silbaugh TS, Garg P, et al: Drug-eluting or bare-metal stents for acute myocardial infarction. *N Engl J Med* 359:1330–1342, 2008.
100. Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators: Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 285:1711–1718, 2001.
101. Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators: intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 350:1495–1504, 2004.
102. Lescol Intervention Prevention Study (LIPS) Investigators: Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA* 287:3215–3222, 2002.
103. American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 129:S1–S45, 2014.
104. The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC); the European Association for Cardio-Thoracic Surgery (EACTS); the European Association for Percutaneous Cardiovascular Interventions (EAPCI), et al: Guidelines on myocardial revascularization. *Eur Heart J* 31: 2501–2555, 2010.
105. American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 61(4):e78–e140, 2013.
106. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report from the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 58(24):e44–e122, 2011.

Percutaneous Coronary Intervention in Acute ST-Segment Elevation Myocardial Infarction

20

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KEY POINTS

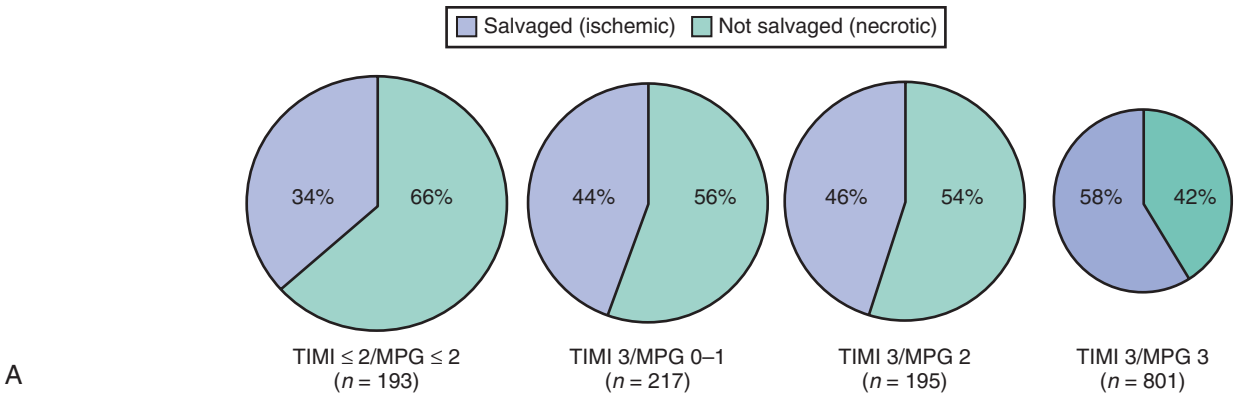
- Catheter-based primary percutaneous coronary intervention (PCI) has become the mainstay of reperfusion therapy and has supplanted thrombolytic therapy as the reperfusion treatment of choice in patients with ST-elevation myocardial infarction (STEMI) in the United States and in Europe.
- PCI is superior to thrombolytic therapy in reducing death, reinfarction, intracranial bleeding, reocclusion of the infarct-related artery, and myocardial ischemia in patients with STEMI irrespective of the patient's risk or whether interhospital transfer for PCI is required.
- PCI retains its myocardial salvaging capacity and its ability to improve clinical outcome over a wider time window after symptom onset than thrombolysis and is the recommended therapy for patients who present early or late after symptom onset.
- Primary stenting is the preferred primary percutaneous coronary intervention (PPCI) approach for patients with STEMI, and drug-eluting stents (DESs)—in particular, second-generation DESs—should be considered the preferred device for use in PPCI. Although randomized trials and meta-analyses offer no firm evidence of an effect of DES on mortality (either an excess or a reduction) or recurrent myocardial infarction (MI), they demonstrate clear superiority in antirestenotic efficacy.
- Randomized trials and registries support the use of the radial artery for vascular access in patients with STEMI who undergo PPCI.
- Use of thrombolysis for facilitated PCI as a strategy to promote reperfusion within the time interval from patient presentation to performance of PCI is associated with worse clinical outcomes than PCI alone and cannot be recommended for STEMI patients.
- Rescue PCI after failed thrombolysis salvages ischemic myocardium and improves clinical outcome and thus is the recommended treatment for these patients.
- The pharmacoinvasive strategy, routine use of a thrombolytic agent or glycoprotein (GP) IIb/IIIa inhibitor prior to planned PCI, was associated with clinical benefit in patients with STEMI. In the setting of this strategy, angiography and planned PCI are performed 3 to 24 hours after presentation.
- Available evidence supports the use of clopidogrel, prasugrel, and ticagrelor before treatment in patients with STEMI who will undergo PPCI. Bivalirudin, a thrombin receptor blocker, has emerged as an effective and safe antithrombotic agent in patients with STEMI undergoing PPCI, and the drug was associated with reduced incidence of bleeding complications compared with unfractionated heparin (UFH).
- The available evidence supports the use of manual aspiration thrombectomy as an adjunctive mechanical strategy in the setting of PPCI in the majority of patients with STEMI. Neither mechanical thrombectomy nor distal protection devices improve results over conventional PPCI and cannot be recommended based on current evidence.
- The role of cell-based myocardial repair and regenerative agents in the management of patients with STEMI warrant further investigation.

Coronary artery disease (CAD) is a leading cause of death worldwide. Acute coronary syndromes (ACSs)—and in particular, acute MI—are important contributors to the death and disability related to this disease. MI can be recognized by clinical features that include typical electrocardiography (ECG) features, elevated biomarkers of myocardial necrosis, and imaging findings or pathologic examination.[1] Acute MI results mostly from acute thrombotic occlusion of an epicardial coronary artery that typically occurs as a consequence of atherosclerotic plaque disruption, fissuring, or erosion that leads to exposure of thrombogenic material such as plaque lipid content, collagen, and subendothelial extracellular matrix to circulating blood. Other causative factors of lesser importance include acute plaque expansion—such as that which occurs as a result of intraplaque hemorrhage, leading to acute closure without or with minimal intraluminal thrombus formation—embolism, spontaneous dissection, coronary inflammation, and extracoronary factors. Interruption of coronary blood flow results in myocardial ischemia in the blood-deprived myocardial area; if the ischemia is severe enough and of sufficient duration, it results in myocardial necrosis. With the exception of sudden cardiac death, acute STEMI represents the most malignant presentation of ACSs that result from acute thrombus-mediated closure of a coronary artery. Earlier angiographic studies performed in patients within 24 hours of MI have proven the role of acute thrombus formation in causing acute coronary occlusion and STEMI.[2] Because acute coronary thrombosis is often abrupt in onset, and the ensuing ischemic damage is irreversible, the rationale is strong for prompt reperfusion therapy—that is, pharmacologic or mechanical removal of occlusive thrombi—aimed at early restoration of coronary blood flow to the infarct-related artery. Timely reperfusion results in myocardial salvage, increased electrical stability, and reduced incidence of fatal ventricular arrhythmias in the acute phase in addition to preservation of left ventricular (LV) function and improvement in short- and long-term patient survival. Although current evidence suggests that the incidence of STEMI is trending downward[3,4] and that STEMI-related mortality has decreased,[5] STEMI still represents a severe condition associated with poor short- and long-term prognosis, particularly in the setting of suboptimal reperfusion (Fig. 20-1).[6] Abundant evidence over the last three decades supports the role of reperfusion therapy, thrombolysis, or PPCI in improving both survival and quality of life in patients with STEMI. However, despite the proven efficacy of timely reperfusion, the proportion of patients with STEMI who receive suboptimal reperfusion or no reperfusion remains unacceptably high.[7] Of note, the number of patients with STEMI who receive no reperfusion therapy has remained unchanged at 20% to 30% of all STEMI cases.[8]

The main focus of this chapter is to summarize recent developments in the field of PPCI in patients with acute STEMI.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION VERSUS THROMBOLYSIS AS A REPERFUSION STRATEGY FOR STEMI

Rapid restoration of coronary blood flow in the occluded coronary artery and the subtended myocardial tissue is the fundamental aim of early STEMI therapy. *Primary percutaneous coronary intervention* refers to a strategy of emergent coronary angiography followed by coronary angioplasty with or without stenting of the infarct-related



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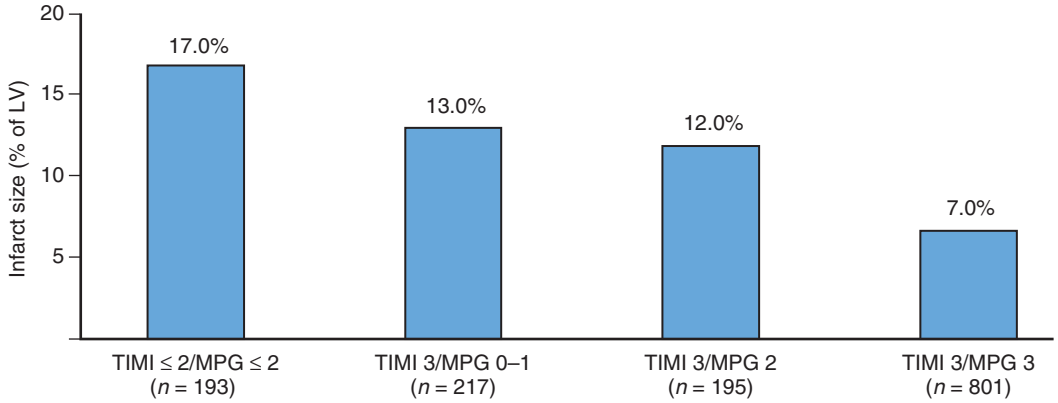

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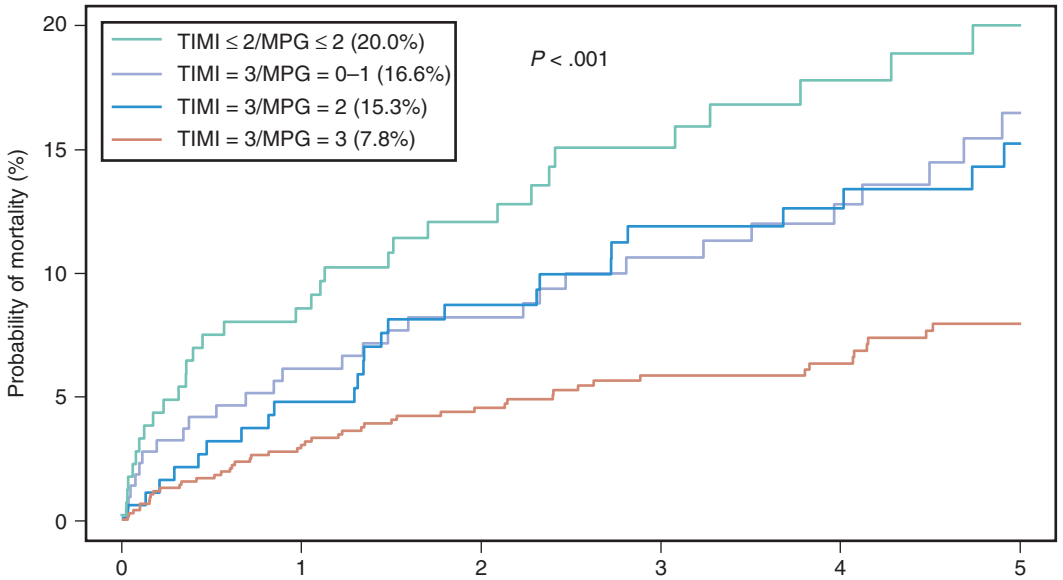


Numbers at risk						
TIMI ≤ 2/MPG ≤ 2	193	169	127	100	82	63
TIMI = 3/MPG = 0–1	217	186	164	134	109	76
TIMI = 3/MPG = 2	195	176	154	133	112	85
TIMI = 3/MPG = 3	801	714	588	458	373	289

C

FIGURE 20-1 Efficacy of reperfusion and its association with 5-year mortality in patients with ST-elevation myocardial infarction. **A,** Size and proportion of initial area at risk salvaged. **B,** Infarct size in the single photon emission computed tomography (SPECT) imaging obtained 7 to 14 days after primary percutaneous coronary intervention. **C,** Kaplan-Meier estimates of 5-year mortality according to reperfusion efficacy. *LV,* Left ventricle; *MPG,* myocardial perfusion grade; *TIMI,* thrombolysis in myocardial infarction. (From Ndrepepa G, Schömig A, Kastrati A: Efficacy of reperfusion with primary percutaneous coronary intervention in patients with acute ST segment elevation myocardial infarction. *Clin Res Cardiol* 100[11]:1047-1048, 2011.)

artery and without prior administration of thrombolytic therapy. Mechanical reperfusion by PPCI has become the standard of care for patients with STEMI, and current guidelines recommend PPCI as the default reperfusion strategy for patients with STEMI who present within the first few hours after the onset of symptoms.[9,10] PPCI has become the dominant reperfusion strategy in patients with STEMI in North America[10] and Europe (Fig. 20-2).[7] Evidence from randomized studies shows that catheter-based mechanical reperfusion in patients with STEMI is superior to thrombolytic therapy in terms of improving of early and late survival, as well as in reducing the incidence of reinfarction, intracranial bleeding, reocclusion of the infarct-related artery, and recurrent myocardial ischemia.[11]

The introduction of thrombolytic therapy represented an important development in the treatment of STEMI. The application of thrombolytic agents early after symptom onset was associated with reduced mortality compared with no reperfusion. A meta-analysis of initial thrombolytic trials demonstrated that the absolute mortality benefit at 5 weeks following thrombolysis was 3% for patients who presented within 6 hours, 2% for patients who presented between 7 and 12 hours, and 1% (statistically insignificant) for those who presented between 13 and 18 hours after the symptom onset.[12] Despite the clear benefits of thrombolysis compared with no reperfusion, it has serious limitations: these relate to the high proportion of patients with relative or absolute contraindications to this therapy; life-threatening bleeding complications that disproportionately affect older adult patients; a narrow window of therapeutic action after symptom onset due to rapid time-dependent loss of efficacy; limited ability to restore normal blood flow in the infarct-related artery, even if applied in a timely fashion; and frequent reocclusions of the infarct-related artery, which results in recurrent ischemia or reinfarction within subsequent months. Apart from markedly attenuating these limitations, PPCI has other advantages over thrombolytic therapy that include (1) restoration of significantly higher rates of thrombolysis in myocardial infarction (TIMI) flow grade 3 in the infarct-related artery, a benefit that is both relatively independent of time from symptom onset and durable because of enhanced stability of the reopened vessel; (2) salvage of greater amounts of myocardium; (3) delineation of coronary anatomy and hemodynamic status, which results in improved risk stratification; and (4) facilitation of patient care and earlier hospital discharge.[13]

PPCI improves survival even in patients with STEMI who have contraindications to thrombolytic therapy[14] and in patients who present outside the therapeutic window of thrombolysis.[15,16] Superiority of PPCI over thrombolysis has been witnessed, particularly in high-risk patients[17] and in centers without on-site cardiac surgery.[18] The Danish Trial in Acute Myocardial Infarction 2 (DANAMI-2) demonstrated that the benefit of PPCI is largest in high-risk patients: in patients with a TIMI risk score of 5 or more, the reduction in the mortality with PPCI was significant (25.3% vs. 36.2% with thrombolysis; $P = .02$) and was not observed in the low-risk group (TIMI risk score 0 to 4).[17] The benefit of PPCI over thrombolysis was maintained at long-term follow-up. A further report from the DANAMI-2 trial showed that the 8-year composite of death or reinfarction was 34.8% in patients treated by PPCI versus 41.3% in patients treated with thrombolysis ($P = .003$). Of note, PPCI reduced the risk of reinfarction (13% vs. 18.5%) and mortality (26.7% vs. 33.3%) among patients randomized at referral hospitals.[19] A recent meta-analysis that included 23 randomized controlled trials (RCTs; $n = 8140$) and 32 observational studies ($n = 185{,}900$) analyzed a series of outcomes for patients treated with PPCI or thrombolysis. In randomized trials, PPCI was associated with reductions of short-term (6-week) mortality by 34% (Fig. 20-3), long-term (≥1 year) mortality by 24%, short-term reinfarction by 65%, long-term reinfarction by 51%, and stroke by 63% compared with thrombolysis. In observational studies, PPCI was associated with reductions of short-term mortality by 23% (see Fig. 20-3), long-term mortality by 12% (statistically insignificant), short-term reinfarction by 53%, long-term reinfarction by 42% (statistically insignificant), and stroke by 61% compared with thrombolysis. The differences in major bleeding between both reperfusion strategies did not reach the level of statistical significance in randomized trials or observational studies.[20] The study reinforced the recommendation that PPCI should be offered to STEMI patients if transport to hospitals that offer invasive treatment can be completed within 120 minutes. Recent evidence also points out cost-effectiveness of PPCI compared with thrombolysis.[21,22]

Because of this evidence, the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines define *primary percutaneous coronary intervention* as a class 1 indication in patients with STEMI under three conditions: (1) ischemic symptoms have been present for fewer than 12 hours (level of evidence A); (2) ischemic symptoms have been present for fewer than 12 hours in patients who have contraindications to thrombolysis irrespective of time delay from the first medical contact (level of evidence B); and (3) irrespective of the time delay from the STEMI onset, cardiogenic shock or severe heart failure are present (level of evidence B).[10] In the recent guidelines of the European Society of Cardiology (ESC) for STEMI treatment, reperfusion in patients with STEMI who present within 12 hours of symptom onset was recommended as a class 1 indication (level of evidence A). PPCI is the preferred strategy (class 1 indication) if performed by an experienced team within 120 minutes from the first medical contact (level of evidence A) and in patients with severe heart failure or cardiogenic shock unless the expected PCI-related delay is excessive and the patient presents early after symptom onset (level of evidence B). Furthermore, coronary stenting is the preferred PPCI approach (class I indication, level of evidence A) compared with balloon angioplasty.[9] The lack of availability of centers equipped to offer timely PPCI for patients with STEMI, rather than issues that pertain to the clinical effectiveness of this reperfusion strategy, are currently perceived as the most important factor that impedes a broader application of this treatment to patients with STEMI.

At present, it seems that the era of head-to-head comparative studies between PPCI and pharmacologic thrombolytic therapy is over, and the superiority of PPCI over thrombolysis is almost unanimously accepted. However, only one-third of the hospitals in the United States are capable of performing PPCI.[23] Recognizing the importance of the problem, several regions in the United States have proposed or established triage and transfer protocols to direct patients with STEMI to hospitals with PCI capability without delay. A series of prehospital timing benchmarks have been proposed, the achievement of which was associated with favorable system performance; that is, they achieved a time interval from first medical contact (FMC) to PCI of 90 minutes or less (Table 20-1 and Fig. 20-4).[24]

SYSTEMS THAT OPTIMIZE REPERFUSION IN PATIENTS WITH STEMI

Over the last decade, considerable efforts have been made to build and apply STEMI systems of care with focus on speedy application of reperfusion therapy to patients with STEMI. Earlier studies were focused on hospital-based strategies applied to improve application of thrombolytic therapy to STEMI patients. Recognizing the powerful salvaging capacity of mechanical reperfusion if offered in a timely manner, much of the current research in the United States, Europe, and Canada has been focused on STEMI networks that involve PPCI. In 2007, the AHA launched the Mission: Lifeline initiative to encourage communities to develop their own systems to optimize reperfusion therapy in patients with STEMI.[25] In general, the systems of care consist of a series of multidisciplinary, orchestrated, hospital-wide measures aimed at reduction of the time to treatment in patients with ACSs, particularly STEMI.

In 2006, the results of a survey were published that included 365 hospitals in the United States that applied at least one strategy to decrease door-to-balloon (DTB) time.[26] The mean of median DTB times of each hospital was 100.4 (± 23.5) minutes, and 40% of hospitals had DTB times greater than 110 minutes. The authors identified 28 strategies used by hospitals to reduce DTB times. After adjusted analysis of the association between hospital strategies and DTB times, six strategies were associated with a positive impact on DTB times

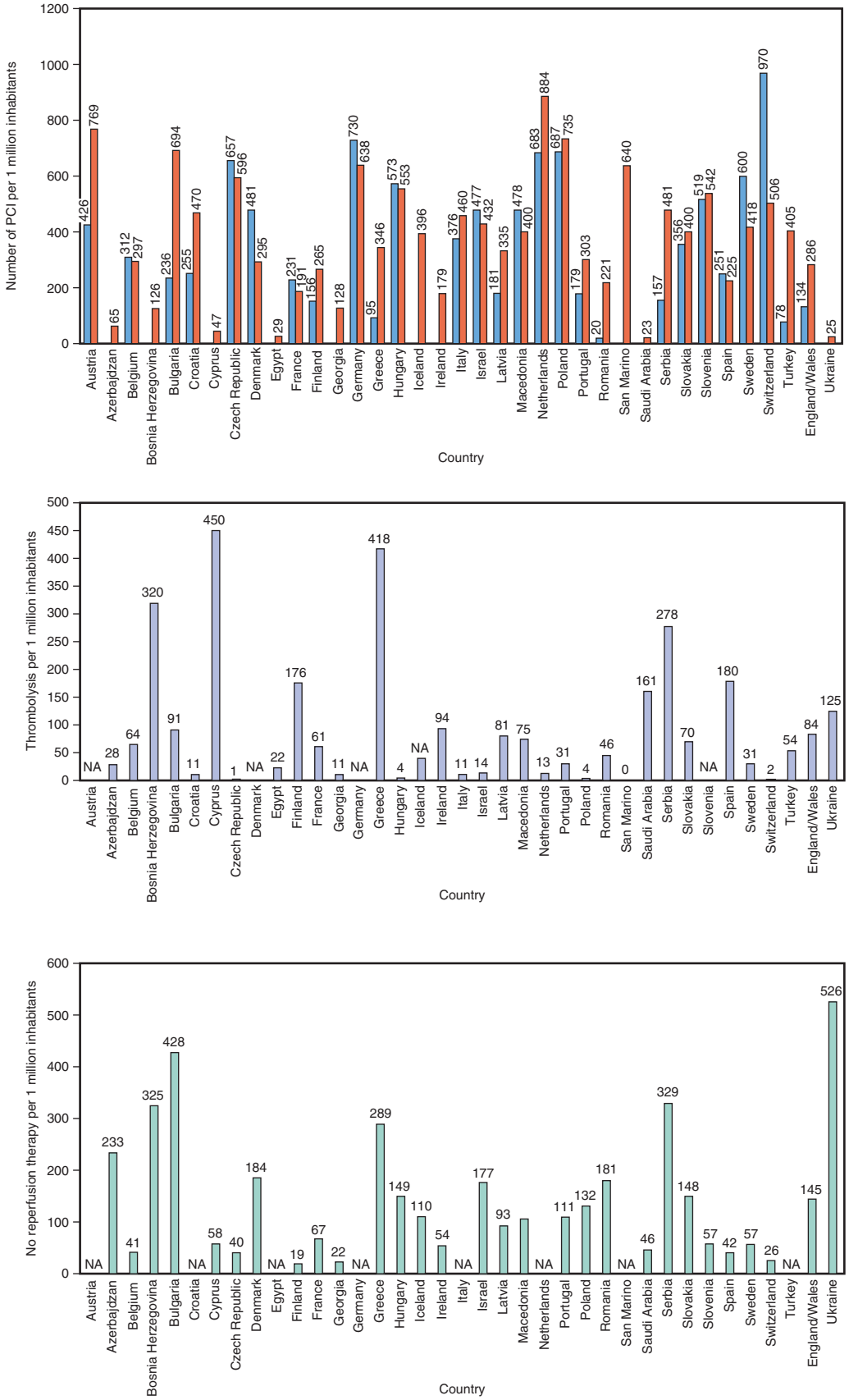


FIGURE 20-2 Numbers of patients with ST-elevation myocardial infarction (STEMI) receiving therapy with primary percutaneous coronary intervention (PCI), thrombolysis, or no reperfusion per 1 million inhabitants in 37 European countries. In the graph showing the PCI numbers, the *blue bars* are data from 2007; *red bars* are data from 2010 and 2011. (From Kristensen SD, Laut KG, Fajadet J, et al: Reperfusion therapy for ST elevation acute myocardial infarction 2010/2011: current status in 37 ESC countries. *Eur Heart J* 35[29]:1957-1970, 2014.)

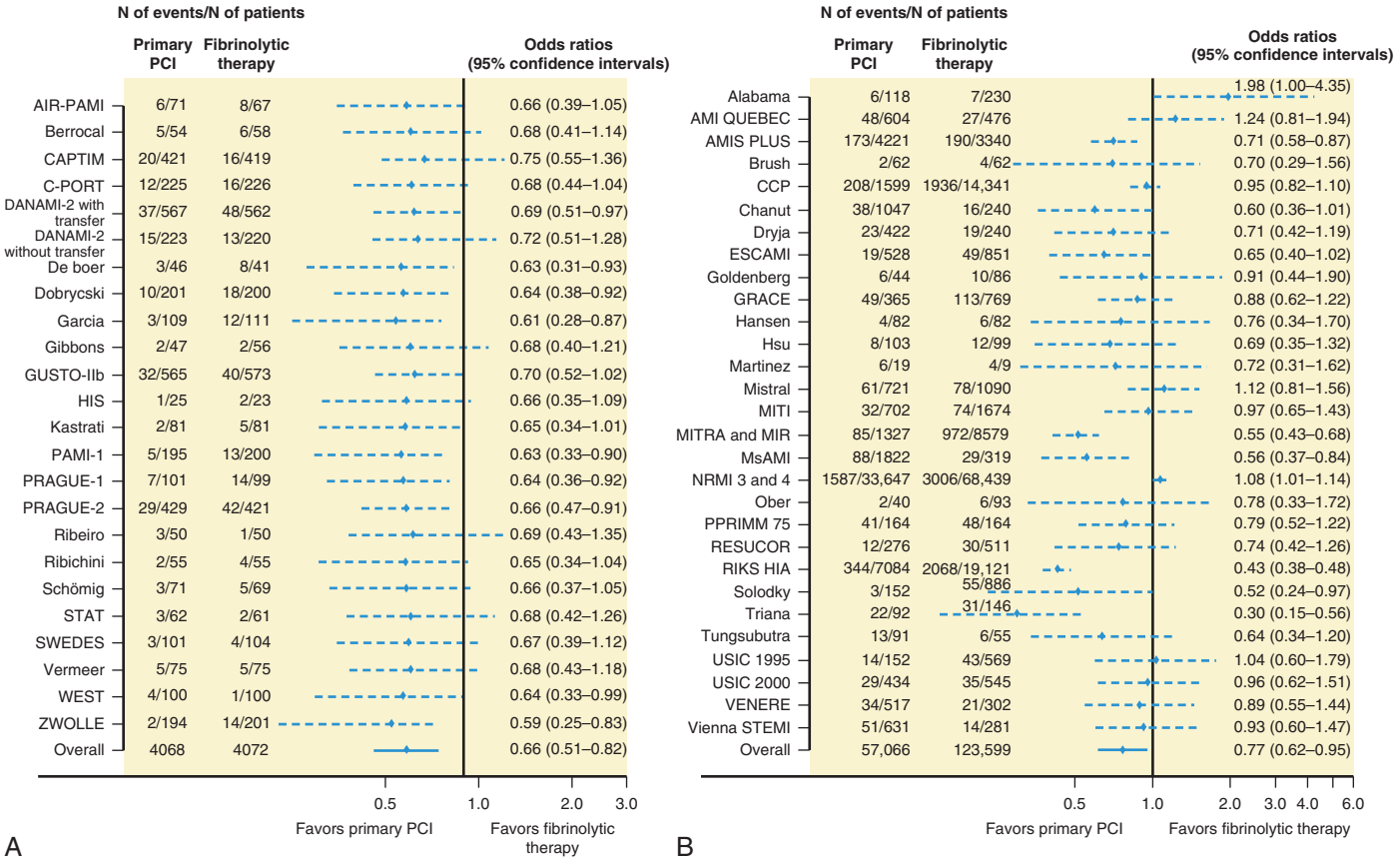


FIGURE 20-3 Bayesian forest plots of all-cause short-term mortality rates in studies that have compared primary percutaneous coronary intervention (PCI) with thrombolysis. **A,** Randomized controlled trials. **B,** Observational studies. (From Huynh T, Perron S, O'Loughlin J, et al: Comparison of primary percutaneous coronary intervention and fibrinolytic therapy in ST-segment-elevation myocarcial infarction: bayesian hierarchical meta-analyses of randomized controlled trials and observational studies. *Circulation* 119[24]:3101-3109, 2009.)

TABLE 20-1 Prehospital Timing Benchmarks in the Management of Acute ST-Elevation Myocardial Infarction

Time Delay	Target
Preferred for FMC to ECG and diagnosis	≤10 min
Preferred for FMC to fibrinolysis (FMC to needle)	≤30 min
Preferred for FMC to primary PCI (door to needle) in hospitals with primary PCI	≤60 min
Preferred for FMC to primary PCI	≤90 min (≤60 min if early presenter with large area at risk)
Acceptable for primary PCI rather than fibrinolysis	≤120 min (≤90 min if early presenter with large area at risk); if this target cannot be achieved, consider fibrinolysis
Preferred for successful fibrinolysis to angiography	3 to 24 hours

Steg PG, James SK, Atar D, et al: ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 33(20):2569-2619, 2012.
ECG, Electrocardiogram; *FMC,* first medical contact; *PCI,* percutaneous coronary intervention.

(Table 20-2). Although the association between these strategies and DTB times was significant, causality remains unproven. Later, the Door-to-Balloon Alliance—a national campaign initiated by the ACC and composed of clinicians, organizations, and hospitals working jointly to improve reperfusion in patients with acute MI—proposed two additional strategies to improve systems of care for patients with STEMI: a senior management commitment and a team-based approach.[27] The evidence on the performance of each of these individual strategies proposed to reduce DTB times has been recently reviewed.[28] A report from the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Get With the Guidelines registry showed that performance of prehospital ECG was associated with a 10-minute reduction in the FMC-to-balloon time.[29] Moreover, data from the same registry have shown that direct referral of patients to the catheterization lab—that is, bypassing the emergency department—was associated with a 20-minute reduction on average in the interval from FMC to time of device placement.[30] However, the evidence in support of the individual component strategies remains limited. In general, it is widely accepted that great variability and heterogeneity exist in the use of these strategies across various hospitals, regions, or countries.

Recently, experts have proposed certain essential components that a contemporary system of care for patients with STEMI should have (Table 20-3). Analysis of various regional systems of care of patients

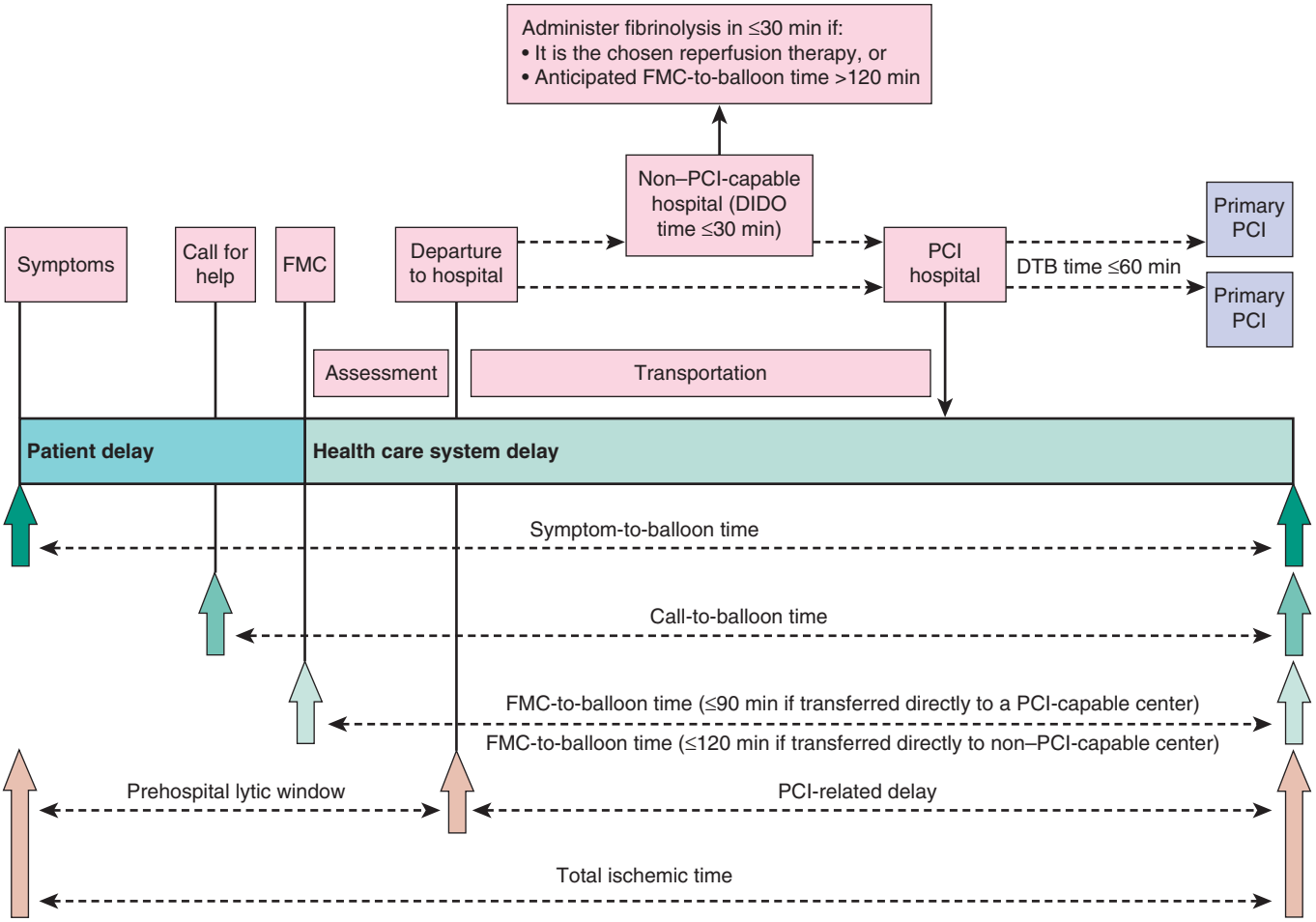


FIGURE 20-4 Timeline metrics in management of ST-elevation myocardial infarction. DIDO, door-in door-out; DTB, door-to-balloon time; FMC, first medical contact; PCI, percutaneous coronary intervention. (From Gershlick AH, Banning AP, Myat A, et al: Reperfusion therapy for STEMI: is there still a role for thrombolysis in the era of primary percutaneous coronary intervention? *Lancet* 382[9892]:624-632, 2013.)

TABLE 20-2 Adjusted Associations Between Hospital Strategies and Door-to-Balloon Times

Strategy	Door-to-Balloon Time Decrease (min)
Emergency physician activation of catheterization laboratory	8.2
Single-call activation of the catheterization laboratory	13.8
Prehospital activation	15.4
Catheterization laboratory ready in 20 minutes (vs. >30 min)	19.3
Attending cardiologist on site	14.6
Real-time data feedback	8.6

From Bradley EH, Herrin J, Wang Y, et al: Strategies for reducing the door-to-balloon time in acute myocardial infarction. *N Engl J Med* 355(22):2308-2320, 2006.

TABLE 20-3 Essential Components of ST-Elevation Myocardial Infarction Systems of Care

Single telephone emergency number
Ambulances (vehicles, helicopters, planes), equipped with 12-lead electrocardiographs (ECGs) and defibrillators and staffed with physicians or well-trained paramedics capable of basic and advanced life support
Occasional automatic ECG interpretation or ECG telemetry
Direct telephone access to the catheterization laboratory
Protocols for standardized care (diagnosis, therapy, and transfer)
Cardiologist or intensive care specialist as a network leader
Involvement of health care authorities
Public information campaigns
Regular meetings of involved parties
Prospective registry

From Huber K, Gersh BJ, Goldstein P, et al: The organization, function, and outcomes of ST-elevation myocardial infarction networks worldwide: current state, unmet needs and future directions. *Eur Heart J* 35(23):1526-1532, 2014.

with STEMI across Europe, the United States, and Canada has shown that for most countries in Europe and for many regions in North America, geographic conditions and availability of PPCI centers enable provision of PPCI given that the systems of care are in place to allow its application.[31]

Although regional STEMI treatment systems that use standardized transfer protocols have been shown to improve the treatment times,[32,33] performance of these systems remains poorly investigated and, even in the most sophisticated systems, treatment delays are relatively common. A recent prospective observational study of 2034 patients transferred for PPCI as part of a regional STEMI system showed that treatment delays occur even in efficient systems of care.[34] Delays of the greatest magnitude were due to diagnostic dilemmas (median delay, 95.5 min) and nondiagnostic initial ECG (median delay, 81 min).

Time-to-Treatment Interval and Outcome of Primary Percutaneous Coronary Intervention for STEMI

Knowledge of the biology of myocardial ischemia and the speed with which it succumbs to necrosis is important to any understanding of the time dependency of efficacy related to reperfusion regimens and to the degree of benefit of reperfusion therapy in general. Abrupt coronary occlusion results in a drastic reduction in the coronary blood flow and myocardial necrosis that progresses gradually and is typically complete about 6 hours after the onset of occlusion. A rapid phase of cell death, mostly in the subendocardial region, follows the coronary occlusion, and about half of the ischemic myocardium that is necrotic at 24 hours has already died at 40 minutes after coronary occlusion.[35] A second phase of cell death occurs more slowly in the midepicardial and subepicardial myocardium. This phase of myocardial necrosis is complete within 6 hours of coronary occlusion, and about one third of the ischemic myocardium is salvageable at 3 hours.[35]

Nevertheless, considerable differences exist between coronary occlusion and acute MI in the *experimental setting* and spontaneously occurring coronary occlusion and STEMI in the *clinical setting*. Factors such as the often stuttering course of coronary occlusion, spontaneous recanalization and persistence of anterograde blood flow in the infarct-related artery, collateral circulation, preconditioning, postconditioning, metabolic need at the time of coronary occlusion, and effects of initial antiischemic (antithrombotic) therapy may modify the time course of myocardial ischemia progression to necrosis and may extend the time during which ischemic myocardium remains viable. Scintigraphic studies have identified viable myocardium in patients with STEMI who present late (>6 hr) after symptom onset and that this viable myocardium appears salvageable if PCI is used as a reperfusion strategy. These studies suggest the existence of two phases of myocardial salvage: an early phase, enabled by early reperfusion (ideally within the first hour), and a late phase, enabled by later reperfusion. During the *early phase,* reperfusion is associated with substantial and time-dependent myocardial salvage. However, reperfusion therapy within the first hour following coronary occlusion, which is expected to lead to large amounts of myocardial salvage and the best clinical outcome, is achievable in a very limited number of patients. A prior study has shown that time to treatment was less than 2 hours for only 27% of patients and less than 1 hour for only 3.2%.[36] Reperfusion in the second, *late phase* results in a less time-dependent and lesser degree of myocardial salvage. Analysis of time to treatment in various studies suggests that most patients are reperfused beyond the "golden hour" of reperfusion—that is, in the late phase of myocardial salvage, in which a slower progression of ischemic myocardium to necrosis occurs due to the presence of residual blood flow, collaterals, or other factors that widen the window of myocardial salvage. Although some studies have suggested that myocardial salvage by PPCI in late presenters is still substantial,[16] evidence available on its clinical value remains limited.

Time-to-treatment interval is an estimate of overall duration of myocardial ischemia that encompasses the time interval from the onset of symptoms of coronary occlusion to the initiation of reperfusion therapy, thrombolysis, or PPCI. This multicomponent metric includes the time interval from symptom onset to FMC by emergency medical service providers (patient delay), the interval from FMC to a PPCI hospital (prehospital system delay), and the interval from hospital arrival to PPCI (DTB time delay). In cases of initial referral to a hospital without PPCI in patients intended to be treated with PPCI, the pre–hospital system delay consists of the time interval from the FMC to the hospital without PCI, the in-hospital time (door-in-door-out [DIDO] time), and the interval from the hospital without PCI to the hospital with PPCI. The term *system delay* signifies the sum of the pre–hospital system and DTB time delay. Apart from disclosing the duration of myocardial ischemia, time-to-treatment interval is an index of quality and readiness of the health care system to provide reperfusion therapy in a timely fashion.

With regard to the impact of time-to-treatment interval on clinical outcome, clinical studies have produced conflicting results. A progressive increase in 1-year mortality with every 15-minute increase in the symptom onset–balloon time interval has been reported.[37] Conversely, data from the National Registry for Myocardial Infarction (NRMI) showed no association between symptom onset–balloon time interval and survival in a cohort of 27,080 consecutive patients with acute MI treated with primary angioplasty.[38] Similarly, an analysis of 2635 patients enrolled in 10 randomized trials of primary angioplasty versus thrombolytic therapy demonstrated that with increasing time-to-presentation interval, major adverse cardiac event (MACE) rates increased after thrombolysis but remained relatively stable after angioplasty.[39] A recent publication from the DANAMI-2 trial that involved only the PPCI substudy showed that 3-year mortality did not differ among patients with symptom onset–balloon times less than 3 hours and from 3 to 5 hours. However, mortality was significantly increased in patients who presented 5 or more hours from symptom onset (hazard ratio [HR], 2.36), and the difference in mortality remained significant after adjustment for potential confounders. A shorter symptom onset–balloon interval was associated with greater rates of a TIMI flow grade of 3 after PPCI and with lower proportions of patients with a left ventricular ejection fraction (LVEF) of 40 or less.[40] Two studies came to different conclusions regarding the relationship between the time from ischemia onset to PPCI (stenting) and infarct size estimated by cardiac magnetic resonance imaging (CMRI).[41,42]

Reasons for the reported inconsistencies with regard to the relationship between the ischemia time estimated by time-to-treatment interval and outcome remain unclear. One possibility may be that the reperfusion is offered in the relatively flat part of the ischemia time–myocardial salvage curve, particularly in those who present late after symptom onset. In this phase the ischemic myocardium may have secured some blood supply through spontaneous reperfusion or existing collaterals to remain viable for a time longer than what is suggested by experimental studies that involve permanent coronary artery occlusion.[35] In the latter scenario, by restoring blood supply, PPCI (but not thrombolysis) may result in myocardial salvage and commensurate clinical benefit apparently independent of time-to-reperfusion interval. Another important reason for the controversial findings may involve the inaccuracy of measurement of the time-to-treatment interval, particularly the patient delay component. It has been reported that patients with STEMI do not seek medical care for 1.5 to 2 hours from symptom onset and that this interval has remained fairly stable over time.[43,44] Other studies have suggested that patient-related delay accounts for up to two-thirds of the overall ischemic time and that it is greatest among women, older adults, patients with diabetes, those of low socioeconomic status, and patients who come to medical attention during nighttime hours.[45] Apart from being the most substantial component, patient delay is the most poorly estimated part of the total ischemic interval. In general, it is accepted that patients provide low-credibility data regarding symptom onset because of recall bias—which is common in patients with STEMI, particularly in patients under the effect of opiates—and the stuttering course with intermittent preinfarction angina symptoms, which obscures the exact time of STEMI onset.

Risk distribution alongside the time-to-treatment interval is rather complex, but it is important in understanding the time-dependent efficacy of PPCI in patients with STEMI. Prior studies have shown that patients who present early after symptom onset have the highest risk scores.[41] This is consistent with the observation that early presenters have the largest cumulative ST-segment elevation,[46] which reflects the largest initial areas at risk and prompts their urgent seeking of medical aid. This group of patients with STEMI benefits from PPCI mostly in terms of myocardial salvage, preservation of ventricular function, and survival due to early intervention to address the ischemic lesion. Patients who present later after symptom onset may have a smaller initial area at risk, which produces milder symptoms; their outcome may also be influenced by the *survivor-cohort effect,* which refers to the fact that such patients have already survived the highest risk of death in the early hours after coronary occlusion. Late presenters may also have a more adverse cardiovascular risk profile. Prior reports show that patients who presented later were older, more often female and

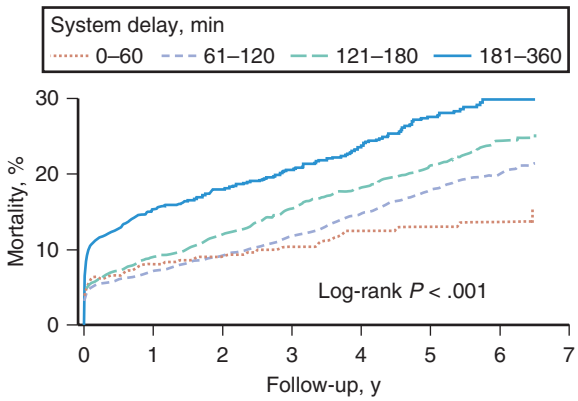
diabetic, and had a history of coronary bypass surgery. Adjusting for these factors considerably attenuates the association between time to treatment and mortality (from highly significant in univariate analysis to a borderline significance after adjustment in a multivariate model).[37] Patients who had a greater delay from symptom onset to admission can also be expected to present more frequently with additional adverse characteristics such as impaired renal function, peripheral arterial disease, and greater inflammatory burden—factors not accounted for in the multivariate model. The lack of adjustment for these characteristics further widens the gap between statistical and biologic adjustments in regard to prognosis. Associated comorbidities and the less favorable cardiovascular risk profile may mask the benefits of mechanical reperfusion as a result of myocardial salvage, and the unfavorable outcome after coronary intervention may erroneously be attributed solely to the longer time-to-reperfusion interval. Therefore it is highly probable that the more adverse baseline risk profile of patients with a longer delay in presentation may explain, at least in part, the apparent association between time-to-treatment interval and mortality. These considerations are important because the apparent reduction of benefit from PCI with increased time to presentation may be interpreted as a poor incentive for a prompt intervention in patients with delayed presentation who might benefit from this treatment.

Although assessment of the performance of PPCI using the time-to-treatment interval as a metric of ischemia duration produced inconsistent results, studies that use other components, such as system delay times or DTB times, in general produced consistent results. A report based on the Danish medical registries of patients with STEMI (n = 6209 patients who underwent PPCI within 12 hours from symptom onset) showed an association and dependence of long-term mortality (median 3.4 years) on the system delay. Thus for delays of zero to 60, 61 to 120, 121 to 180, and 181 to 360 minutes, long-term mortality was 15.4%, 23.3%, 28.1%, and 30.8%, respectively (Fig. 20-5). Of note, in multivariate analysis adjusted for other potential correlates of mortality, the system delay was associated independently with mortality (a 10% increase in the adjusted risk for mortality per 1-hour delay).[47]

Several studies have demonstrated an association between DTB interval and survival in patients with STEMI. In a recent report from the National Cardiovascular Data Registry (NCDR) that included 43,801 patients with STEMI, median DTB time was 93 minutes, and 57.9% of patients were treated within 90 minutes. Longer DTB times were associated with a higher adjusted risk of in-hospital mortality, which increased in a continuous, nonlinear fashion (DTB interval 30 min, mortality 3.0%; 60 min, 3.5%; 90 min, 4.3%; 120 min, 5.6%; 150 min, 7.0%; and 180 min, 8.4%; $P < .001$).[48] The strength of association between DTB time and mortality may depend on the patient's risk profile and the presentation delay. In a study of 2322 patients with STEMI followed up for a median of 83 months, delays in DTB time impacted late survival in high-risk but not low-risk patients and in patients who presented early but not late after the onset of symptoms.[49]

DTB time is an important indicator of patient characteristics[46] and of the experience of the institution providing the PPCI.[50] Comorbid conditions, absence of chest pain, delayed presentation after symptom onset, less specific ECG findings, and hospital presentation during off hours were associated with longer total DTB times.[46] Longer DTB times were also encountered in patients of older age, female sex, nonwhite race, and with complex medical histories.[51] DTB time delays also depended heavily on hospital-related characteristics. Thus presentation at night and treatment at lower-volume facilities were strong independent predictors of longer DTB intervals.[51,52] Greater experience with PPCI is associated with shorter DTB times and lower in-hospital mortality in patients with STEMI treated with PPCI.[50] In one study, PPCI was found to be superior to thrombolysis irrespective of the DTB time the treating institution was able to achieve.[53] A further study demonstrated that a combination of shorter DTB time (<90 min) with a shorter symptom onset–to–door time (<4 hr) was associated with the lowest longer-term mortality.[54] Other studies have also demonstrated that short DTB times (≤90 min) are associated with a lower mortality in early presenters but not in late presenters.[55]

Supported by multiple sources of research, current guidelines for the treatment of STEMI recommend a DTB time of 90 minutes or less.[9,10] DTB time has been and continues to be the focus of considerable efforts and initiatives at regional and national levels aimed at its improvement. However, data on the impact of the improvements in the DTB times on mortality are inconsistent. An earlier analysis from the NRMI reported a significant reduction in mortality, from 8.6% to 3.1%, associated with a decline in DTB times from 111 minutes in 1994 to 79 minutes in 2006.[56] Conversely, a study that involved patients included in a quality improvement database in Michigan found no change in short-term mortality between 2003 and 2008 despite a decrease in DTB time from 113 minutes to 76 minutes.[57] Finally, a recent study of 96,738 admissions for PPCI for STEMI between July 2005 and June 2009—a period that coincided with national efforts to reduce DTB times—at 515 hospitals participating in the CathPCI registry showed that median DTB times declined significantly, from 83 minutes in the first 12 months (2005 to 2006) to 67 minutes in the last 12 months (2008 to 2009) of the survey ($P < .001$). Despite improvements in DTB times, unadjusted in-hospital mortality (4.8% vs. 4.7%, $P = .43$), adjusted in-hospital mortality (5.0% vs. 4.7%, $P = .34$), or unadjusted 30-day mortality (9.7% vs. 9.8%, $P = .64$) remained unaffected.[58] Concerns were raised that DTB time is only one component of total ischemic time, and once it is reduced to a certain level, the time before arrival at a hospital may become a more important factor. Consequently, efforts with the intention to improve outcomes after PPCI should be directed throughout the ischemic time interval to include increasing patients' awareness of the STEMI symptoms, shortening the transfer times between medical facilities, or even improving in-hospital and postdischarge care to improve long-term outcome after PCI.[58]



No. at risk

System delay, min

0–60	347	311	278	230	192	138	87
61–120	2643	2339	1906	1420	1006	667	375
121–180	2092	1836	1503	1183	842	533	278
181–360	1127	923	765	647	491	332	172

FIGURE 20-5 Kaplan-Meier cumulative mortality estimates for patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. Data are stratified according to intervals of system delay (time from contact with the health care system to the time of PPCI). (From Terkelsen CJ, Sørensen JT, Maeng M, et al: System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *JAMA* 304[7]:763-771, 2010.)

PRIMARY PERCUTANEOUS CORONARY INTERVENTION IN LATE PRESENTERS

Registry data have shown that between 9% and 31% of patients with STEMI present more than 12 hours from the symptom onset.[14,59] For

patients with STEMI who present beyond 12 hours from the symptom onset, thrombolysis is associated with little or no benefit or is even harmful; thus it is not recommended. On the other hand, PPCI remains a therapeutic option even though evidence available on the benefit of this modality is limited or controversial. Earlier observational data have suggested a potential benefit of PPCI in patients with STEMI who present more than 12 hours from symptom onset. In the NRMI-2 registry, which included 7258 patients with STEMI, 1631 patients (22%) received invasive treatment within 6 hours of admission, and 5727 patients received conservative therapy. Compared with those who received conservative therapy, patients who received invasive treatment had lower in-hospital mortality (3.4% vs. 6.6%), less recurrent ischemia or angina (10.7% vs. 13.8%), and a reduced incidence of recurrent MI (1.2% vs. 2.2%). The association between invasive treatment and in-hospital mortality persisted after adjustment for factors associated with mortality, showing a 33% reduction in the adjusted risk for mortality with invasive treatment. After matching by propensity score (to adjust for treatment-selection bias), the mortality benefit persisted on bivariate analysis (3.5% vs. 5.0%).[60] Scintigraphic studies have shown that substantial myocardial salvage by PPCI (>50% of initial area at risk salvaged) occurs in 41% of late comers (>12 hr from symptom onset).[61]

Studies that have investigated the efficacy of PCI in late presenters on a randomized treatment-allocation basis have given conflicting results, mostly because some studies addressed the late presenters, whereas other studies addressed the occluded vessel. The Beyond 12 Hours Reperfusion Alternative Evaluation (BRAVE-2) trial[16] randomized 365 patients with STEMI who presented 12 to 48 hours from symptom onset to invasive or conservative treatment. The study demonstrated a significant reduction of the scintigraphic infarct size (median infarct size, 8% vs. 13% of the left ventricle, $P < .001$) and a trend toward a reduction of the secondary end point of death, recurrent MI, or stroke at 30 days (4.4% vs. 6.6%) with invasive treatment.[16] A later update from the BRAVE-2 trial demonstrated a mortality benefit out to 4 years in patients assigned to invasive treatment (11.1% in patients assigned to invasive treatment vs. 18.9% in patients assigned to conservative therapy; $P = .047$; Fig. 20-6).[62] The *Desobstruction Coronaire en Post-Infarctus* (DECOPI) trial[63] randomized 212 patients with first Q-wave MI and an occluded vessel to percutaneous revascularization or medical therapy 2 to15 days after symptom onset. The primary end point was a composite of cardiac death, nonfatal MI, or ventricular tachyarrhythmia. At 6 months, LVEF was 5% higher in the invasive group compared with the conservative-therapy group ($P = .013$), and more patients had a patent artery (82.8% vs. 34.2%, $P < .0001$). At a mean of 34 months of follow-up, no significant differences were found in the primary end point between patients assigned to invasive therapy and those treated conservatively (7.3% vs. 8.7%, $P = .68$), but the overall costs were higher for invasive treatment. The Occluded Artery Trial (OAT) randomized 2166 stable patients who had an occluded infarct-related artery (by cardiac catheterization) to PCI with stenting or optimal medical therapy 3 to 28 days after acute STEMI. The primary end point was a composite of death, MI, or New York Heart Association (NYHA) class IV heart failure. At 4 years, the rate of the composite end point was not statistically different between the PCI and medical therapy groups (17.2% and 15.6%, respectively; HR, 1.16; 95% confidence interval [CI], 0.92 to 1.45; $P = .20$) with no interaction between treatment effect and any subgroup variable (age, sex, race or ethnic group, infarct-related artery, ejection fraction, diabetes, Killip class, and the time from MI to randomization). During a 6-year median survivor follow-up (longest, 9 years), no significant difference was found between the two treatment strategies in the rates of either the primary end point or its individual components.[64] Because of the study size, the OAT trial had an important negative impact on the use of invasive treatment in the stable late presenters with STEMI. A meta-analysis of 10 randomized trials, including OAT, comprised 3560 patients with acute MI who presented between 12 hours to 60 days after symptom onset and demonstrated significant reduction in long-term mortality (6.3% vs. 8.4%) with invasive treatment. Eight of the included studies showed improvements in long-term survival, and a greater improvement was seen in LVEF over time in patients who received invasive treatment (+4.4% change in the LVEF) compared with patients who received medical therapy.[15] However, the results of this meta-analysis need to be interpreted with caution in the light of considerable heterogeneity across the studies.

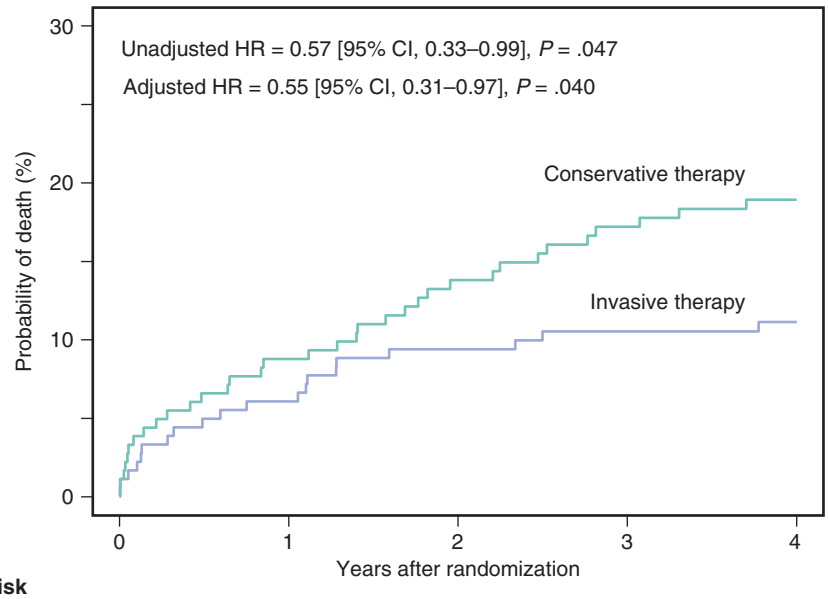


FIGURE 20-6 Kaplan-Meier curves of 4-year mortality in the invasive and conservative therapy groups of the BRAVE-2 trial. *HR,* Hazard ratio. (Modified from Ndrepepa G, Kastrati A, Mehilli J, et al: Mechanical reperfusion and long-term mortality in patients with acute myocardial infarction presenting 12 to 48 hours from onset of symptoms. *JAMA* 301[5]:487-488, 2009.)

In summary, the benefit of PPCI in late presenters with STEMI lacks strong evidence. For patients with STEMI who present between 12 and 24 hours after the onset of symptoms, the current ESC guidelines give a class IIb recommendation (level of evidence B) for the use of PPCI in stable patients with STEMI who present 12 to 24 hours from symptom onset and a class III recommendation (level of evidence A) for the use of PPCI (not recommended) in stable patients more than 24 hours after symptom onset.[9] The ACC/AHA guidelines give a class IIa recommendation (level of evidence B) for the use of PPCI in patients with STEMI who present between 12 and 24 hours and have evidence of ongoing ischemia.[10] The consensus is, however, that patients with STEMI who present late (>12 hr from symptom onset) should undergo coronary angiography. Moreover, it is reasonable to perform PPCI in late presenters with STEMI who manifest severe heart failure or have electrical or hemodynamic instability or persistent ischemia. Some experts also recommend performing PPCI in these patients if subtotal occlusions in the infarct-related artery with collateral circulation in the territory distal to the occlusion were found in coronary angiography.

INTERHOSPITAL TRANSFER FOR PRIMARY PERCUTANEOUS CORONARY INTERVENTION

The lack of PCI facilities in the majority of hospitals that receive patients with STEMI, the wider therapeutic window, and the proven superiority of PPCI over thrombolysis have all led to the concept of emergency interhospital transfer for PPCI, instead of initial thrombolysis in the original hospital, in patients with STEMI. Multiple scenarios are possible in which patients with STEMI can end up in a hospital without a PCI facility. About 20% of patients living in the United States reside in regions that require a drive time in excess of 60 minutes to reach the nearest hospital with a PCI facility.[23] In case the diagnosis of STEMI is not immediately clear to the emergency medical service (EMS) or when patients with STEMI self-present to the nearest emergency department (ED), these patients may also find themselves in hospitals without a PPCI facility. Earlier randomized trials of on-site thrombolysis versus interhospital transfer plus PCI have confirmed that transfer of patients for PPCI is a better treatment than thrombolysis at the initial hospital. The results of these trials have been summarized in two meta-analyses: The first comprised six randomized trials performed before 2003 and included 3750 patients; it showed that a strategy of patient transfer plus PPCI was associated with a 42% reduction in the 30-day incidence of a combined end point of death, reinfarction, and stroke compared with a strategy of on-site thrombolysis.[65] The second quantitative review of studies that involved patient transfer for PCI suggested that for every 100 patients treated, PPCI after interhospital transfer, instead of on-site thrombolysis, prevented seven MACEs, defined as death, nonfatal reinfarction, or nonfatal stroke.[66]

More recent studies have provided further evidence of the benefits of transferring patients for PPCI compared with on-site thrombolysis. A prior study randomized 401 patients who presented to community hospitals to a strategy of on-site thrombolysis or to intravenous (IV) tirofiban and transport for PPCI. The *delay to reperfusion,* defined as the interval from admission to the start of thrombolysis or PPCI, was 35 and 145 minutes, respectively. The composite end point of death, reinfarction, or stroke was lower among patients assigned to the transport-plus-PPCI strategy at 30 days (8.0% vs. 15.5%, $P = .019$) and at 1 year (11.4% vs. 21.5%, $P = .006$).[67] A study of 850 patients with STEMI enrolled in the Primary Angioplasty in Patients Transferred From General Community Hospitals to Specialized PTCA Units With or Without Emergency Thrombolysis (PRAGUE-2) trial[68] showed that the 5-year composite end point of death, reinfarction, stroke, or revascularization was 40% in patients assigned to a strategy of transfer plus PPCI versus 53% in patients assigned to on-site thrombolysis in the first hospital attended ($P < .001$). A large registry that included 16,043 STEMI patients treated with in-hospital thrombolysis, 3078 treated with prehospital thrombolysis and 7084 patients treated with PPCI, indicated that transfer for PCI is better than prehospital thrombolysis even in early presenters in whom the treatment is initiated within 2 hours.[69] A strategy of patient transfer for PPCI, instead of on-site thrombolysis, inevitably incurs additional time delays imposed by transport, logistics, and organizational and technical aspects of PCI procedures. The magnitude of the problem seems to be considerable because only 10% of transferred patients with STEMI achieve the 90-minute-or-less benchmark standard for DTB time.[70] PCI-related time delay is an integral part of treatment algorithms for patients with STEMI. The definition of the *balance time point* in PCI-related delay at which thrombolysis and PPCI are at equipoise, and beyond which PPCI might become inferior to thrombolysis, has been based on regression analyses from randomized trials or registry data.

PCI-related delay has been the subject of intense investigation and, historically, many time intervals have been proposed at which mortality rates of PCI after patient transfer and on-site thrombolysis are at equipoise. In many studies, the PCI-related delay was calculated based on published summarized data and not on individual patient data. Consequently, several prior estimations were subsequently found to be flawed and were corrected, in general, by expanding the metric. A report from the Primary Coronary Angioplasty Versus Thrombolysis (PCAT-2) Trialists' Collaborative Group demonstrated that PPCI was associated with a 67% reduction in 30-day mortality compared with thrombolysis, which amounts to 53 lives saved per 1000 patients treated. For PCI-related delays up to 120 minutes, PPCI was associated with a 26% reduction in mortality compared with thrombolysis, or 19 lives saved per 1000 patients treated (Fig. 20-7). The absolute reduction in mortality with PPCI widened over time from 1.3% within the first hour to 4.2% after more than 6 hours had passed after symptom onset. The most thorough time-based analysis that used individual patient data showed that PPCI is superior to thrombolysis up to a PCI-related delay of 120 minutes.[53] In this study, even in the group of patients who presented within 1 hour, mortality was lower with PPCI (4.7% vs. 6.0%), indicating that even in early presenters with PCI-related delays of 60 minutes or less, there is no reason to prefer thrombolysis instead of PPCI as a reperfusion strategy.[53] In 192,509 patients entered into the NRMI 2-4 registries, the mean PCI-related day at which mortality benefits of PPCI and thrombolysis were at equipoise was 114 minutes (95% CI, 96 to 132 min).[71] Of note, the study showed that PCI-related delay was not static and varied considerably depending on the risk characteristics of patients, such as age, symptom duration, and infarct location. Thus, PCI-related delay varied from less than 1 hour for patients younger than 65 years of age with anterior infarction who presented within 2 hours to almost 3 hours for patients older than 65 years of age with nonanterior infarction who presented more than 2 hours from symptom onset. A regression analysis that included 27 trials with 4399 patients randomized to PPCI and 4474 patients randomized to thrombolysis found that the higher the risk of patients, the larger the reduction in mortality achieved by PPCI. It was calculated that for each 10-minute increase of PCI-related delay, a 0.75%, 0.45%, and 0.0% mortality benefit was appreciated in high-, medium-, and low-risk patients, respectively.[72] A recent report from the NRMI 2–5 registries assessed the impact of PCI-related delay in 107,028 patients with STEMI within 12 hours of pain onset: 11,662 patients underwent PCI after transfer, and 95,366 patients underwent on-site thrombolytic therapy. In the whole sample, in-hospital mortality was 4.9% among patients treated with PCI and 8.1% among patients treated with on-site thrombolysis. Among matched patients (9506 patients in each treatment strategy), in-hospital survival was similar (4.8% vs. 6.2%), but the composite end points of death/MI or death/MI/stroke were lower with PCI. The PCI-related benefit was time dependent. The mortality was lower with PCI compared with on-site thrombolysis for PCI-related delays less than 60 minutes, it was reduced for PCI-related delays of 60 to 90 minutes, and the difference was almost absent at PCI-related delays in excess of 90 minutes (Fig. 20-8). The number needed to treat to show superiority of PPCI over on-site thrombolysis went from 23 to 44 to 250 for PCI-related delays under 60 minutes, from 60 to 90 minutes, and more than 90 minutes, respectively. The regression analysis showed that the mortality benefit of PCI over on-site thrombolysis

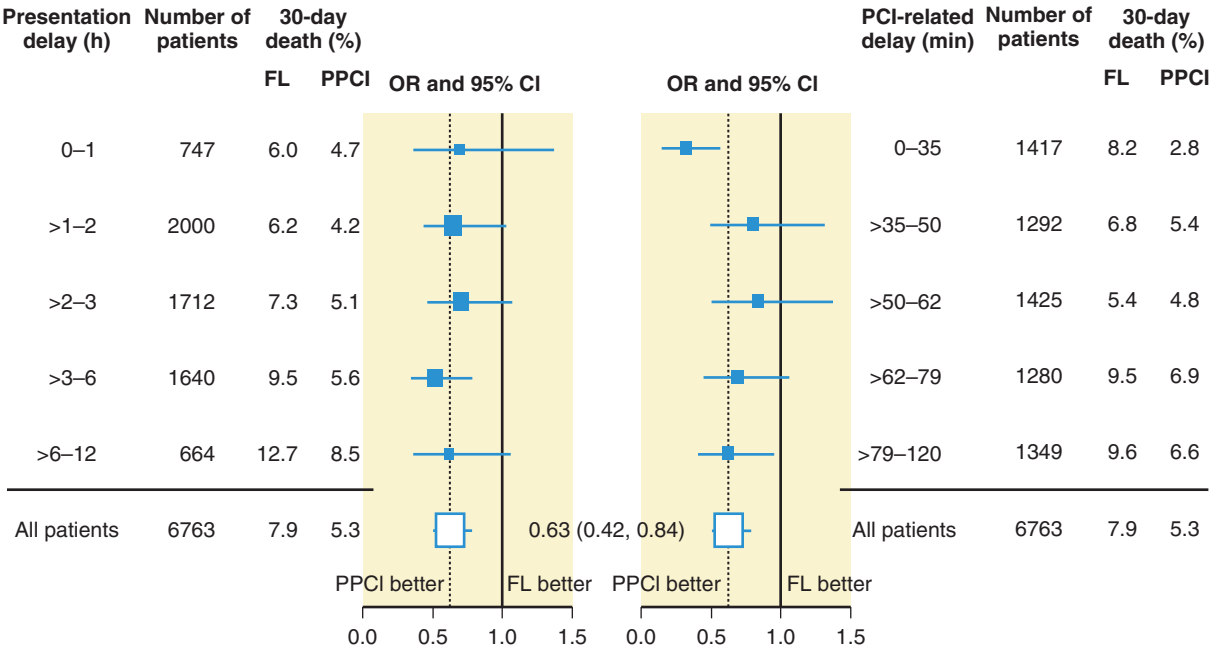


FIGURE 20-7 Thirty-day deaths in patients randomized to primary percutaneous coronary intervention (PPCI) or fibrinolysis (FL). *Left panel:* Thirty-day deaths with odds ratios (ORs) and 95% confidence intervals (CIs) according to presentation delay. *Right panel:* Thirty-day deaths with ORs and 95% CIs according to PCI-related delay. (From Boersma E; Primary Coronary Angioplasty vs. Thrombolysis Group: Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J* 27[7]:779-788, 2006.)

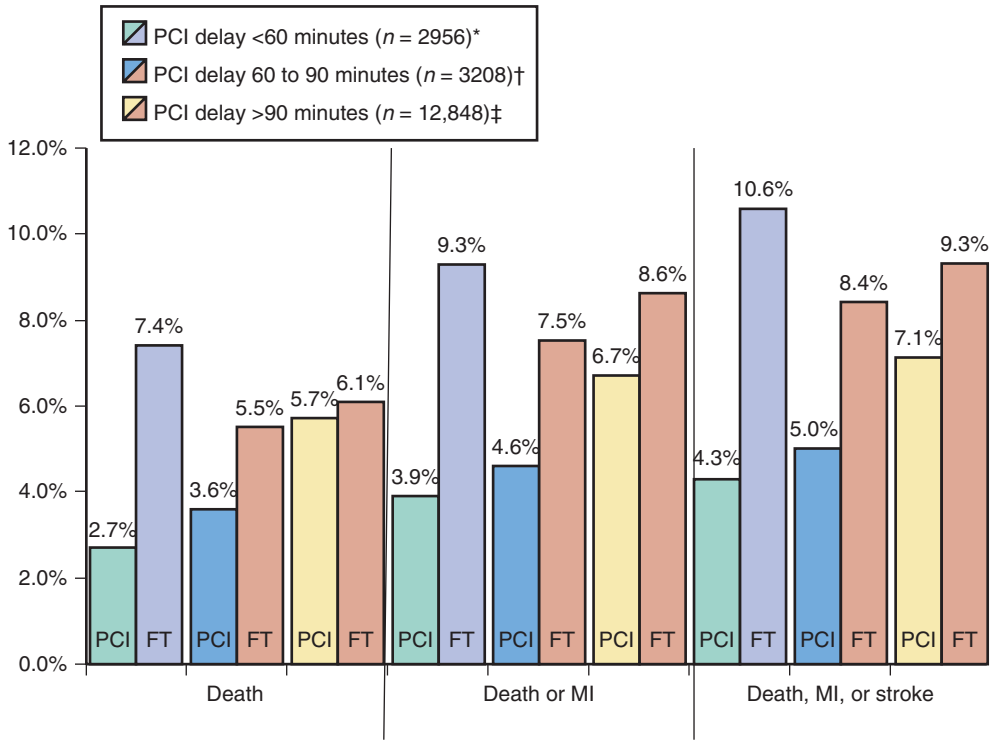


FIGURE 20-8 Clinical outcomes among matched patients stratified by percutaneous coronary intervention (PCI)–related delay. *Standardized difference greater than 10% for all outcomes; †standardized difference greater than 10% for only death or myocardial infarction (MI) and for death, MI, or stroke; ‡standardized difference greater than 10% for all outcomes. *FT,* Fibrinolytic therapy. (From Pinto DS, Frederick PD, Chakrabarti AK, et al: Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. *Circulation* 124[23]:2512-2521, 2011).

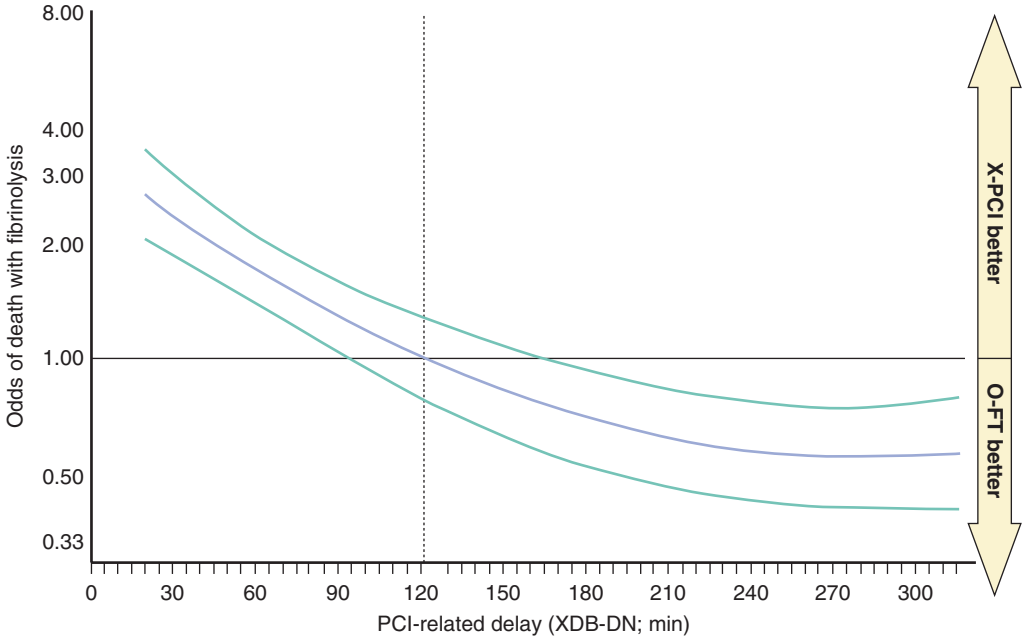


FIGURE 20-9 Relationship between percutaneous coronary intervention–related delay (minutes) and in-hospital mortality. *Dotted lines* represent 95% confidence interval. *O-FT,* On-site fibrinolytic therapy; *XDB-DN,* transfer delay (transfer door-to-balloon–door-to-needle time); *X-PCI,* transfer for primary percutaneous coronary intervention. (From Pinto DS, Frederick PD, Chakrabarti AK, et al: Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. *Circulation* 124[23]:2512-2521, 2011.)

for PCI-related delays beyond 120 minutes, which occurred in 48% of the patients, was negated (Fig. 20-9). The equipoise for mortality for patients who presented within 2 hours from symptom onset was longer (about 132 min). For the composite end point of death/MI/stroke, equipoise in efficacy occurred at about 158 minutes.[73]

Although these studies show that longer delays reduce the survival benefit of PPCI, a longer PCI-related delay could be acceptable and beneficial in high-risk STEMI patients, such as those in cardiogenic shock. In essence, flexible PCI-related delay according to the risk profile of STEMI patients is suggested. The assessment of the relationship between PCI-related time delay and outcome provides helpful information for optimization of the PPCI network. In an attempt to shorten PCI-related time delay, direct transportation of patients to hospitals capable of performing PPCI, rather than transporting them to the nearest hospital without a PCI facility, has also been suggested.[74] Concerns have also been raised that transfer of patients for PCI may be associated with issues related to antithrombotic/anticoagulant adjunct therapy. Administration of low-molecular-weight heparin (LMWH) and glycoprotein (GP) IIb/IIIa inhibitors at the STEMI-referring hospital was associated with longer delays to reperfusion compared with administration at the STEMI-receiving hospital, whereas early use of unfractionated heparin (UFH) was not. The transferred patients who underwent treatment were more likely to receive excess doses of UFH or LMWH (28% and 54% increase in the adjusted risk, respectively) and were at increased risk for major bleeding (a 10% increase in the adjusted risk for bleeding).[75]

For patients who require interhospital transfer for PPCI, delays in the referral hospital are relatively frequent. To quantify the delays in the referral hospital, a new performance measure—the DIDO time—has been introduced, and a DIDO time of 30 minutes or less has been recommended. The performance of this metric was assessed in a retrospective cohort of 14,821 patients recruited in the ACTION registry. The study showed that the DIDO time was 68 minutes (interquartile range, 43 to 120 min), and only 11% of the patients had a DIDO time of 30 minutes or less. The study identified older age, female sex, off-hours presentation, and non-EMS transport to the first hospital as independently associated with a DIDO time over 30 minutes. Patients with a DIDO time of 30 minutes or less were significantly more likely to have a DTB time of 90 minutes or less, compared with patients with a DIDO time over 30 minutes (60% vs. 13%), and they had a significantly lower in-hospital mortality (2.7% vs. 5.9%; adjusted odds ratio [OR] for in-hospital mortality, 1.56; 95% CI, 1.15 to 2.12). Thus, based on the results of this study, a DIDO time of 30 minutes or less is rarely achieved, and this parameter contributes to reperfusion delays and in-hospital mortality.[76]

In summary, prompt referral of patients with acute MI to centers with PCI facilities should be the primary objective of the first-contact emergency medical system. This is currently feasible for the large majority of patients with STEMI in the United States and should be attempted in the future for all patients with STEMI who seek medical aid. Nearly 80% of the adult population in the United States lives within 60 minutes of a hospital with a PCI facility, and even among those who live closer to hospitals without a PCI facility, almost three fourths would experience a less than 30-minute additional delay related to direct referral to a hospital with a PCI facility.[77] The development of regional systems for STEMI care is a matter of utmost importance for improving the treatment of patients with STEMI. A maximal 90- to 120-minute PCI-related delay seems to be reasonable. A flexible consideration of what degree of PCI-related delay is acceptable for high-risk STEMI patients also seems justified.

FACILITATED PERCUTANEOUS CORONARY INTERVENTION

Although the superiority of PPCI over thrombolysis as a reperfusion strategy in patients with STEMI has been sufficiently demonstrated, the interaction between pharmacologic reperfusion and subsequent mechanical intervention has met with variable results and still remains under investigation. *Facilitated PCI* refers to a deliberate strategy of administration of pharmacologic therapy aimed at restoring antegrade flow in the infarct-related artery prior to proceeding to definitive revascularization by PCI in patients with STEMI. It was conceived as

an option for filling the time gap between patient presentation and performance of PCI. The pharmacologic regimen consists of drugs known for their ability to restore flow, such as full-dose or half-dose thrombolysis, or a combination of half-dose thrombolysis with GP IIb/IIIa antagonists. Because data about the ability of GP IIb/IIIa antagonists to reopen the infarct-related artery are controversial, the isolated use of these drugs may or may not be part of the strategy of facilitated PCI. Two factors underpin the rationale behind the concept of facilitated PCI: first, ventricular function and prognosis have been found to be better in patients with STEMI who present at the time of PPCI with a spontaneous TIMI flow grade of 2 or 3 compared with those who have a TIMI flow grade of 0 or 1 in the infarct-related artery; second, a large proportion of patients with STEMI are unable to receive mechanical reperfusion without a certain time delay for a variety of reasons. Facilitated PCI was hypothesized to offer a reduction in ischemia time along with earlier reperfusion, higher TIMI flow rates in the infarct-related artery, facilitated guidewire/balloon passage, decreased clot burden, and a lower incidence of distal embolization.

The Bavarian Reperfusion Alternatives Evaluation (BRAVE) trial was the first randomized trial to evaluate the impact of facilitated PCI with reteplase plus abciximab on LV infarct size estimated by single photon emission computed tomography (SPECT). Although the study reported a higher rate of pre-PCI TIMI flow grade 3 in the infarct-related artery in the facilitated PCI group, no reduction in infarct size was observed in this group.[78] These results were confirmed by several subsequent clinical trials.

The Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction 4 (ASSENT-4) PCI study was a randomized trial of patients with STEMI who presented within 6 hours from the symptom onset, were scheduled to undergo PCI after an anticipated delay of 1 to 3 hours, and were assigned to standard PCI ($n = 838$) or PCI preceded by administration of full-dose tenecteplase ($n = 829$).[79] All patients received aspirin and a bolus without an infusion of UFH. The ASSENT-4 PCI investigators planned to enroll 4000 patients, but the Data and Safety Monitoring Board (DSMB) recommended early cessation after higher in-hospital mortality was observed in the facilitated PCI group than in the group undergoing standard PCI. The primary end point of ASSENT-4 PCI was death, congestive heart failure (CHF), or cardiogenic shock within 90 days of randomization. This occurred in 19% of patients in the facilitated PCI group and in 13% of the group that received standard PCI (relative risk [RR], 1.39; 95% CI, 1.11 to 1.74; $P = .005$). More in-hospital strokes (1.8% vs. 0%, $P < .001$) were reported, and the incidence of ischemic complications such as reinfarction (6% vs. 4%, $P = .03$) and repeat target-vessel revascularization (TVR; 7% vs. 3%, $P = .004$) were higher among patients treated with facilitated PCI than among those treated with standard PCI. The ASSENT-4 PCI trial concluded that a strategy of facilitated PCI that consisted of full-dose thrombolysis (tenecteplase) plus antithrombotic cotherapy and preceding PCI by 1 to 3 hours was associated with worse clinical outcome than a strategy of PPCI alone; therefore it cannot be recommended.[79]

The meta-analysis of Keeley and colleagues,[80] which included 17 trials of STEMI patients assigned to facilitated PCI ($n = 2237$) or PPCI ($n = 2267$) showed that facilitated PCI was associated with significantly worse short-term outcomes (up to 42 days) than PPCI alone in terms of death (5% vs. 3%), nonfatal reinfarction (3% vs. 2%), urgent TVR (4% vs. 1%), major bleeding (7% vs. 5%), hemorrhagic stroke (0.7% vs. 0.1%), and total stroke (1.1% vs. 0.3%). The increased rates of adverse events were observed mainly when thrombolytic therapy was used to facilitate PCI.[80]

The Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial[81] served to further confirm not only the inefficacy but also the detrimental effects of facilitated PCI in patients with STEMI. The study enrolled 2452 patients with STEMI who presented within the first 6 hours from symptom onset who were randomly assigned to a strategy of facilitated PCI with half-dose reteplase plus abciximab versus abciximab alone versus conventional PCI with abciximab given in the catheterization laboratory. All patients received UFH or enoxaparin before PCI and a 12-hour infusion of abciximab after PCI. The primary end point was the composite of death from all causes, ventricular fibrillation occurring more than 48 hours after randomization, cardiogenic shock, and CHF during the first 90 days after randomization. In the combination therapy–facilitated group, the abciximab-facilitated group, and the PPCI group, the primary end point occurred in 9.8%, 10.5%, and 10.7% of the patients ($P = .55$); 90-day mortality rates were 5.2%, 5.5%, and 4.5% ($P = .49$); and early ST-segment resolution occurred in 43.9%, 33.1%, and 31.0%, respectively ($P = .01$ and $P = .03$, respectively). Overall, a graded increase was observed in the rates of bleeding, intracranial hemorrhage, and transfusions in the PCI-facilitated groups.[81]

The evidence offered by the ASSENT-4 PCI trial,[79] the meta-analysis by Keeley and colleagues,[80] and the FINESSE trial[81] discourage the use of thrombolytics either at full- or half-doses combined with GP IIb/IIIa inhibitors as pharmacologic facilitation of PCI. The reasons for the failure of facilitated PCI are not entirely clear. However, pre-PCI thrombolysis may be associated with increased risks of bleeding and enhanced platelet activation.

ROUTINE USE OF PERCUTANEOUS CORONARY INTERVENTION AFTER THROMBOLYSIS: THE PHARMACOINVASIVE STRATEGY

Whereas the strategy of facilitated PCI was associated with worse outcome, the pharmacoinvasive strategy—routine use of a thrombolytic agent or GP IIb/IIIa inhibitor prior to subsequent planned PCI—was associated with clinical benefit in patients with STEMI. As a rule, in the setting of this strategy, angiogram and planned PCI are performed after 3 to 24 hours of presentation. This strategy is mostly applied in patients undergoing transfer from one hospital without PCI to a hospital with a PCI facility. The main reason for PCI following thrombolysis is the suboptimal outcome of thrombolysis in terms of suboptimal blood flow restoration and clinical outcome.

The Which Early ST-Elevation Myocardial Infarction Therapy (WEST)[82] and the *Grupo de Análisis de la Cardiopatía Isquémica Aguda* (GRACIA-2)[83] randomized trials reported comparable efficacy and safety of pharmacoinvasive and PPCI strategies. Both studies, however, included limited numbers of patients and consequently were underpowered for clinical end points. The GRACIA-1 trial[84] randomized 500 patients with STEMI, after receiving full-dose thrombolysis with recombinant tissue plasminogen activator (TPA), to either angiography and PCI (within 24 hr of thrombolysis) if indicated or an ischemia-guided conservative approach. The primary end point was a composite of death, reinfarction, or revascularization at 12 months. The invasive therapy was associated with a significant reduction in the incidence of the primary end point (23% vs. 51%; RR, 0.44; 95% CI, 0.28 to 0.70; $P < .001$). The Southwest German Interventional Study in Acute Myocardial Infarction (SIAM III) trial[85] randomized 163 patients to immediate (transferred <6 hr after thrombolysis for angiography and stenting of the infarct-related artery) or delayed stenting (elective angiography and stenting of the infarct-related artery 2 weeks after thrombolysis). Immediate stenting was associated with a significant reduction in the 6-month composite end point of ischemic events, death, reinfarction, or target-lesion revascularization (TLR; 25.6% vs. 50.6%, $P = .001$).

More recent studies have further increased the evidence in favor of a pharmacoinvasive approach as a reperfusion strategy in patients with STEMI. The Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI) trial included 600 patients 75 years of age or younger with at least 1 high-risk feature (extensive ST-segment elevation, left bundle branch block of new onset, previous MI, Killip class >2, or LVEF ≤35%) who presented within 12 hours from symptom onset and were treated initially in non–PCI-equipped hospitals with half-dose reteplase, abciximab, heparin, and aspirin.[86] Patients were randomized to immediate transfer for PCI (299 patients) or standard care with transfer for rescue PCI (301 patients). The primary outcome was a composite of 30-day death, reinfarction, or

refractory ischemia. In the group assigned to immediate PCI, 97% (289 patients) underwent angiography and 85.6% (255 patients) underwent PCI. In the group assigned to standard care, 30.3% (91 patients) underwent rescue PCI. The primary end point occurred in 4.4% of patients assigned to immediate PCI and in 10.7% of the patients assigned to standard care with rescue PCI as required ($P = .004$), and no differences were observed in major bleeding (3.4% vs. 2.3%, $P = .47$) or stroke (0.7% vs. 1.3%, $P = .50$). In the immediate PCI group, the time interval from reteplase to angiography/PCI was 2.25 hours.[86] The Trial of Routine Angioplasty and Stenting After Thrombolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI)[87] included 1059 high-risk patients with STEMI who presented to non-PCI hospitals within 12 hours from symptom onset. Patients were randomized to standard treatment that also included rescue PCI (522 patients) or a strategy of immediate transfer for PCI within 6 hours after thrombolysis (537 patients). All patients received aspirin, tenecteplase, and heparin or enoxaparin; concomitant clopidogrel was strongly encouraged. The primary end point was the composite of death, reinfarction, recurrent ischemia, new or worsening CHF, or cardiogenic shock within 30 days. In the group assigned to transfer for PCI, 98.5% underwent coronary angiography, and 84.9% received PCI 2.8 hours after randomization; in the group assigned to standard care, 88.7% underwent coronary angiography, and 67.4% received PCI 32.5 hours after randomization. At 30 days, the primary end point occurred in 11.0% of the patients assigned to immediate PCI and in 17.2% of the patients assigned to standard treatment ($P = .004$). Most of the benefit was due to a reduction in reinfarction or recurrent ischemia, and the bleeding rates were similar in both groups.

A series of meta-analyses have supported the pharmacoinvasive strategy for patients with STEMI. A meta-analysis that included seven trials with 2961 patients to compare early routine PCI after thrombolysis with standard therapy in patients with STEMI found that early routine use of PCI after thrombolysis reduced the 30-day rate of reinfarction (2.6% vs. 4.7%, $P = .003$), the combined end point of death or reinfarction (5.6% vs. 8.3%, $P = .004$), and recurrent ischemia (1.9% vs. 7.1%; $P < .001$) without affecting the rates of major bleeding (4.9% vs. 5.0%, $P = .70$) or stroke (0.7% vs. 1.3%, $P = .21$).[88] The benefits of routine use of PCI after thrombolysis were maintained at 6 to 12 months of follow-up. Another meta-analysis of nine trials with a total of 3325 patients showed a 24% reduction in total mortality ($P = .06$), a 45% reduction in recurrent MI ($P < .001$), and a 65% reduction in recurrent ischemia ($P < .001$) with no significant difference in the incidence of major bleeding or stroke in patients managed with early or immediate PCI after thrombolysis as opposed to standard care.[89] A more recent meta-analysis that included 3195 patients (eight trials) showed that the composite end point of 30-day mortality, reinfarction, and ischemia was lower in the routine early PCI group compared with the ischemia-guided PCI group after thrombolysis (7.3% vs. 13.5%; OR, 0.47; 95% CI, 0.32 to 0.68; $P < .001$) driven by significant reduction in both reinfarction (OR, 0.62; 95% CI, 0.42 to 0.90; $P < .011$) and ischemia (OR, 0.21; 95% CI, 0.10 to 0.47; $P < .001$). The 30-day mortality and major bleeding rates between strategies were not significantly different. This meta-analysis supported the use of routine early PCI within 24 hours of thrombolysis when PPCI was not feasible.[90]

The Strategic Reperfusion Early After Myocardial Infarction (STREAM) study[91] evaluated whether a thrombolytic therapy approach (prehospital or early thrombolysis with contemporary antiplatelet and anticoagulant therapy) coupled with timely angiography (urgent in case of reperfusion failure or routine at 6 to 24 hr) provides a clinical outcome similar to that with PPCI in patients with STEMI who present early after symptom onset. In the STREAM study, 1892 patients with STEMI (≥2 mm ST elevation in two contiguous leads) who presented within 3 hours of symptom onset and who could not undergo PPCI within 1 hour of FMC were assigned to a strategy of early thrombolysis followed by coronary angiography in 6 to 24 hours or rescue PCI, if needed ($n = 944$), or standard PPCI ($n = 948$). The primary end point was a composite of death from any cause, cardiogenic shock, CHF, or reinfarction at 30 days. The early thrombolysis group received tenecteplase (the dose was halved in patients ≥75 years of age at the 20% planned recruitment), aspirin, clopidogrel, and enoxaparin in the ambulance or ED. Patients in the early thrombolysis group were more likely to have TIMI grade 3 blood flow compared with the PPCI group (58.5% vs. 20.7%). The median time from symptom onset to the start of reperfusion therapy (tenecteplase or arterial sheath insertion) was 100 minutes in the early thrombolysis group versus 178 minutes in the PPCI group. In the thrombolysis group, emergency angiography was required in 36.3% of the patients; the remaining patients underwent angiography at a median of 17 hours after randomization. No significant differences were reported in the primary end point between both treatment strategies (12.4% in the early thrombolysis vs. 14.3% in the PPCI group [RR, 0.86; 95% CI, 0.68 to 1.09; $P = .21$]; Fig. 20-10). The rates of intracranial hemorrhage were 1.0% in the thrombolysis group and 0.2% in the PPCI group ($P = .04$), but the difference was no longer significant after protocol amendment (0.5% vs. 0.3%, $P = .45$). The main conclusion of the STREAM trial was that prehospital thrombolysis followed by routine angiography within 6 to 24 hours in stable patients (or immediate or rescue PCI in cases of failed reperfusion or unstable patients) is a reasonable alternative to PPCI when expected treatment delay is more than 1 hour.[91] A recent report from the STREAM trial showed the frequency of *aborted MI,* defined as ST-segment resolution of 50% or greater, was significantly higher among patients undergoing a pharmacoinvasive therapy than with PPCI (11.1% vs. 6.9%, $P < .01$).[92] Some limitations of the STREAM trial are worth mentioning: exclusion of patients who could receive PCI within 60 minutes potentially biases the study in favor of thrombolysis (plus the trial protocol was amended); also, more than one third of patients were recruited in an expensive system of care designed to promote prehospital thrombolysis, which may not be directly applicable to other systems of care. Moreover, the high rate of no (or poor) responders to thrombolysis (36.3% rate of urgent angiography in the thrombolysis group) may support a strategy that expedites transfer to a PCI-capable facility of every patient undergoing thrombolysis after STEMI.

In aggregate, these studies demonstrated that the approach of routine catheterization and PCI after an initial primary thrombolysis strategy is beneficial in patients with STEMI. Among factors that seem to have had a positive impact on the outcome of routine use of PCI after thrombolysis are recent advances in PCI technology and adjunctive pharmacologic therapy.

RESCUE PERCUTANEOUS CORONARY INTERVENTION

Rescue PCI is defined as PCI performed within 12 hours after failure of thrombolysis in patients with continuing or recurrent myocardial ischemia. In the absence of coronary angiography, partial (<50%) resolution of ST-segment elevation on the surface ECG, continuation of chest discomfort, and/or hemodynamic instability or heart failure—even though they are known to be imprecise—are used as markers of failed thrombolysis. Even with the use of the most advanced fibrin-specific thrombolytic agents available, thrombolysis restores optimal epicardial blood flow to TIMI flow grade 3 in just over half of STEMI patients. Furthermore, 5% to 10% of patients will suffer coronary reocclusions after an initial successful thrombolysis. The less-than-optimal results with thrombolysis are explained by considering that the plaque/thrombosis ratio at the site of coronary occlusion is on average 80% plaque to 20% thrombotic material,[93] and plaque expansion often contributes more than acute thrombosis to the acute coronary occlusion.[94] In the presence of these and other factors, the establishment of TIMI flow grade 3 by thrombolysis is less likely. Patients with an occluded infarct-related artery (TIMI flow grade 0 to 1) and those with suboptimal blood flow restoration (TIMI flow grade 2) have increased mortality compared with patients with restoration of TIMI flow grade 3 in the infarct-related artery. It has been estimated that nearly 125,000 STEMI patients per year in the United States will have suboptimal reperfusion with thrombolytic therapy.[95] In the past, patients with failed thrombolysis have been treated with conservative therapy and watchful waiting, repeat thrombolysis, or rescue PCI.

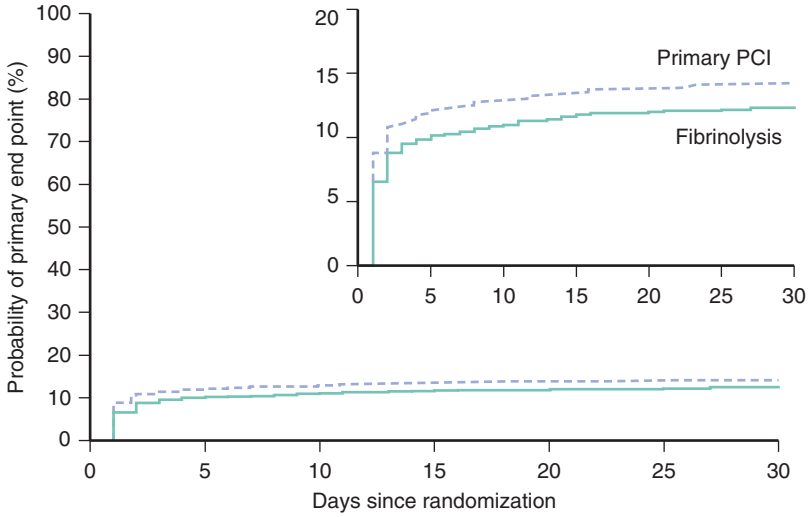


FIGURE 20-10 Kaplan-Meier curves for the primary end point, a composite of death from any cause, cardiogenic shock, congestive heart failure, or reinfarction within 30 days ($P = .21$ by the log-rank test). *Inset:* The same data on an enlarged Y-axis. *PCI,* Percutaneous coronary intervention. (From Armstrong PW, Gershlick AH, Goldstein P, et al: Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 368[15]:1379-1387, 2013.)

The efficacy of rescue PCI for failed thrombolysis has been assessed in a number of randomized trials (six trials in a 2007 meta-analysis).[95] Earlier trials included limited numbers of patients (from 28 to 151 patients) and underestimated the benefits of rescue PCI because it consisted of percutaneous transluminal coronary angioplasty (PTCA) without stenting. The superiority of coronary stenting over angioplasty in rescue PCI interventions has been shown in the Stent or PTCA for Occluded Coronary Arteries After Failed Thrombolysis in Patients With Acute Myocardial Infarction (STOPAMI-4) trial,[96] which showed a significantly higher salvage index (35% vs. 25% of the initial perfusion defect salvaged by rescue interventions) obtained by paired scintigraphic studies performed 7 to 10 days apart. The most important randomized trials in the setting of rescue interventions for failed thrombolysis have been the Middlesbrough Early Revascularization to Limit Infarction (MERLIN) trial[97] and the Rescue Angioplasty or Repeat Thrombolysis (REACT) trial.[98] The MERLIN trial randomized 307 patients with STEMI and failed thrombolysis (failure of ST-segment elevation in the lead with maximal elevation to resolve by 50%) to emergency coronary angiography with or without rescue PCI or conservative therapy. The primary end point was all-cause mortality at 30 days. It should be emphasized that coronary stents were used in just half of the patients. Thirty-day all-cause mortality was similar in the rescue and conservative groups (9.8% vs. 11%, $P = .7$). The combined incidence of MACEs was reduced in the rescue PCI group (37.3% vs. 50.0%, $P = .02$) driven by less subsequent revascularization (6.5% vs. 20.1%, $P = .01$). Reinfarction (7.2% vs. 10.4%, $P = .03$) and CHF (24.2% vs. 29.2%, $P = .3$) were less common among patients undergoing rescue PCI. Incidences of stroke (4.6% vs. 0.6%, $P = .03$) and blood transfusion (11.1% vs. 1.3%, $P = .001$) were increased among patients treated by rescue PCI versus those treated by conservative therapy.[97] The 3-year follow-up of the patients in the MERLIN trial showed that compared with conservative treatment, rescue angioplasty did not confer a survival benefit at 3 years (17.6% vs. 16.9%, $P = .90$) but was associated with fewer unplanned revascularization procedures (14.4% vs. 33.8%, $P < .01$).

The REACT trial[98] included 427 patients with STEMI within 6 hours of symptom onset and 90-minute ECG criteria for failed thrombolysis (less than 50% ST-segment resolution in the leads with previous maximal ST-segment elevation). Patients were randomly assigned to one of three options: rescue PCI ($n = 144$), repeat thrombolysis ($n = 142$), or conservative therapy ($n = 141$). Coronary stents were used in 68.5% of patients, and 43.4% of patients received GP IIb/IIIa receptor blockers. The 6-month probability of event-free survival was significantly higher in patients assigned to rescue PCI (84.6%) compared with patients assigned to conservative therapy (70.1%) or repeat thrombolysis (68.7%, $P = .004$). In a subsequent report from the REACT trial,[99] the authors report the primary composite end points of death, recurrent MI, cerebrovascular events, and severe heart failure at 1 year and mortality at a median of 4.4 years. The 6-month advantage in the event-free-survival was maintained at 1 year of follow-up (81.5%, 67.5%, and 64.1% in rescue PCI, conservative therapy, and repeat thrombolysis arms, respectively; $P = .004$), and a significant reduction was seen in mortality at a median of 4.4 years: mortality rates were 11.2% in the rescue-PCI arm, 22.4% in the conservative-therapy arm, and 22.3% in the repeat-thrombolysis arm (HR was 0.43 [95% CI, 0.23 to 0.97] for rescue PCI vs. conservative therapy and was 0.41 [95% CI, 0.22 to 0.75] for rescue PCI vs. repeat thrombolysis). Of importance was the finding that repeat thrombolysis did not offer any benefit compared with conservative therapy.[99]

A 2007 meta-analysis[95] of randomized trials showed that rescue PCI was associated with an insignificant 31% reduction in the relative risk for all-cause mortality and significant reductions in the risk for heart failure (27%) and reinfarction (42%) compared with conservative treatment. Moreover, repeat thrombolysis was not associated with improvements in mortality or reinfarction, but it increased the risk of minor bleeding by 84%.

In summary, rescue PCI improves clinical outcome and should be recommended in patients with STEMI after failed thrombolysis.

TECHNICAL ASPECTS OF PRIMARY PERCUTANEOUS CORONARY INTERVENTION IN STEMI

From a technical point of view, PPCI is not substantially different from elective PCI, although it is characterized by more frequent use of thrombus aspiration devices and direct stenting. However, PCI in the early phase of a STEMI can be more difficult and requires more expertise than routine PCI in a stable patient. The goal of PPCI is to open

occluded coronary arteries and restore normal blood flow to the ischemic region. PPCI is performed in conditions of increased risk due to hemodynamic and electrical instability, increased thrombogenicity associated with STEMI, and increased bleeding risk due to adjuvant treatments; this is true particularly if PCI is performed following failed thrombolysis and complete occlusion of the stenotic coronary artery. The latter finding impedes visualization of the coronary artery, makes guidewire and balloon passage through the occluded lesion more difficult, and predisposes to distal embolization of thrombotic material with a potential for further worsening of microcirculation. Operators who perform PPCI in STEMI must act rapidly to restore coronary blood flow in the infarct-related artery as early as possible to stop evolving ischemia and progression to necrosis and to increase chances of myocardial salvage and infarct size reduction. Vascular access is achieved via the femoral artery, although radial artery access is increasingly being preferred. Adjunct antithrombotic therapy is used periprocedurally (see the section below, *Periprocedural Antithrombotic/Anticoagulant Therapy in Patients with STEMI Undergoing PPCI*). After the procedure, the patient is monitored continuously, and in the absence of complications, the patient is discharged from the hospital within a few days.

PRIMARY STENTING IN PATIENTS WITH STEMI

In the early days of mechanical reperfusion for STEMI, balloon angioplasty was the mainstay of therapy. However, although superior to thrombolysis, balloon angioplasty often produces suboptimal results; these are mostly related to recurrent ischemia and reocclusion that occurs within the first days and weeks after the procedure, as well as a high incidence of late vessel narrowing (restenosis). Despite these limitations of balloon angioplasty, in the early days of mechanical reperfusion for STEMI, coronary stenting in the setting of STEMI was avoided because of the fear that implantation of a metallic structure within the highly thrombogenic milieu of the infarct-related artery (including thrombotic material and balloon-induced plaque disruption) would predispose to acute stent thrombosis and coronary reocclusion. Furthermore, in the early days of PCI, the profound anticoagulation needed to prevent stent thrombosis markedly increased the risk of bleeding, which added additional risk for patients. Refinement in stent technology and advances in periprocedural and long-term antithrombotic therapy transformed primary stenting from an infrequently used therapeutic option, usually in bail-out situations, to the dominant form of PPCI in patients with STEMI.

Earlier studies showed superiority of balloon angioplasty over thrombolysis, and later the superiority of stenting over balloon angioplasty alone was demonstrated. A meta-analysis summarized the results of 13 trials, which randomized 6922 patients with acute MI to coronary stenting (3460 patients) or balloon angioplasty alone (3462 patients).[100] Five trials included patients with cardiogenic shock. In this meta-analysis, primary stenting significantly reduced the need for repeat revascularization at 1 year (11.3% vs. 18.3%) but had no effect on mortality (5.1% vs. 5.2%) or reinfarction (3.7% vs. 3.9%). The meta-regression analysis demonstrated a significant association between patients' risk profile and mortality benefits from primary stenting at 1 year.[100] These conclusions, however, are subject to limitations related to significant variations in the crossover rates and possible confounding effects of thienopyridine treatment in patients treated with primary stenting. Against this, an analysis of the Primary Angioplasty in Myocardial Infarction (PAMI) trial showed not only better angiographic results with primary stenting but also showed a sustained benefit in mortality out to 5 years after the infarct.[101] Mechanistically, compared with balloon angioplasty, stents achieve a better immediate angiographic result due to a larger postprocedural arterial lumen, fewer early ischemic events as a result of the sealing of plaque rupture and dissection, and enhanced longer-term patency durability due to attenuation of elastic recoil and constrictive remodeling. These studies transformed coronary stenting from a feared therapeutic option to an almost default strategy in PPCI.

DRUG-ELUTING STENTS IN PATIENTS WITH STEMI

The development of drug-eluting stents (DESs) represented an important milestone in the evolution of PCI. Compared with bare-metal stents (BMSs), the DES has reduced the need for TVR by 60% to 70% in the setting of randomized clinical trials. In general, although the results of current research have been reassuring, concerns remain about a possible excess of stent thrombosis—especially late events beyond 1 year—after DES implantation because of inhibition or delayed reendothelialization of the stented segment.[102] Specifically, it has been postulated that the risk of stent thrombosis might be higher if a DES is implanted in a patient who has had a STEMI. Several putative mechanisms have been offered to explain the higher rates of stent thrombosis after DES implantation in patients with STEMI: these include 1) an increased risk of stent malapposition—thrombus "jailing" and subsequent dissolution, as well as coronary spasm at culprit lesions during the acute event, which may increase the risk of stent undersizing; 2) a modulation of drug-release kinetics by superimposed thrombotic material; and 3) uptake of lipophilic drugs by necrotic core material, which may lead to further prolongation of tissue exposure due to very slow turnover that can exacerbate delayed healing.[102] Despite these still unresolved issues, recent evidence about the use of DESs in STEMI has been mostly reassuring, and DES implantation is increasingly being used in the setting of PPCI.

Recent information on the use of DESs in patients with STEMI has emerged from registries, randomized trials, and meta-analyses. A series of randomized trials have investigated the efficacy and safety of the first-generation DESs versus the BMSs in patients with STEMI, and their results have been summarized in multiple meta-analyses. Important comparative evidence comes from a recent patient-level meta-analysis[103] (individual data obtained in 11 out of 13 trials) with 6298 patients (3980 randomized to DESs [99% sirolimus-eluting or paclitaxel-eluting stents] and 2318 randomized to BMSs). At a mean of 3.3 years follow-up, DES implantation significantly reduced the occurrence of TVR (12.7% vs. 20.1%; HR, 0.57; 95% CI, 0.50 to 0.66; $P < .001$; Fig. 20-11) without any significant difference in all-cause mortality (8.5% vs. 10.2%, $P = .11$), cardiac mortality (5.7% vs. 6.8%, $P = .19$), reinfarction (9.4% vs. 5.9%, $P = .36$), or stent thrombosis (5.8% vs. 4.3%, $P = .38$). However, with regard to the occurrence of stent thrombosis or reinfarction, the assumption of proportionality was not met, and the Cox model with time-varying regression coefficients showed an increase in the risk for these events over long-term follow-up. Thus, 2 years after the study began, the rate of stent thrombosis (HR, 2.81; 95% CI, 1.28 to 6.19; $P = .04$) and reinfarction (HR, 2.06; 95% CI, 1.22 to 3.49; $P = .03$; Fig. 20-12) increased significantly among patients with a DES compared with those who had received a BMS.

Another recent meta-analysis[104] of 15 trials comprised 7867 patients and compared first-generation DESs with BMSs in patients with STEMI; it further evidenced an increased risk for very late stent thrombosis associated with DESs. Whereas the overall risk for definite stent thrombosis was similar for DES and BMS (RR, 1.08; 95% CI, 0.82 to 1.43) time-dependent effects were seen, and risk ratio increased from 0.80 (95% CI, 0.58 to 1.12) in the first year to 2.10 (95% CI, 1.20 to 3.69) in the subsequent years with an interaction between the time and risk ratio for stent thrombosis ($P = .009$). Of note, the study concluded that an early benefit in terms of reduction of TVR and a trend toward less definitive stent thrombosis with the use of a first-generation DES in PPCI for STEMI was offset in subsequent years by an increased risk of very late stent thrombosis. It must be mentioned, however, that first-generation DESs are rarely used in current practice.

Newer-generation DESs incorporate a series of technical refinements compared with BMSs or first-generation DESs and are increasingly being used in patients with STEMI. Briefly, they consist of cobalt- or platinum-chromium platforms and have thinner struts and improved biocompatibility, which makes them more tissue friendly, and they have a reduced thickness of durable or biodegradable polymer matrices (Fig. 20-13). The new-generation stents release antiproliferative drugs such as sirolimus, everolimus, zotarolimus, biolimus, A9,

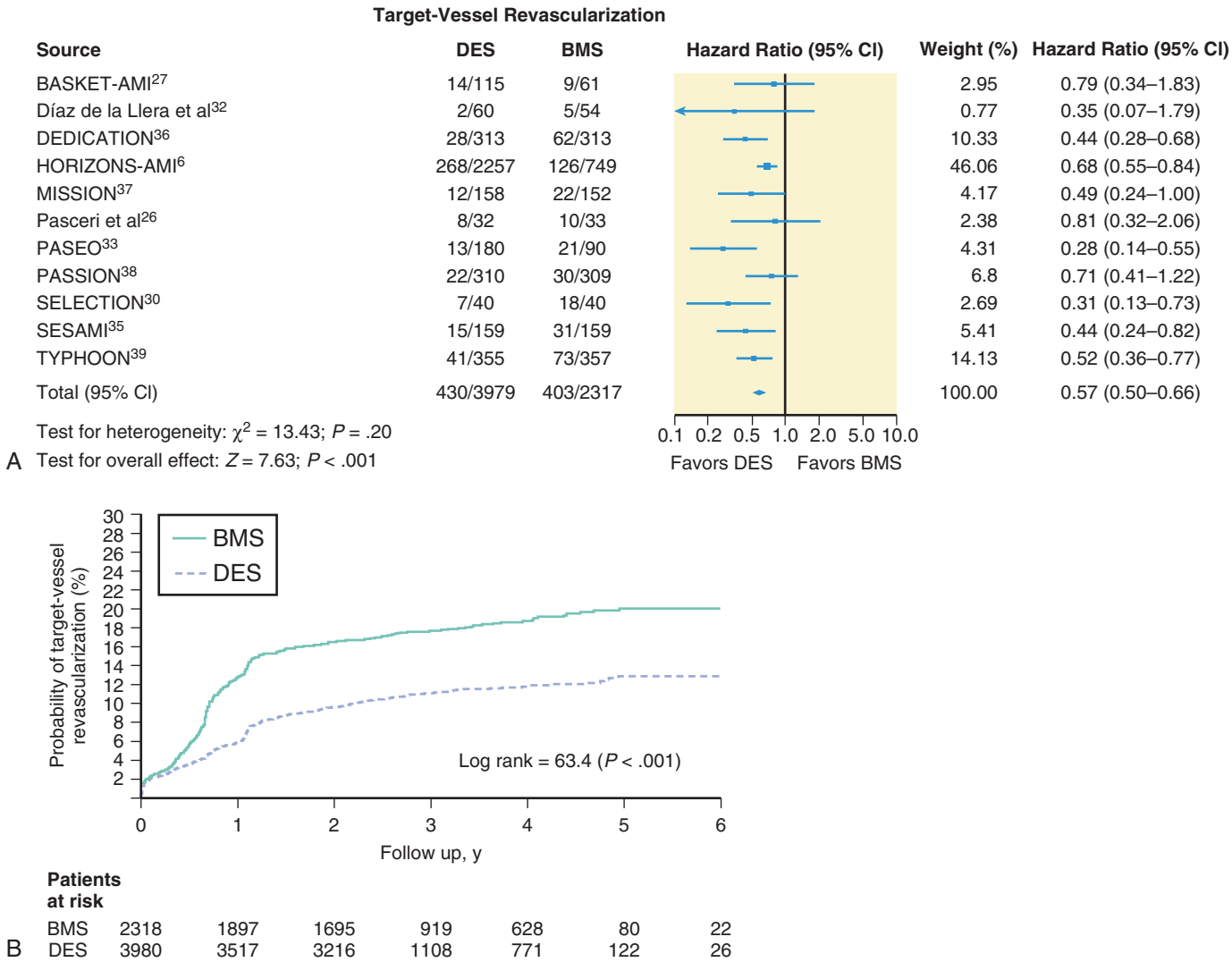
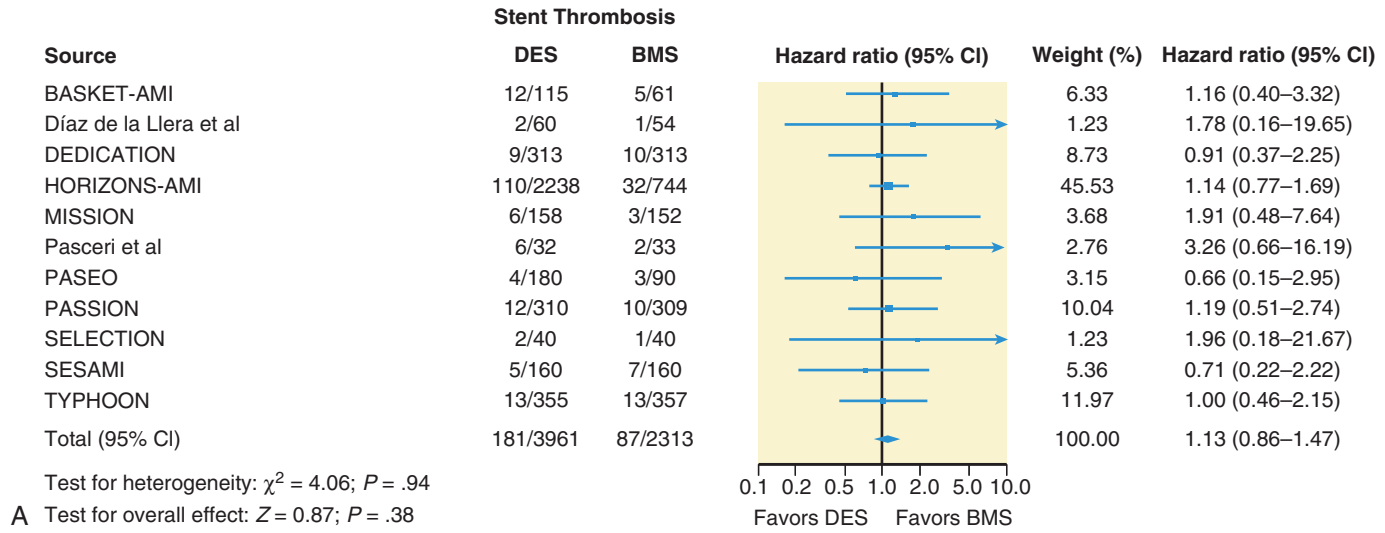


FIGURE 20-11 Target-vessel revascularization (TVR) at long-term follow-up. **A,** Absolute numbers of TVRs and hazard ratios for this end point with drug-eluting stent (DES) versus bare-metal stent (BMS) use for individual trials and the pooled population (fixed-effect model). Hazard ratios are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log hazard ratio. **B,** Kaplan-Meier curves of probability of TVR in each of the stent groups for the pooled population. *CI,* Confidence interval. Trial abbreviations: *BASKET-AMI,* Basel Stent Kosten-Effektivitäts in Acute Myocardial Infarction; *DEDICATION,* Drug Elution and Distal Protection in ST-Elevation Myocardial Infarction; *HORIZONS-AMI,* Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; *MISSION,* MISSION! Intervention Study; *PASEO,* Paclitaxel or Sirolimus-Eluting Stent Versus Bare-Metal Stent in Primary Angioplasty; *PASSION,* Paclitaxel-Eluting Versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation; *SELECTION,* Single-Center Randomized Evaluation of Paclitaxel-Eluting Stent Versus Conventional Stent in Acute Myocardial Infarction; *SESAMI,* Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction; *TYPHOON,* Trial to Assess the Use of Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty. (Modified from De Luca G, Dirksen MT, Spaulding C, et al: Drug-eluting vs bare-metal stents in primary angioplasty: a pooled patient-level meta-analysis of randomized trials. *Arch Intern Med* 172[8]:611-621, 2012.)

novolimus, and myolimus over weeks to months after implantation.[105] Several randomized trials and meta-analyses have investigated their efficacy and safety in patients with STEMI. The Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction (COMFORTABLE AMI) trial[106] randomized 1161 patients with STEMI with symptom onset within 24 hours to receive a biolimus-eluting stent ($n = 575$), with the biolimus embedded in a biodegradable polymer, or a BMS ($n = 582$). The primary end point was a composite of cardiac death, target vessel–related reinfarction, and ischemia-driven TLR at 1 year. At 1 year, the primary end point occurred in 4.3% of the patients assigned to biolimus stenting and in 8.7% of the patients assigned to a BMS (HR, 0.49; 95% CI, 0.30 to 0.80; $P = .004$). The difference was driven by a lower risk of target vessel–related reinfarction (0.5% vs. 2.7%) and ischemia-driven TLR (1.6% vs. 5.7%) in patients who received a biolimus-eluting stent (Fig. 20-14). The risk of definite stent thrombosis was lower (0.9% vs. 2.1%) in patients treated with a biolimus-eluting stent, but the difference was statistically insignificant ($P = .10$). A more recent publication from the COMFORTABLE-AMI trial showed that the favorable results with the biolimus-eluting stent were durable up to 2 years of follow-up.[107] The clinical Evaluation of the Xience-V Stent in Acute Myocardial Infarction (EXAMINATION) trial[108] randomized



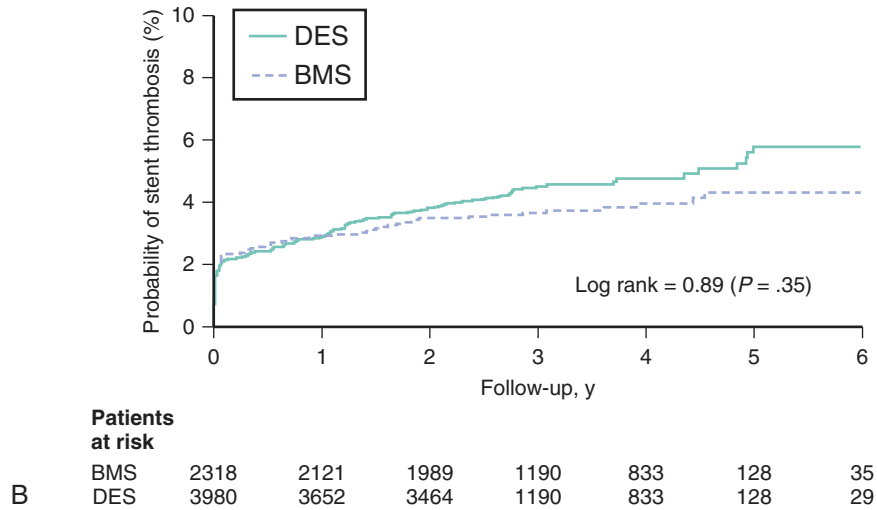


FIGURE 20-12 Definite and probable stent thrombosis at long-term follow-up. Definitions are according to the Academic Research Consortium. **A,** Absolute numbers of stent thrombosis and hazard ratios for this end point with drug-eluting stent (DES) versus bare-metal stent (BMS) for individual trials and the pooled population (fixed-effect model). Hazard ratios are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log hazard ratio. **B,** Kaplan-Meier curves of probability of in-stent thrombosis in each of the stent groups for the pooled population. Trial abbreviations are as in Figure 20-11. *CI,* Confidence interval. (From De Luca G, Dirksen MT, Spaulding C, et al: Drug-eluting vs bare-metal stents in primary angioplasty: a pooled patient-level meta-analysis of randomized trials. *Arch Intern Med* 172[8]:611-621, 2012.)

1504 patients with STEMI up to 48 hours after symptom onset to receive an everolimus-eluting stent (with a durable fluoropolymer) or a BMS. The primary end point was a composite of all-cause death, recurrent MI, or revascularization at 1 year. The primary end point was similar in both groups (11.9% in the everolimus stent group vs. 14.2% in the BMS group, $P = .19$). The use of everolimus-eluting stents was associated with a lower risk of TLR (2.1% vs. 5.0%, $P = .003$) and definite stent thrombosis (0.5% vs. 1.9%, $P = .018$) and no difference in all-cause mortality (3.5% vs. 3.5%) or cardiac mortality (3.2% vs. 2.8%, $P = .76$).

The overall efficacy and safety of earlier and newer DESs was addressed in a recent network meta-analysis that included 22 trials with 12,453 randomized patients. At 1-year follow-up, cobalt-chromium everolimus-eluting stents were associated with significantly lower rates of all-cause death or MI (OR, 0.65; 95% CI, 0.46 to 0.90); cardiac death or MI (OR, 0.63; 95% CI, 0.42 to 0.92), target-vessel revascularization (OR, 0.45; 95% CI, 0.29 to 0.66), and definite stent thrombosis (OR, 0.32; 95% CI, 0.11 to 0.78) compared with BMSs. Differences in stent thrombosis were apparent as early as 30 days and were maintained for 2 years. Cobalt-chromium everolimus-eluting stents were associated with lower rates of 1-year definite stent thrombosis than paclitaxel-eluting stents (OR, 0.33; 95% CI, 0.11 to 0.87). Sirolimus-eluting stents were also associated with significantly lower rates of 1-year cardiac death and MI than BMSs. Chromium-cobalt everolimus-eluting stents, paclitaxel-eluting stents, and sirolimus-eluting stents—but *not* zotarolimus-eluting stents—had significantly lower rates of 1-year TVR than BMSs. Sirolimus-eluting stents showed lower rates of TVR compared with paclitaxel-eluting stents.[109] The results of this meta-analysis highlighted the steady improvements in clinical outcomes with the evolution from BMSs to first-generation and second-generation DESs.

Because of an increased risk for very late stent thrombosis with DESs, particularly with the first generation of these devices, the efficacy and safety of drug-eluting balloons in combination with BMSs has

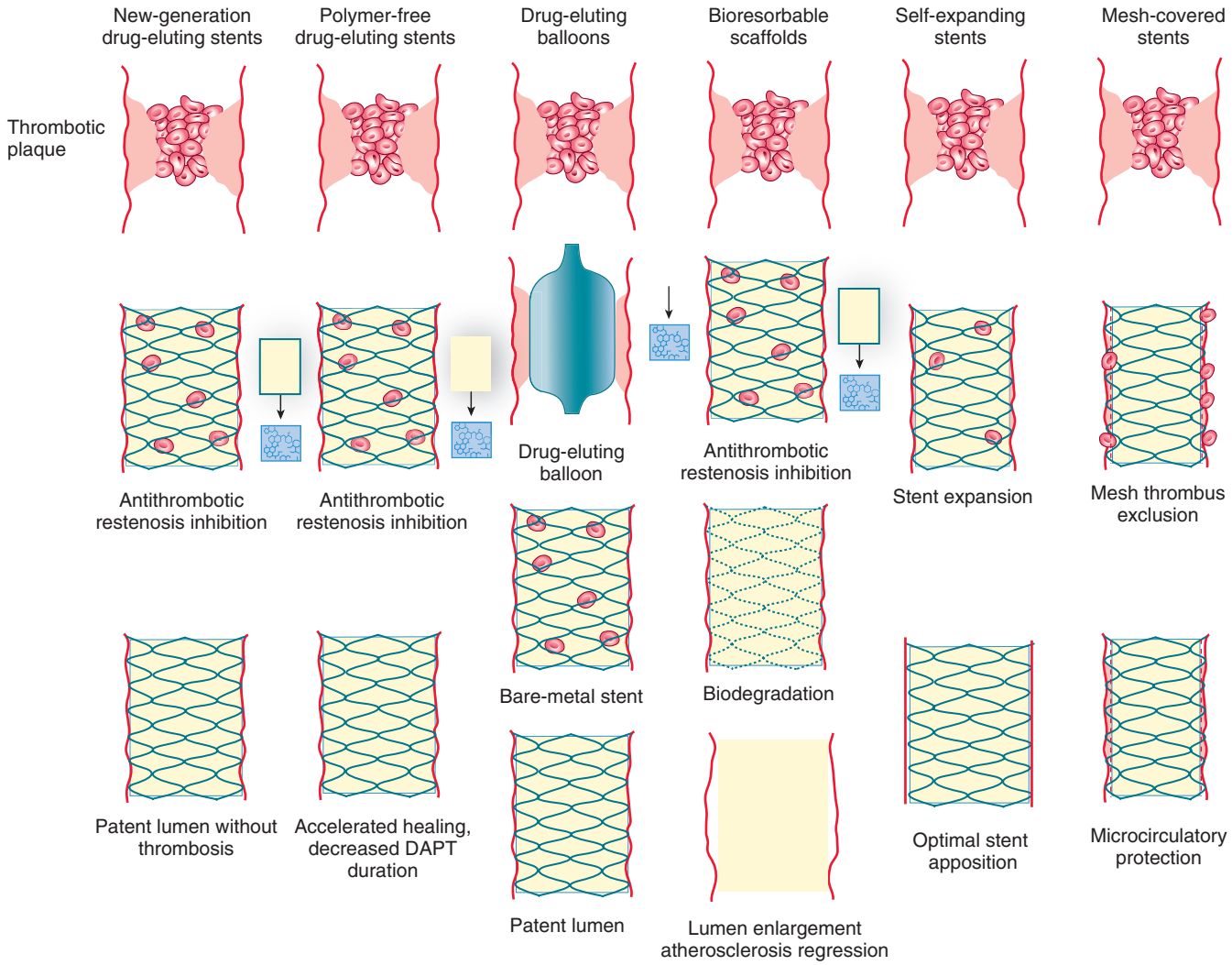


FIGURE 20-13 Novel intracoronary devices and putative mechanisms to improve outcomes of mechanical reperfusion. New-generation drug-eluting stents release antiproliferative drugs over a period of weeks to months to reduce restenosis. Polymer-free drug-eluting stents release antiproliferative drugs over a period of days to weeks via various mechanisms of drug binding and release. Drug-eluting balloons could be applied either before or after implantation of a bare-metal stent with the aim to suppress neointimal hyperplasia within the stent to maintain vessel patency. Bioresorbable scaffolds have a biodegradable coating that releases antiproliferative drugs over a period of weeks to months and a metallic or polymer stent backbone that biodegrades over months to years. Self-expanding stents aim to overcome stent undersizing caused by vessel constriction and thrombus apposition. Mesh-covered stents target distal embolization and associated no-reflow by means of thrombus exclusion and microcirculatory protection. *DAPT,* Dual antiplatelet therapy. (From Windecker S, Bax JJ, Myat A, et al: Future treatment strategies in ST-segment elevation myocardial infarction. *Lancet* 382[9892]:644-657, 2013.)

been proposed as an alternative treatment strategy and was investigated in the Drug-Eluting Balloon in Acute Myocardial Infarction (DEB-AMI) trial.[110] In this trial, 150 patients were randomized to a strategy of a BMS, a drug-eluting balloon (paclitaxel) plus a BMS, or a paclitaxel-eluting DES. The primary end point was 6-month angiographic in-stent late-luminal loss. The study concluded that a strategy of drug-eluting balloon followed by bare-metal stenting was inferior to standard drug-eluting stenting and failed to show superiority compared with bare-metal stenting alone. Several novel stent platforms that included bioabsorbable vascular scaffolds in conjunction with various antiproliferative drugs are under investigation. A recent network meta-analysis that investigated the safety and efficacy of bioabsorbable polymer-based biolimus-eluting stents versus durable-polymer DESs and BMSs concluded that polymer-based biolimus-eluting stents were associated with superior clinical outcomes compared with BMSs and first-generation DESs but demonstrated similar rates of cardiac death/MI, MI, and TVR compared with second-generation durable-polymer DESs.[111]

In summary, ample evidence from multiple sources proves a clear antirestenotic advantage of the DES over the BMS in patients with STEMI. Moreover, DESs—and in particular, second-generation DESs—may also confer a safety benefit over BMSs in the early phase after intervention. Although some concerns persist regarding very late adverse events, stenting with a DES is considered the preferred approach for patients with STEMI who undergo PPCI.

DIRECT STENTING

Evidence in favor of *direct stenting*—that is, stent implantation without predilation—comes from observational studies and at least one small randomized study. A 2002 study randomized 206 patients with STEMI to direct stent implantation or stent implantation after balloon

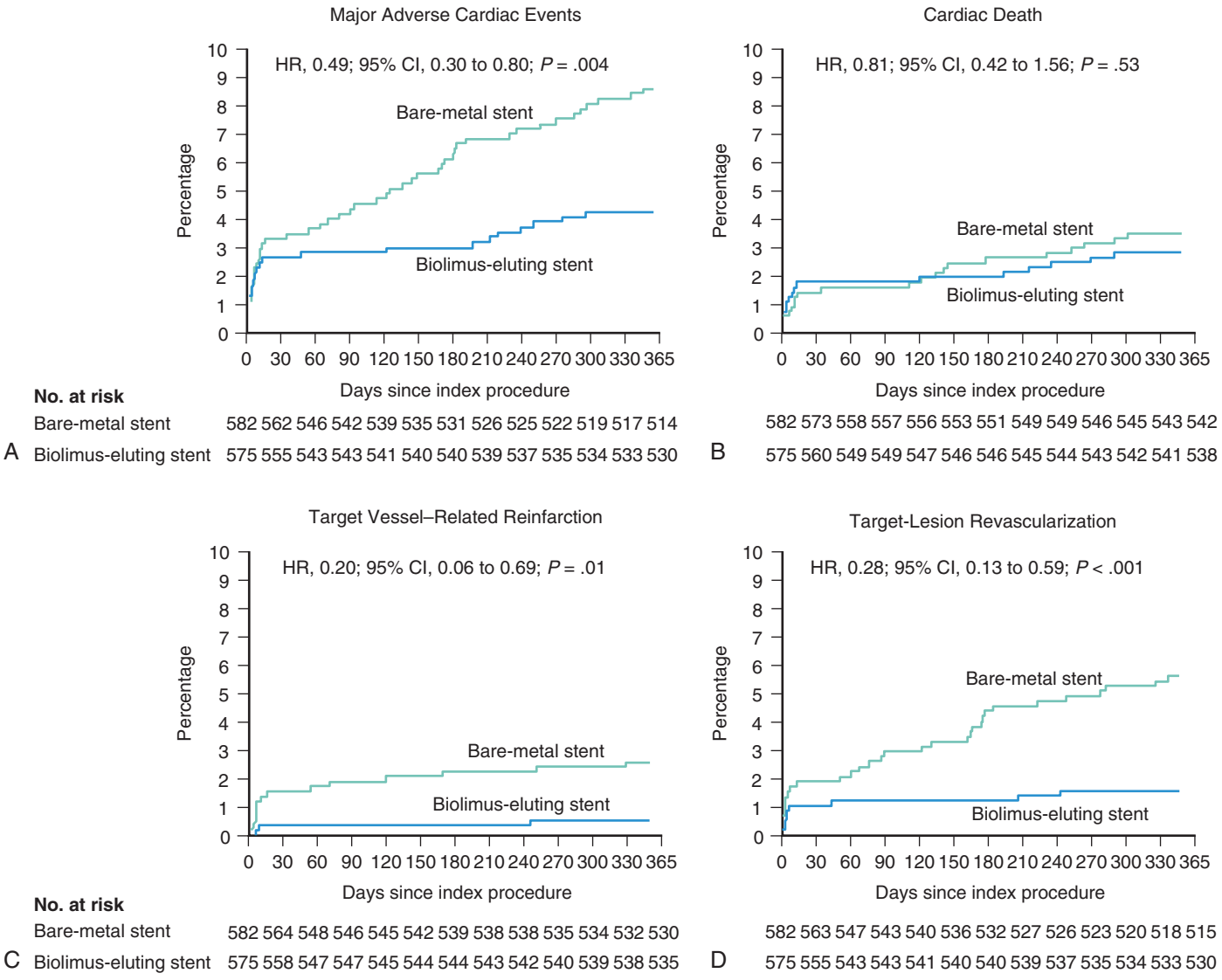


FIGURE 20-14 Kaplan-Meier curves for major adverse cardiac events (MACEs)—cardiac death, target vessel–related reinfarction, and ischemia-driven target-lesion revascularization—among patients randomized to receive either the biolimus-eluting stent or the bare-metal stent. *CI,* Confidence interval; *HR,* hazard ratio. (From Räber L, Kelbæk H, Ostojic M, et al: Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. *JAMA* 308[8]:777-787, 2012.)

predilation. Although the postintervention TIMI flow or TIMI corrected frame count did not differ significantly between the two strategies, the composite angiographic (corrected TIMI frame count, slow-flow/no-reflow or distal embolization) end point (11.7% vs. 26.9%, $P = .01$) or ST-segment resolution (79.8% vs. 61.9%, $P = .01$) were better among patients with direct stenting compared with patients who had stent implantation after predilation.[112] Support in favor of using direct stenting also comes from the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial[113] in which 698 patients were treated with direct stenting. Direct stenting compared with conventional stenting (after predilation) was associated with better ST-segment resolution at 60 minutes after the procedure (median 74.8% vs. 68.9%, $P = .01$) and a lower rate of all-cause death (1.6% vs. 3.8%, $P = .01$) and stroke (0.3% vs. 1.1%, $P = .049$) with nonsignificant differences in TLR, MI, stent thrombosis, and major bleeding. Rates of death at 1 year remained lower in patients with direct stenting (HR, 0.42; 95% CI, 0.21 to 0.86; $P = .02$) after adjustment and in a propensity score–based analysis (HR, 0.92; 95% CI, 0.88 to 0.95; $P = .02$). Recent observational studies have also suggested that direct stenting is associated with improved ST-segment resolution and better early and 1-year survival compared with conventional stenting after predilation.[114] Based on these studies, we suggest the use of direct stenting, preferably after thrombus aspiration for most culprit lesions in patients with STEMI. Heavy calcification of the vessel or poor visualization of the distal edge is a contraindication for this strategy.

RADIAL ARTERY VERSUS FEMORAL ARTERY VASCULAR ACCESS FOR PRIMARY PERCUTANEOUS CORONARY INTERVENTION

Although vascular access via the femoral artery was considered as almost a default strategy for vascular access for PCI in general, including PPCI, evidence favoring the use of radial artery for vascular access is rapidly increasing. The most important argument for the use of radial artery comes from multiple sources that show significant

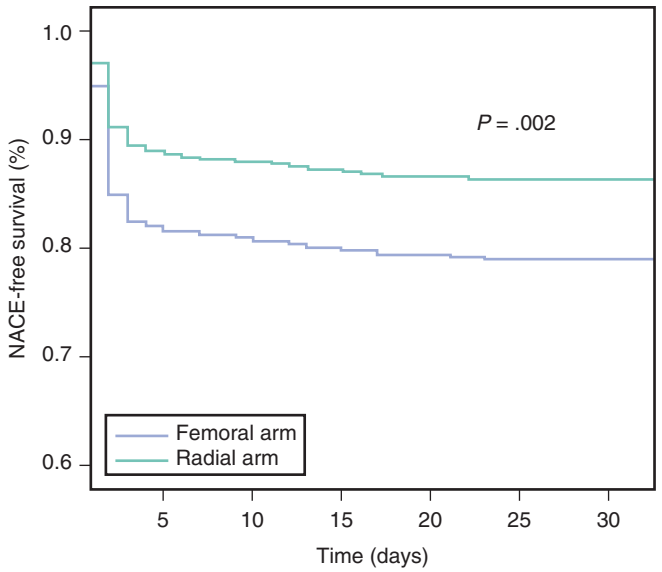


FIGURE 20-15 Time-to-event curves for net adverse cardiac events (NACEs), a composite of cardiac death, myocardial infarction, target-lesion revascularization, stroke, and bleeding. (From Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al: Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS [Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome] study. *J Am Coll Cardiol* 60[24]:2481-2489, 2012.)

reductions in bleeding complications with the radial artery compared with the femoral artery route. Recent randomized trials and large registries offer support for the use of a radial artery approach in PPCI procedures. In a prespecified analysis of the Radial Versus Femoral Access for Coronary Intervention (RIVAL) trial,[115] which included 1958 patients with STEMI, the radial approach was associated with significantly lower primary outcomes of death, MI, stroke, or major bleeding unrelated to coronary artery bypass grafting (CABG) at 30 days (3.1% vs. 5.2%, $P = .026$). However, caution is always required in the interpretation of subgroup analysis, particularly in a trial with an overall negative result. The two strategies were directly compared in the Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE-STEACS) study,[116] which randomized 1001 patients with STEMI to undergo primary or rescue PCI via radial or femoral artery approaches. The primary end point was the 30-day rate of *net adverse clinical events* (NACEs), defined as a composite of cardiac death, stroke, MI, TLR, and bleeding. The primary end point occurred in 13.6% of the patients in the radial artery arm and in 21.0% of the patients in the femoral artery arm ($P = .003$; Fig. 20-15). The difference was driven in large part by a reduction in cardiac mortality (5.2% vs. 9.2%, $P = .020$) with radial artery access. However, radial compared with femoral access was also associated with significantly lower rates of bleeding (7.8% vs. 12.2%, $P = .026$) and shorter hospital stays (5 days vs. 6 days, $P = .03$). Another recent randomized trial showed that a radial artery approach was superior to a femoral artery approach in reducing the major bleeding/vascular complications (1.4% vs. 7.2%, $P < .001$), although the antithrombotic regimen used consisted of high-dose heparin (>100 IU/kg) and high rates of GP IIb/IIIa inhibitor antagonist use. Thirty-day NACEs—defined as death, MI, stroke, or major bleeding vascular complications—was also lower with radial access (4.6% vs. 11%, $P = .0028$) but not 6-month mortality (2.3% vs. 3.1%, $P = .64$).[117] A decision-analytic model that used the data from the RIVAL and RIFLE-STEACS trials suggested that a substantial delay in DTB time would need to be introduced during transradial PCI to eliminate the observed mortality benefits of a transradial approach.[118]

Two recent large registries in Italy and the United States offer additional support for the use of a radial artery approach for PPCI. The *Registro Regionale Angioplastiche dell'Emilia-Romagna* (REAL) registry of 11,068 patients showed that the 2-year risk-adjusted mortality rates were lower for the transradial than for the transfemoral group (8.8% vs. 11.4%, $P = .0250$). The rate of vascular complications that required surgery or blood transfusion were also significantly decreased in the transradial group (1.1% vs. 2.5%, $P = .0052$).[119] A recent report from the CathPCI registry—which included 294,769 patients who underwent PCI for STEMI between 2007 and 2011—showed that over a 5-year period, the use of transradial PCI versus transfemoral PCI increased from 0.9% to 6.4% ($P < .001$).[120] Transradial PCI was associated with a longer median DTB time (78 vs. 74 min, $P < .001$) but a lower adjusted risk for bleeding (OR, 0.62; 95% CI, 0.53 to 0.72; $P < .001$) and a lower adjusted risk of in-hospital mortality (OR, 0.76; 95% CI, 0.57 to 0.99; $P = .0455$).

THROMBECTOMY AND DISTAL PROTECTION DEVICES IN PRIMARY PERCUTANEOUS CORONARY INTERVENTION

Although PPCI is a highly effective therapy in patients with STEMI, concerns have been raised that conventional PCI using balloons and stents may dislodge thrombotic material and/or atherosclerotic plaque debris into the distal microcirculation and result in distal embolization and impaired myocardial perfusion. Distal embolization during mechanical reperfusion is considered an important contributor to microvascular dysfunction and no-reflow phenomenon. Distal embolization does occur during PCI for STEMI, and visible debris is aspirated in 73% of patients.[121] Thus, apart from direct stenting and systemic or intracoronary use of pharmacologic agents such as GP IIb/IIIa inhibitors, several thrombectomy and protection devices have been developed to reduce thrombotic burden, limit distal embolization, and improve myocardial perfusion, and these may potentially improve the clinical outcome.

In principle, two categories of devices might be used in an attempt to reduce distal embolization: *thrombectomy devices* (manual thrombus aspiration or mechanical thrombectomy) and *embolic protection devices* (distal occlusive devices, proximal occlusive devices, and distal embolic filters). With regard to mechanical thrombectomy, randomized trials did not show a benefit in terms of clinical outcome. A recent meta-analysis that included seven trials with 1598 patients showed no difference between the mechanical thrombectomy and conventional PPCI arms in the incidence of MACEs (RR, 1.10; 95% CI, 0.59 to 2.05), mortality ($P = .57$), recurrent MI ($P = .32$), TVR ($P = .19$), or final infarct size ($P = .47$). A benefit in ST-segment resolution at 60 minutes ($P = .007$), but not in the TIMI blush grade ($P = .48$), were also noted.[122] Based on these data, the current mechanical thrombectomy devices are not recommended for use in the setting of PPCI in patients with STEMI.

Earlier randomized trials that used manual aspiration thrombectomy reported encouraging results in terms of clinical outcomes and led to increased usage of manual aspiration as an adjunctive therapy to PPCI. In the Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS),[123] 1071 patients with STEMI were randomized to aspiration thrombectomy with the 6-French Export catheter plus conventional PCI versus PCI alone. The primary end point was a myocardial blush grade of 0 or 1. A myocardial blush grade of 0 to 1 occurred in 17.1% of the patients in the thrombus-aspiration group and in 26.3% of those in the conventional-PCI group ($P < .001$); complete resolution of ST-segment elevation occurred in 56.6% and 44.2% of patients, respectively ($P < .001$), and a trend was seen toward lower 30-day mortality in the group with aspiration thrombectomy (2.1% vs. 4.1%, $P = .07$). No significant differences were apparent in reinfarction (0.8% vs. 1.9%), TVR (4.5% vs. 5.8%), major bleeding (3.8% vs. 3.4%), and MACEs (6.8% vs. 9.4%) at 30 days. At 1 year, all-cause mortality was 4.7% in the thrombus-aspiration group and 7.6% in the conventional-PCI group ($P = .04$).

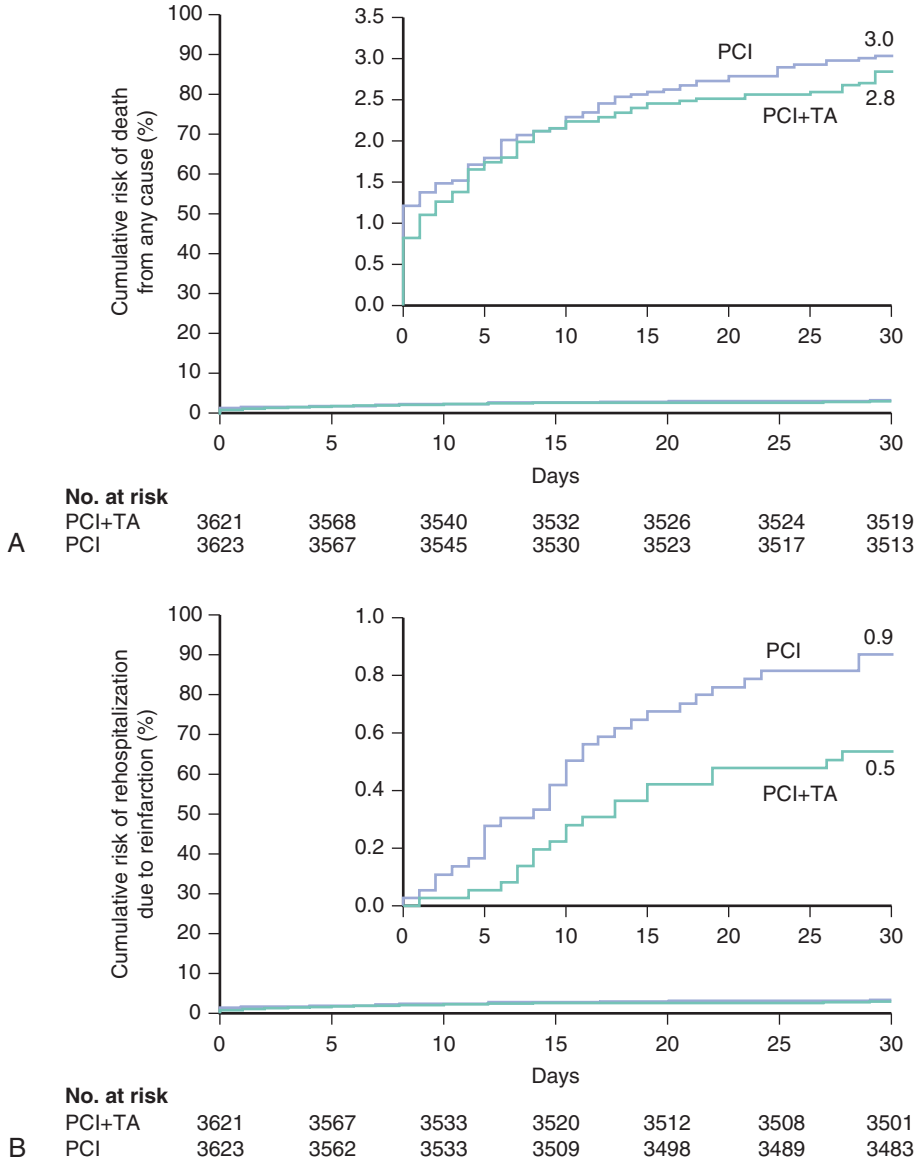


FIGURE 20-16 Kaplan-Meier curves are shown for the cumulative probability of death from any cause (**A**) and of hospitalization due to reinfarction (**B**) up to 30 days after percutaneous coronary intervention (PCI) only or after PCI with thrombus aspiration (PCI+TA). The insets show the same data on an enlarged Y axis. (From Fröbert O, Lagerqvist B, Olivecrona GK, et al: Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 369[17]:1587-1597, 2013.)

The 1-year combined incidence of death or nonfatal reinfarction was 5.6% in the thrombus-aspiration group and 9.9% in the conventional-PCI group ($P = .009$). The implication of the TAPAS data is that a strategy of systematic protection of microvascular function using aspiration thrombectomy, including use in patients without visible thrombus, may be clinically important; although benefits, and reductions in cardiac mortality in particular, must be interpreted with caution because the study was not powered for this end point. Concerns have also been raised related to the single-center nature of the trial and that the very short door-to-aspiration and DTB times (medians, 28 min and 26 min, respectively) may make the results difficult to generalize. Moreover, the fact that the aspiration-thrombectomy group received mostly direct stenting whereas the conventional-PCI group received mostly balloon dilation followed by stenting may have led to increased distal embolization in the conventional-PCI group. The Thrombectomy With Export Catheter in Infarct-Related Artery During Primary Percutaneous Coronary Intervention (EXPIRA) trial[124] used contrast-enhanced magnetic resonance imaging (MRI) to assess myocardial reperfusion in 175 patients with STEMI who were randomly assigned to standard PCI (87 patients) or manual thrombectomy plus PCI (88 patients). The primary end points were the occurrence of a myocardial blush grade of 2 or more and a rate of 90-minute ST-segment resolution greater than 70%. Myocardial blush grade of 2 or more and ST-segment resolution occurred more frequently in the manual thrombectomy–plus PCI group (88% vs. 60%, $P = .001$, and 64% vs. 39%, $P = .001$). In the acute phase, microvascular obstruction was significantly lower in the thrombectomy-PCI group, and at 3 months, the infarct size was significantly reduced only in the manual thrombectomy–plus PCI group. At 9 months, cardiac death occurred significantly less often in the manual thrombectomy–plus PCI group (0% vs. 4.6%, $P = .02$).

However, the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial[125] did not show a benefit of manual aspiration thrombectomy compared with PPCI alone in terms of reduction of 30-day all-cause mortality. The TASTE trial was a multicenter, prospective, randomized, controlled, open-label clinical study with enrollment of patients from the national comprehensive Swedish Coronary Angiography and Angioplasty Registry (SCAAR) with end points evaluated through national registries. The study randomly assigned 7244 patients with STEMI undergoing PCI to manual thrombus aspiration (TA) followed by PCI or to PCI only. The primary end point was all-cause mortality at 30 days. The 30-day mortality was 2.8% in the TA group and 3.0% in the PCI-only group (HR, 0.94; 95% CI, 0.72 to 1.22; $P = .63$; Fig. 20-16). Trends were noted toward lower

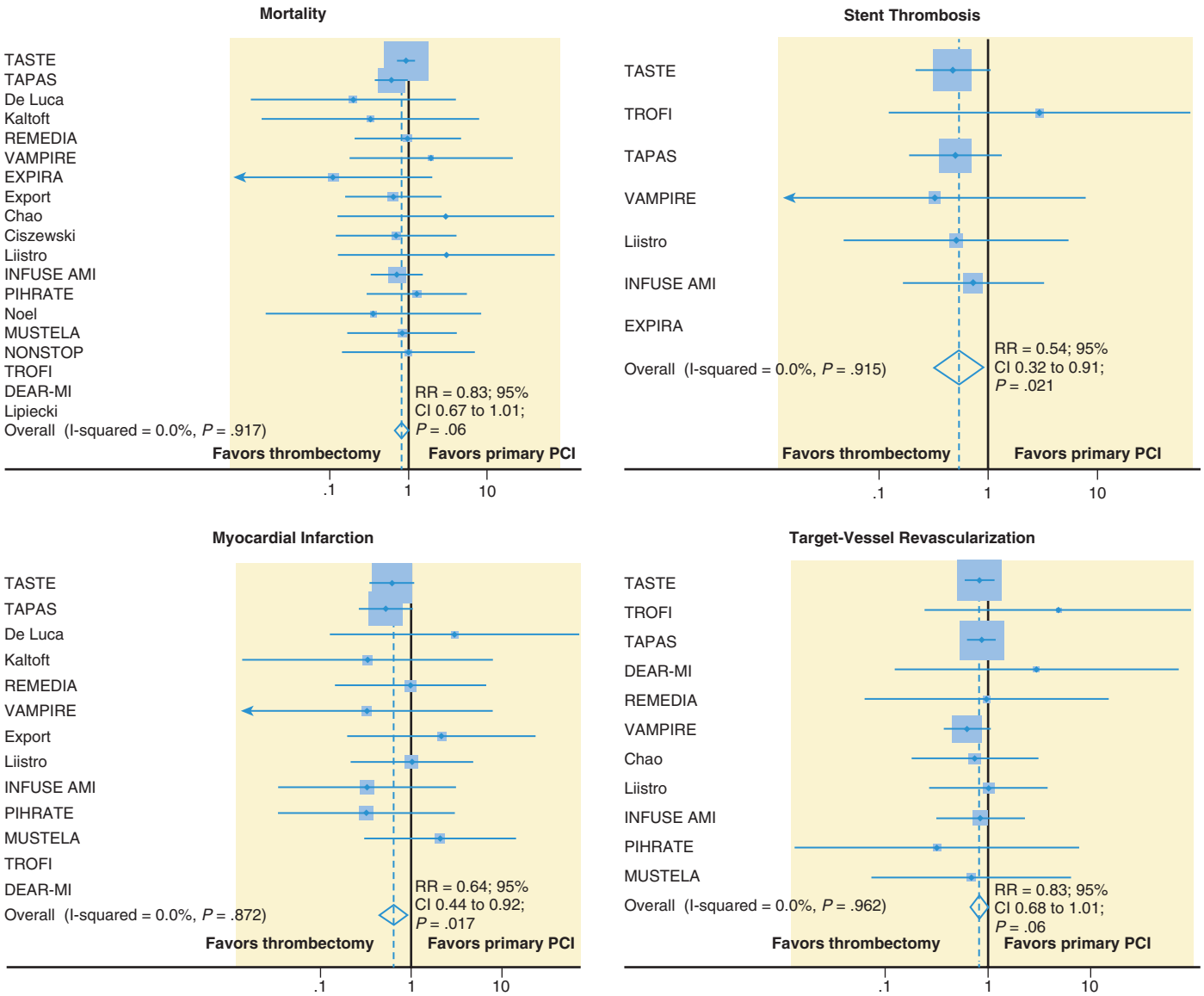


FIGURE 20-17 Summary plot for clinical outcomes for aspiration thrombectomy versus conventional primary percutaneous coronary intervention (PCI). *CI,* Confidence interval; *RR,* risk ratio. (From Kumbhani DJ, Bavry AA, Desai MY, et al: Aspiration thrombectomy in patients undergoing primary angioplasty: totality of data to 2013. *Catheter Cardiovasc Interv* 84[6]:973-977, 2014.)

rates of stent thrombosis (0.2% vs. 0.5%, $P = .06$) and hospitalization for recurrent MI at 30 days (0.5% vs. 0.9%, $P = .09$) in patients assigned to manual TA. The frequencies of stroke and neurologic complications were similar between the groups. The results were consistent across all major prespecified subgroups, including subgroups defined according to thrombus burden and coronary flow before PCI.[125] Although the results of the TASTE trial did not support mortality benefit at 30 days with manual aspiration, longer follow-up out to 1 year should be examined because potential late benefits may accrue.

The most recent evidence regarding the efficacy of manual aspiration thrombectomy comes from a meta-analysis that included 11,321 patients from 20 RCTs with the TASTE trial included. The composite end point of MACE was lower in the aspiration-thrombectomy arm compared with conventional PCI alone (5.6% vs. 6.9%; RR, 0.81; 95% CI, 0.70 to 0.94; $P = .006$). The 30-day mortality was similar between the two arms (2.5% vs. 2.9%; RR, 0.87; 95% CI, 0.69 to 1.09; $P = .22$). However, late mortality (6 to 12 months) was significantly reduced with aspiration thrombectomy (3.3% vs. 5.2%; RR, 0.64; 95% CI, 0.44 to 0.92; $P = .016$) compared with PCI alone. A trend was also seen toward fewer TVRs with aspiration thrombectomy (3.2% vs. 3.9%, RR, 0.83; 95% CI, 0.68 to 1.01; $P = .06$). Reinfarction (0.8% vs. 1.3%; RR, 0.64; 95% CI, 0.44 to 0.92; $P = .017$) and stent thrombosis (0.4% vs. 0.8%; RR, 0.54; 95% CI, 0.32 to 0.91; $P = .021$) were both significantly lower in patients undergoing adjunctive aspiration thrombectomy. Frequency of stroke was similar between the treatment arms.[126] In aggregate, this meta-analysis—which included all RCTs available—demonstrated a significant reduction in adverse clinical outcomes with manual aspiration thrombectomy (Fig. 20-17).

Although visible debris has been aspirated in a majority of patients with STEMI who have undergone PPCI, investigation of the efficacy of various distal protection devices on a randomized basis gave disappointing results. The Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD) trial randomized 501 patients with STEMI who presented within 6 hours of symptom onset for PPCI or rescue intervention after failed thrombolysis to receive either PCI with a balloon occlusion and a distal aspiration microcirculatory protection system or angioplasty without distal protection. Coprimary end points were ST-segment resolution measured

30 minutes after PCI and infarct size measured by technetium Tc99m sestamibi imaging between 5 to 14 days. Visible debris was retrieved from 73% of the patients, and no significant difference was found between the groups regarding complete ST-segment resolution (63.3% vs. 61.9%, $P = .78$) or infarct size (median, 12.0% vs. 9.5%, $P = .15$). The composite end point of MACE rates at 6 months was similar in the distal protection and control groups (10.0% vs. 11.0%, $P = .66$). The study concluded that although a distal balloon occlusion and aspiration system effectively retrieves embolic debris in most acute STEMI patients who undergo emergent PCI, distal embolic protection did not result in improved microvascular flow, greater reperfusion success, reduced infarct size, or enhanced event-free survival.[127] Two additional randomized trials that used a different distal protection device came to similar conclusions regarding the lack of efficacy of these devices in improving reperfusion indices or clinical outcomes when used as an adjunct to PPCI in patients with STEMI.[128,129] Although the exact reasons for the failure of distal protection devices to improve reperfusion in patients with STEMI remain obscure, the embolization caused by crossing the lesion with the device, impaired microcirculation by the device (nonembolic effects), dislodgement and embolization of vasoconstrictor material not halted by the device, and failure to protect downstream side branches have been proposed as putative mechanisms.

Based on the results of randomized trials and meta-analyses, the current guidelines restrict their endorsement of thrombus extraction to manual aspiration devices only and do not recommend the use of mechanical thrombectomy or distal protection devices in the setting of PPCI in patients with STEMI.

PERIPROCEDURAL ANTITHROMBOTIC/ ANTICOAGULANT THERAPY IN PATIENTS WITH STEMI UNDERGOING PRIMARY PERCUTANEOUS CORONARY INTERVENTION

Anticoagulant drug therapy is always used in patients with STEMI who undergo PPCI to prevent subsequent thrombotic vessel closure. Although UFH was and still is the most commonly used peri-PPCI anticoagulant, alternative drugs such as enoxaparin and bivalirudin seem to have a comparable efficacy in PPCI procedures.

In the open-label Acute Myocardial Infarction Treated With Primary Angioplasty and Intravenous Enoxaparin or Unfractionated Heparin to Lower Ischemic and Bleeding Events at Short- and Long-Term Follow-Up (ATOLL) trial, 910 patients with STEMI were randomized to receive enoxaparin (IV bolus of 0.5 mg/kg) or UFH (IV bolus of 70 to 100 U/kg of weight or 50 to 70 U/kg of weight with GP IIb/IIIa inhibitors) before PPCI.[130] Patients received aspirin (75 to 500 mg/day), clopidogrel (93%), and GP IIb/IIIa inhibitors (80%) according to local practice, and radial artery was used for vascular access in 67.4% of the patients. The primary end point was 30-day incidence of death, complication of MI, procedure failure, or major bleeding. The null hypothesis was not rejected, and the primary end point occurred in 28% of patients assigned to enoxaparin and in 34% of patients assigned to UFH (RR, 0.83; 95% CI, 0.68 to 1.01; $P = .06$). The incidence of death (4% vs. 6%), complication of MI (4% vs. 6%), procedure failure (26% vs. 28%), or major bleeding (5% vs. 5%) did not differ between the groups who received enoxaparin or UFH; however, the composite end point of death, recurrent ACS, or urgent revascularization was significantly reduced by enoxaparin (7% vs. 11%; RR, 0.59; 95% CI, 0.38 to 0.91; $P = .015$). A recent meta-analysis addressed the efficacy and safety of enoxaparin versus UFH during PCI procedures. Among 30,966 patients from 23 trials, 10,243 patients underwent PPCI for STEMI. In patients who underwent PPCI, enoxaparin compared with UFH reduced the rates of death (RR, 0.52; 95% CI, 0.42 to 0.64; $P < .001$), death or MI (RR, 0.56; 95% CI, 0.42 to 0.76; $P < .001$), and major bleeding (RR, 0.72; 95% CI, 0.56 to 0.93; $P = .01$).[131] Based on these results, enoxaparin seems to be a reasonable alternative to UFH for patients with STEMI undergoing PPCI via a radial approach. Although IV enoxaparin may be a reasonable alternative to UFH in patients with STEMI undergoing PPCI via a femoral approach, the optimal dosing of the drug remains uncertain.

Bivalirudin, a direct thrombin inhibitor, has been studied in several randomized trials of PPCI. In the HORIZONS-AMI trial,[132] 3602 patients with STEMI who presented within 12 hours after the onset of symptoms were randomized to PPCI with heparin plus a GP IIb/IIIa inhibitor or bivalirudin alone. Coprimary end points—major bleeding and net adverse clinical events (the combined end point of major bleeding, death, reinfarction, TVR, or stroke) at 30-days—were used to judge the efficacy of treatment. Anticoagulation with bivalirudin alone, as compared with heparin plus GP IIb/IIIa inhibitors, was associated with a reduced 30-day rate of net adverse clinical events (9.2% vs. 12.1%, $P = .005$) and a lower rate of major bleeding (4.9% vs. 8.3%, $P < .001$). Of importance was the finding that treatment with bivalirudin alone reduced the 30-day incidence of cardiac (1.8% vs. 2.9%, $P = .03$) and all-cause mortality (2.1% vs. 3.1%, $P = .047$). The rate of stent thrombosis within the first 24 hours was higher following treatment with bivalirudin (1.3% vs. 0.3%, $P < .001$), although this did not persist at 30 days. The advantages of bivalirudin were sustainable up to 3 years after PCI. Thus at 3 years after PCI, patients who had received bivalirudin had lower rates of all-cause mortality (5.9% vs. 7.7%), cardiac mortality (2.9% vs. 5.1%), reinfarction (6.2% vs. 8.2%), and non–CABG-related major bleeding (6.9% vs. 10.5%) with no significant differences in the rates of ischemia-driven TVR, stent thrombosis, or composite adverse events.[133] The HORIZONS-AMI trial demonstrated that reduction of bleeding by bivalirudin was associated with significant improvements in the clinical outcome, which included reductions in early and long-term mortality. A subsequent publication from the HORIZONS-AMI trial suggested that reduction of cardiac mortality by bivalirudin is only partly attributed to prevention of bleeding. An array of antiinflammatory, antiapoptotic, antiischemic mechanisms were listed—including protection from reperfusion injury and amelioration of microvascular obstruction—through which bivalirudin may facilitate myocardial salvage.[134] A subgroup analysis of the HORIZONS-AMI trial showed also that the benefits of bivalirudin in terms of reduction of bleeding rates persist in patients who switch from heparin (mostly used in the ED) to bivalirudin.[135] These results strongly support the use of bivalirudin as an anticoagulant/antithrombotic regimen in the setting of PPCI.

The recently published European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) trial[136] randomly assigned 2218 patients with STEMI who were being transported for PPCI to prehospital administration of either bivalirudin or a heparin, either UFH or LMWH, with optional GP IIb/IIIa inhibitors. The dose of bivalirudin was similar to that used in the HORIZONS-AMI trial, but the drug was continued for 4 hours after the procedure to reduce the risk of stent thrombosis observed in the HORIZONS-AMI trial. The primary outcome at 30 days was a composite of death or major bleeding not associated with CABG. Compared with heparin, bivalirudin reduced the risk of the primary outcome (5.1% vs. 8.5%; RR, 0.60; 95% CI, 0.43 to 0.82; $P = .001$; Fig. 20-18). Prehospital bivalirudin reduced the risk of major bleeding (2.6% vs. 6.0%), but it increased the risk of acute stent thrombosis (1.1% vs. 0.2%) and had no impact on 30-day mortality (2.9% vs. 3.1%) or reinfarction (1.7% vs. 0.9%) compared with heparin plus optional GP IIb/IIIa inhibitors. Although differences were noted between the trials in regard to the route used for vascular access (radial artery was used in 47% of the patients in the EUROMAX trial, and the newer antithrombotic drugs prasugrel or ticagrelor were used in more than half of the patients) and use of thrombectomy (32% in the EUROMAX trial), the results of the EUROMAX and HORIZONS-AMI trials are mostly consistent. Compared with heparin, bivalirudin decreased the risk of major bleeding, but it increased the risk of acute stent thrombosis.

Although acute stent thrombosis is a serious, albeit rare complication of PPCI, and some patients—such as those with prior stent thrombosis—may be more prone to develop this complication, currently no risk-validation schemes are available. Nevertheless, if the risk

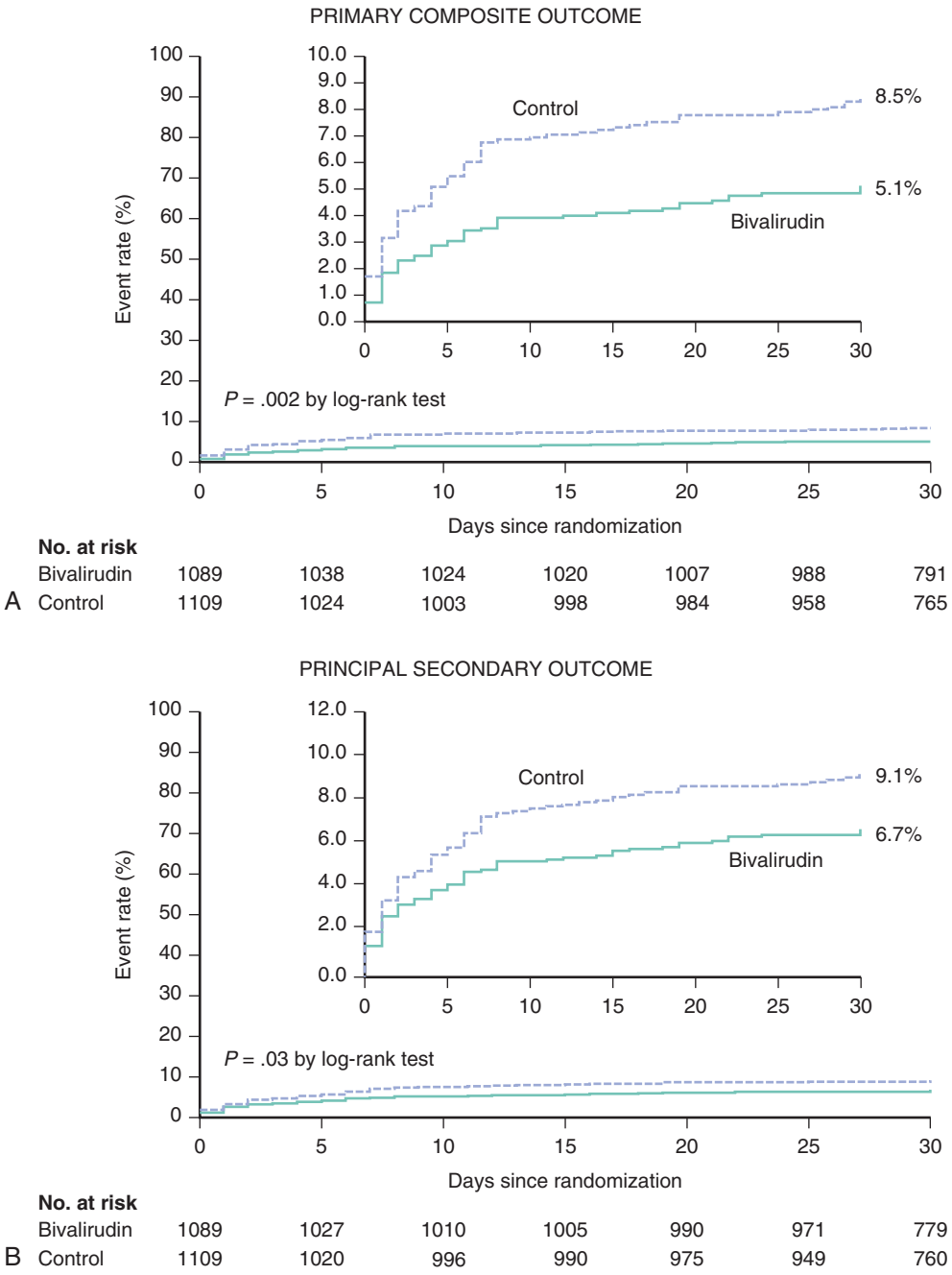


FIGURE 20-18 Kaplan-Meier curves of study outcomes. **A,** Rates of events for the primary composite outcome, death or major bleeding not associated with coronary artery bypass grafting (CABG), at 30 days. **B,** Rates of events for the principal secondary outcome—a composite of death, reinfarction, or non-CABG major bleeding—at 30 days. *Inset:* A more detailed version of the overall graph. (From Steg PG, van 't Hof A, Hamm CW, et al: Bivalirudin started during emergency transport for primary PCI. *N Engl J Med* 369[23]:2207-2217, 2013.)

for stent thrombosis is perceived as high, UFH plus GP IIb/IIIa inhibitors may be a reasonable alternative to bivalirudin.

The Bavarian Reperfusion Alternatives Evaluation (BRAVE-4) study[137] tested whether a PCI strategy based on prasugrel plus bivalirudin is superior to a strategy based on clopidogrel plus UFH in terms of net clinical outcomes. Owing to slow recruitment, the trial was stopped prematurely after enrollment of 548 of the 1240 planned patients. At 30 days, the primary composite end point of death, MI, unplanned revascularization of the infarct-related artery, stent thrombosis, stroke, or bleeding was observed in 15.6% of patients randomized to prasugrel plus bivalirudin and in 14.5% of the patients randomized to clopidogrel plus heparin (RR, 1.09; one-sided 97.5% CI, 0 to 1.79; $P = .68$). The composite ischemic end point of death, MI, unplanned revascularization of the infarct-related artery, stent thrombosis, or stroke occurred in 4.8% of the patients in the prasugrel-plus-bivalirudin group and in 5.5% of the patients in the clopidogrel-plus-heparin group ($P = .89$). Bleeding defined according to the HORIZONS-AMI criteria occurred in 14.1% of the patients in the prasugrel-plus-bivalirudin group and in 12.0% of the patients in the clopidogrel-plus-heparin group ($P = .54$). Results were consistent across various subgroups of patients. The study did not evidence any advantages with a strategy of combining the bivalirudin with prasugrel

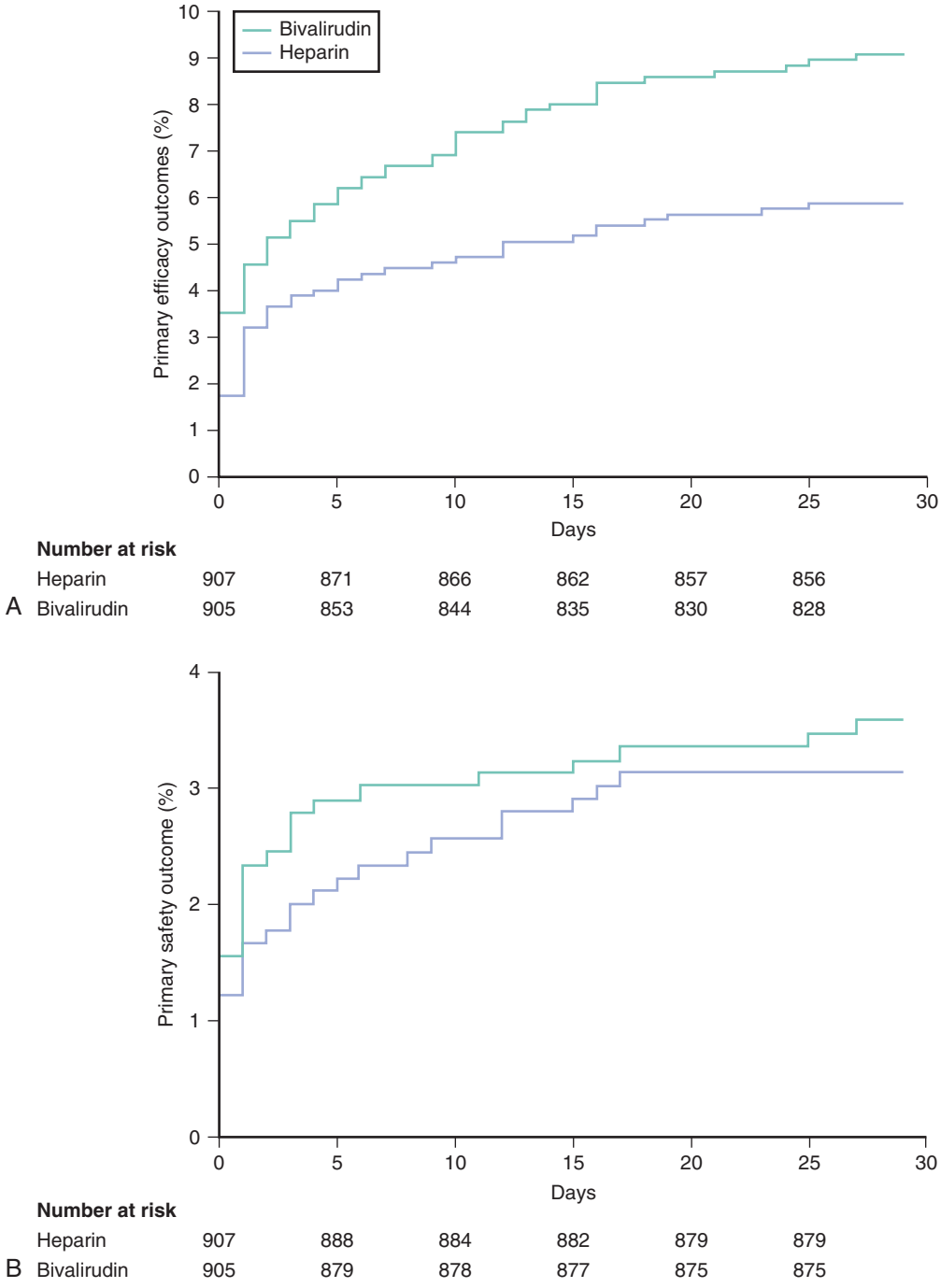


FIGURE 20-19 Event curves for the primary outcomes. **A,** Primary efficacy outcome (combination of death, cerebrovascular accident, reinfarction, and unplanned target-lesion revascularization) censored for the first event. **B,** Primary safety outcome (major bleeding) censored for the first event. (From Shahzad A, Kemp I, Mars C, et al: Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet* 384[9957]:1849-1858, 2014.)

compared with a strategy of using UFH plus clopidogrel in regard to the ischemic or bleeding complications. However, these data should be interpreted with caution because of premature termination of the trial, which markedly reduced the power of the study.

The recently published How Effective Are Antithrombotic Therapies in PPCI (HEAT-PPCI) trial recruited 1829 patients who received PPCI at a single United Kingdom hospital who were assigned to receive heparin (a preprocedural bolus dose of 70 U/kg of weight) or bivalirudin (a bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/hour for the duration of the procedure). At 4 weeks, the primary efficacy end point—MACE, defined as all-cause mortality, cerebrovascular accident, reinfarction, or unplanned TLR—occurred in 8.7% of bivalirudin-treated patients and in 5.7% of heparin-treated patients (RR, 1.52; 95% CI, 1.09 to 2.13; $P = .01$; Fig. 20-19). Definite or probable stent thrombosis occurred in 3.4% of bivalirudin-treated patients and in 0.9% of heparin-treated patients (RR, 3.91; 95% CI, 1.61 to 9.52; $P = .001$); major bleeding occurred in 3.5% of bivalirudin-treated patients and in 3.1% of heparin-treated patients (RR, 1.15; 95% CI, 0.70

to 1.89; $P = .59$). The study concluded that the use of heparin, rather than bivalirudin, was associated with reduced MACEs, fewer stent thromboses and reinfarctions, no difference in bleeding complications, and the potential for substantial savings in drug costs.[138] It remains to be seen whether the results of this trial will have an impact on the current class I recommendation for the use of bivalirudin in patients with STEMI.[9,10]

Platelet inhibition by various antithrombotic agents used before, during, and after the PCI procedure is an integral part of PCI in patients with STEMI. Antithrombotic therapy that mostly consists of $P2Y_{12}$ receptor blockers is an integral part of PPCI procedures. In the current practice of PPCI, clopidogrel, prasugrel, and ticagrelor are mostly used, and current guidelines give all of them a class I recommendation for use during PPCI. Although the efficacy or safety of clopidogrel in addition to aspirin versus aspirin only in patients with STEMI undergoing PPCI was never investigated, the drug is commonly used during PPCI, and current guidelines give aspirin a class I recommendation for use during PPCI.[9,10]

The efficacy and safety of clopidogrel was investigated in the PCI-Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) study, which consisted of a prospectively planned analysis of the 1863 patients who underwent PCI after mandated angiography in the CLARITY–TIMI 28 trial.[139] Patients received aspirin and were randomized to receive either clopidogrel (300-mg loading dose, then 75 mg/day) or placebo initiated with thrombolysis; both were given until coronary angiography, which was performed 2 to 8 days after initiation of the study drug. The primary outcome was a composite of cardiovascular death, recurrent MI, or stroke from PCI to 30 days after randomization. Pretreatment with clopidogrel significantly reduced the incidence of the primary end point (3.6% vs. 6.2%, adjusted OR, 0.54; 95% CI, 0.35 to 0.85; $P = .008$), and no significant excess was observed in the rates of TIMI major or minor bleeding (2.0% vs. 1.9%, $P > .99$). Based on the results of experimental and randomized trials, a 600-mg loading dose of clopidogrel is preferred to a 300-mg loading dose because of the more rapid and extensive platelet inhibition and better clinical outcome with the 600-mg loading dose.[140]

The impact of the timing of clopidogrel relative to PCI was investigated in several observational and randomized studies. A recent meta-analysis estimated the impact of clopidogrel timing on outcome in 37,814 patients recruited in randomized studies (8608 patients, 25% with STEMI) or observational analyses or studies. The analysis based on the randomized studies showed that clopidogrel pretreatment, compared with treatment after catheterization, was not associated with a reduction of death (absolute risk, 1.54% vs. 1.97%; OR, 0.80; 95% CI, 0.57 to 1.11; $P = .17$) but was associated with a lower risk of the secondary composite end point of MI, stroke, or urgent revascularization (9.83% vs. 12.35%, OR, 0.77; 95% CI, 0.66 to 0.89; $P < .001$). No significant association was found between pretreatment and major bleeding overall (3.57% vs. 3.08%, $P = .18$).[141]

Prasugrel (60-mg loading dose) was compared with clopidogrel (300-mg loading dose) in the Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI 38) trial.[142] Overall, the study found that in patients with ACSs who were scheduled for PCI, prasugrel therapy was associated with significantly reduced rates of ischemic events, including stent thrombosis, but with an increased risk of major bleeding that included fatal bleeding. A total of 3534 patients with STEMI (26%) were enrolled. Of these, 1769 patients received prasugrel and 1765 received clopidogrel. The primary end point of cardiovascular death, nonfatal MI, or nonfatal stroke at 30 days was 6.5% in patients assigned to prasugrel and 9.5% in patients assigned to clopidogrel (HR, 0.68; 95% CI, 0.54 to 0.87; $P = .0017$). This effect was maintained at 15 months of follow-up (10.0% vs. 12.4%; HR, 0.79; 95% CI, 0.65 to 0.97; $P = .0221$). The secondary end point of cardiovascular death, MI, or urgent TVR was reduced by prasugrel both at 30 days (6.7% vs. 8.8%; HR, 0.75; 95% CI, 0.59 to 0.96; $P = .0205$) and 15 months (9.6% vs. 12.0%; HR, 0.79; 95% CI, 0.65 to 0.97; $P = .025$). Stent thrombosis was reduced by prasugrel, both at 30 days (1.2% vs. 2.4%, $P = .0084$) and at 15 months (1.6% vs. 2.8%, $P = .0232$). TIMI major bleeding unrelated to CABG surgery did not differ between the study drugs at 30 days ($P = .3359$) or 15 months ($P = .6451$). TIMI major bleeding after CABG surgery was significantly increased with prasugrel ($P = .0033$).[143] This analysis provided strong support for the use of prasugrel over clopidogrel in patients undergoing PPCI procedures.

Ticagrelor differs from clopidogrel or prasugrel in that it reversibly binds to the platelet $P2Y_{12}$ receptor. As with prasugrel, ticagrelor has a more rapid onset of action and is associated with a more potent inhibition of platelets compared with clopidogrel. In the subset of 7544 patients with STEMI from the Platelet Inhibition and Patient Outcomes (PLATO) trial treated with PCI, ticagrelor (initial 180 mg loading followed by 90 mg twice daily) was compared with clopidogrel (300 to 600 mg loading followed by 75 mg/day). The primary end point of death from vascular causes, MI, or stroke occurred in 9.4% of the ticagrelor group and in 10.8% of the clopidogrel group ($P = .07$). The differences between ticagrelor and clopidogrel were significant in all-cause mortality (5.0% vs. 6.1%, $P = .05$) with a trend for reduction in cardiovascular mortality (4.5% vs. 5.5%, $P = .07$), definite stent thrombosis (1.6% vs. 2.4%, $P = .03$), and MI (4.7% vs. 5.8%, $P = .03$) without a detectable difference in major bleeding (9.0% vs. 9.2%, $P = .76$).[144]

Cangrelor has been investigated in randomized trials that included mixed groups of patients either against placebo or against clopidogrel. The evidence for the use of cangrelor during PPCI procedures is limited.

In aggregate, these studies showed that newer $P2Y_{12}$ receptor inhibitors, such as prasugrel and ticagrelor, lead to extensive and rapid platelet inhibition and are superior to clopidogrel in terms of reduction of ischemic adverse events and potentially mortality in patients with ACS in general but also in subgroups who present with STEMI.

Studies that have investigated the efficacy and safety of GP IIb/IIIa receptor inhibitors have been performed mostly in the era prior to modern, potent oral $P2Y_{12}$ inhibitors, therefore their relevance for current-day practice of PPCI is limited. A meta-analysis of abciximab use in primary stenting, including high-risk patients with STEMI, showed a significant reduction in the composite end point of death or reinfarction with abciximab out to 3 years of follow-up (12.9% vs. 19.0%, $P = .008$); mortality alone was also reduced (10.9% vs. 14.3%, $P = .052$).[145] Another recent meta-analysis that included 16 trials with 10,085 patients showed that GP IIb/IIIa inhibitors, mostly abciximab, did not reduce 30-day mortality (2.8% vs. 2.9%, $P = .75$) or reinfarction (1.5% vs. 1.9%, $P = .22$) but were associated with a higher risk of major bleeding (4.1% vs. 2.7%, $P < .001$).[146] An interaction between the patient's risk and the benefits from GP IIb/IIIa inhibitors in terms of mortality was observed ($P = .008$).[146]

Abciximab is the most extensively investigated GP IIb/IIIa inhibitor in the setting of PPCI. A series of studies have also shown that abciximab, tirofiban, and eptifibatide seem to have an equivalent efficacy. The Bavarian Reperfusion Alternatives Evaluation (BRAVE-3) trial included 800 patients, all pretreated with a 600-mg loading dose of clopidogrel, who were randomized to abciximab or placebo. Infarct size measured with sestamibi SPECT imaging at discharge (15.7% vs. 16.6%, $P = .47$) or 30-day incidence of death, reinfarction, stroke, or urgent revascularization (5% vs. 3.8%, $P = .40$) did not differ significantly among patients assigned to abciximab or placebo (Fig. 20-20).[147] The trial raised doubt concerning the routine use of abciximab in the setting of PPCI after pretreatment with $P2Y_{12}$ inhibitors. The Ongoing Tirofiban in Myocardial Infarction Evaluation (On-TIME 2) trial came to different conclusions; in this trial, a high bolus dose of tirofiban was administered in the ambulance on top of UFH (5000 U bolus), aspirin (500 mg), and clopidogrel (600-mg loading dose). MACEs—a composite of death, recurrent MI, or urgent TVR at 30 days—were significantly reduced (5.8% vs. 8.6%, $P = .043$) with a strong trend toward a decrease in mortality (2.2% vs. 4.1%, $P = .051$) with tirofiban.[148]

Based on studies that show a beneficial effect of abciximab on the microcirculation, the efficacy of direct intracoronary (IC) GP IIb/IIIa

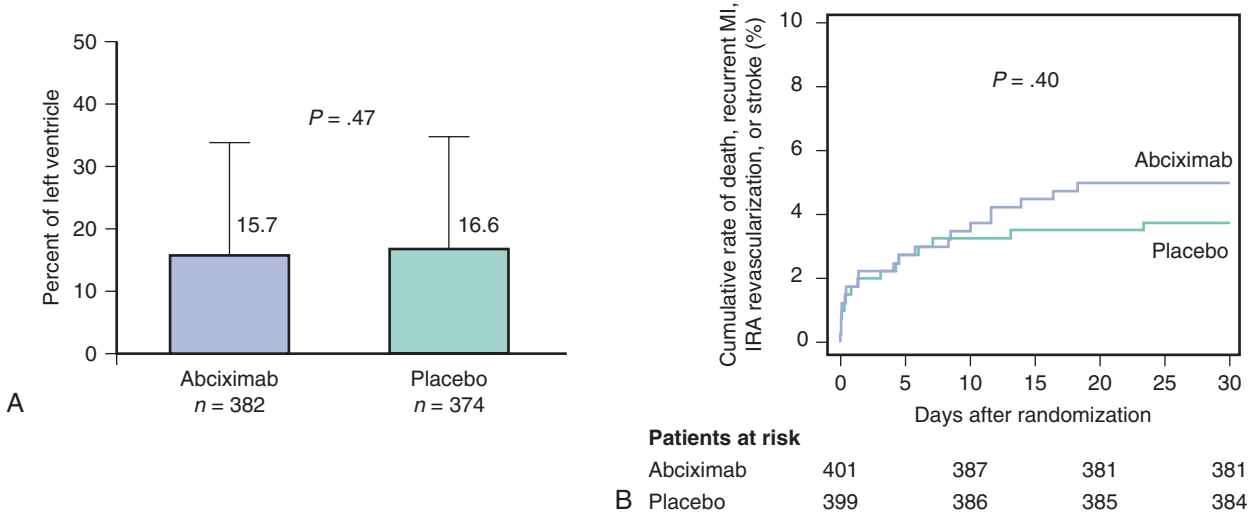


FIGURE 20-20 Results of the BRAVE-3 trial. **A,** Scintigraphic infarct size (primary end point) in patients randomized to abciximab or placebo. **B,** The 30-day cumulative rate of death, recurrent myocardial infarction, infarct-related artery (IRA) revascularization, or stroke in patients randomized to abciximab or placebo. (From Mehilli J, Kastrati A, Schulz S, et al: Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. *Circulation* 119[14]: 1933-1940, 2009.)

receptor inhibitors was also tested. The Comparison of Intracoronary Versus Intravenous Abciximab Administration During Emergency Reperfusion of ST-Segment Elevation Myocardial Infarction (CICERO) study[149] randomized 534 patients with STEMI to IV or IC abciximab infusion. In this trial, IC administration of abciximab did not improve myocardial reperfusion as assessed by ST-segment resolution, the primary end point; however, it improved myocardial reperfusion as assessed by myocardial blush and reduced the enzymatic infarct size compared with IV administration. The Abciximab Intracoronary Versus Intravenous Drug Application in ST-Elevation Myocardial Infarction (AIDA STEMI) trial[150] randomized 2065 patients to IC abciximab ($n = 1032$) or IV abciximab ($n = 1033$). The primary end point was a composite of all-cause mortality, recurrent infarction, or new CHF within 90 days of randomization. Compared with IV administration, IC abciximab resulted in a similar rate of the primary end point (7.0% vs. 7.6%; OR, 0.91; 95% CI, 0.64 to 1.28; $P = .58$.). The incidence of death (4.5% vs. 3.6%, $P = .36$) and reinfarction (1.8% vs. 1.8%, $P = .99$) did not differ significantly among patients in both treatment groups. However, fewer patients in the IC abciximab group had new CHF (2.4% vs. 4.1%, $P = .04$). The study concluded that in patients with STEMI undergoing PPCI, compared with IV abciximab, IC abciximab did not result in a difference in the combined end point of death, reinfarction, or CHF. The recently published MRI substudy of the AIDA STEMI trial did not show a benefit of IC abciximab compared with IV abciximab on myocardial damage and/or reperfusion injury.[151]

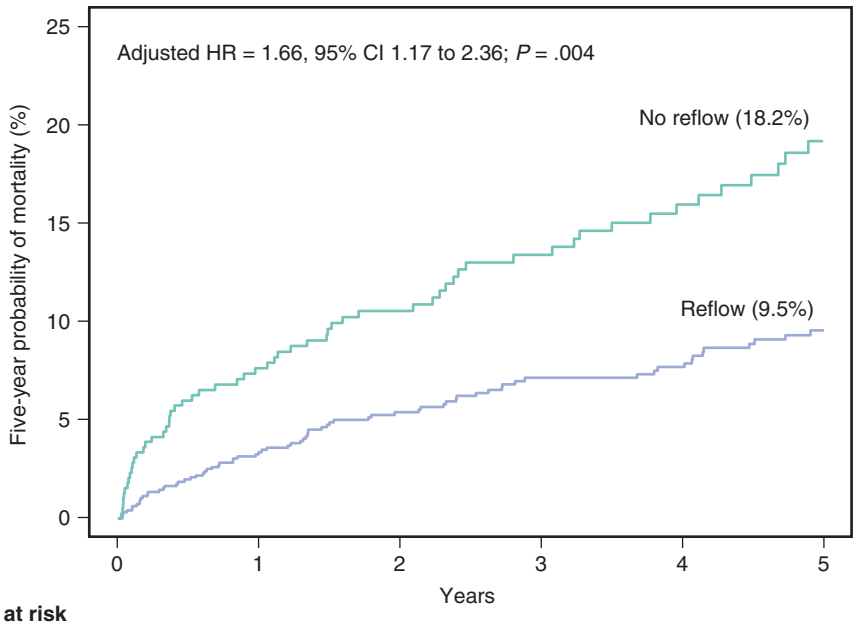
In aggregate, these studies showed that the role of GP IIb/IIIa inhibitors in the current practice of PPCI is markedly reduced because of the availability of potent antiplatelet inhibitors. Current guidelines give a class IIa recommendation (level of evidence A) for abciximab and a class IIa recommendation (level of evidence B) for the use of tirofiban and eptifibatide as antithrombotic therapy during PPCI procedures.[10]

No properly designed studies have been undertaken to discern the value of activated factor X (FXa) inhibitors in patients with STEMI treated with PCI. A PCI subset analysis from the Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS-6) trial could not show any benefit with the use of fondaparinux.[152]

ADJUNCT PHARMACOLOGIC THERAPIES TO IMPROVE MYOCARDIAL TISSUE REPERFUSION IN PATIENTS WITH STEMI UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

No-reflow phenomenon and microvascular obstruction are frequent in patients with STEMI treated with PPCI, and their presence is associated with reduced myocardial salvage, increased infarct size, impaired LV function, and increased risk of short- and long-term mortality (Fig. 20-21).[153] In recent years, various pharmacologic and nonpharmacologic approaches have been used as adjunct therapy to PCI to enhance myocardial reperfusion and salvage and to improve outcome in patients with STEMI. Among the nonpharmacologic approaches, thrombectomy (discussed above), post conditioning, and intraaortic balloon counterpulsation are used with the intention to improve myocardial reperfusion after PPCI and to reduce infract size.

Ischemic post conditioning refers to transient episodes of deliberate ischemia/reperfusion caused by repetitive inflation/deflation of an occluding balloon in the infarct-related artery, and it has been demonstrated to reduce infarct size in experimental studies. In small, randomized human studies, the impact of ischemic post conditioning on infarct size has been controversial. A small randomized study of 50 patients with STEMI showed that post conditioning reduced infarct size and myocardial edema estimated with MRI.[154] Conversely, another recent study that randomized 76 STEMI patients to standard PCI or post conditioning did not show a reduction in the infarct size estimated with delayed-enhancement MRI. However, infarct size was significantly reduced by post conditioning in patients with large initial areas at risk ($P < .001$).[155] It must be mentioned, however, that many additional studies that have used biochemical markers of necrosis have shown a reduction of infarct size by post conditioning. *Remote ischemic conditioning,* or repetitive cycles of ischemia in a tissue remote from the heart, has also been shown to significantly increase myocardial salvage when performed in patients with STEMI in the ambulance en route to a PPCI center.[156] Despite these results, the clinical benefit of post conditioning remains largely unexplored. A recent randomized trial did not show an impact of ischemic post conditioning on infarct



Patients at risk						
Reflow	996	890	742	591	485	374
No reflow	410	355	291	234	191	139

FIGURE 20-21 Kaplan-Meier curves of 5-year mortality in patients with reflow and no reflow after primary percutaneous coronary intervention for ST-elevation myocardial infarction. *CI,* Confidence interval; *HR,* hazard ratio. (From Ndrepepa G, Tiroch K, Fusaro M, et al: 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. *J Am Coll Cardiol* 55[21]: 2383-2389, 2010.)

size or secondary study outcomes, which included markers of necrosis, myocardial salvage, ejection fraction, and adverse cardiac events[157]; in addition, a meta-analysis of 15 trials showed no improvement in surrogate or clinical outcomes with ischemic post conditioning at 5 months following PPCI.[158] Another meta-analysis of 19 trials showed that ischemic post conditioning during PPCI in patients with STEMI appears to reduce myocardial injury and damage (reduced infarct size by cardiac enzymes or imaging), and it also was found to improve global and regional LV function.[159]

The impact of intraaortic balloon counterpulsation on infarct size was investigated in the Counterpulsation to Reduce Infarct Size Pre-PCI for Acute Myocardial Infarction (CRISP-AMI) trial.[160] The trial included 337 patients with anterior wall STEMI who were randomized to receive intraaortic balloon pumping (IABP, initiated before PCI and continued for at least 12 hours) plus PCI or PCI alone. The primary outcome was infarct size (expressed as a percentage of the LV) measured by CMRI performed 3 to 5 days after PCI. The mean infarct size was not significantly different between the patients in the IABP–plus PCI group versus the PCI-alone group (42.1% vs. 37.5%, $P = .06$). At 30 days, no significant difference was evident with regard to major vascular complications ($P = .09$) or major bleeding or transfusions ($P = .49$). At 6 months, all-cause mortality was 1.9% ($n = 3$) among patients assigned to IABP, and it was 5.2% ($n = 9$) among patients assigned to PCI alone ($P = .12$).

Pharmacologic interventions to reduce myocardial injury during PPCI include a wide range of agents used to target a multitude of components involved in the genesis of reperfusion injury in patients with STEMI undergoing PPCI. Encouraged by beneficial effects of bivalirudin on clinical outcome, the impact of the drug on infarct size compared with UFH plus abciximab was investigated in a CMRI substudy of the HORIZONS-AMI trial. Infarct size was not significantly different after treatment with bivalirudin, compared with heparin plus abciximab, either within 7 days (median, 9.3% vs. 20.0%, $P = .28$) or at 6 months (median, 6.7% vs. 8.2%, $P = .73$).[161] In the Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction (INFUSE-AMI) trial,[161a] patients randomized to IC abciximab compared with no abciximab (aspiration thrombectomy was used in both arms) had a significant reduction in 30-day infarct size (median, 15.1% vs.17.9%, $P = .03$). It has been demonstrated that aspirin,[162] clopidogrel,[163] and prasugrel[164] reduce infarct size. These drugs are most commonly used during PPCI. Evidence on the impact of statin loading before PPCI on infarct size remains inconclusive.

IC and IV adenosine, a potent vasodilator of arterioles, has been tested as adjunctive therapy to PPCI in patients with STEMI. In experimental studies, adenosine reduces ischemia-reperfusion injury, limits infarct size, and improves LV function. However, most of the recent research on the use of adenosine as an adjunct to PPCI has been disappointing. A recent randomized study of IC adenosine found no evidence that selective, high-dose IC administration of adenosine distal to the occlusion site of the culprit lesion in STEMI patients results in incremental myocardial salvage or a decrease in microvascular obstruction.[165] A recent meta-analysis of RCTs showed no reduction in the infarct size with IC adenosine.[166] Based on these results, no clear benefit has been proven with the use of adenosine as an adjunct to PPCI.

Sodium nitrite, a selective nitric oxide donor, has multiple vascular functions that include arteriolar vasodilation, platelet inhibition, and antiinflammatory actions. Sodium nitrite was shown to markedly reduce infarct size in experimental settings, and the agent is under investigation as a protective agent against reperfusion injury in the clinical setting. The recently published Nitrites in Acute Myocardial Infarction (NIAMI) trial,[167] a randomized placebo-controlled study, did not demonstrate a reduction in infarct size (measured with CMRI at 6 to 8 days and at 6 months) by sodium nitrite administered intravenously immediately prior to reperfusion in patients with acute STEMI.

Nicorandil, a combined nitrate and K^+ATP channel agonist, has proven beneficial in reducing infarct size in animal models, but this

effect was not confirmed in randomized studies. A randomized placebo-controlled trial of patients with acute MI undergoing mechanical reperfusion showed that IV nicorandil did not reduce infarct size (assessed with total creatine kinase [CK] activity), nor did it improve the LVEF.[168] In the same study, IV atrial natriuretic peptides modestly reduced infarct size compared with placebo.[168] A 2009 meta-analysis showed that nicorandil treatment reduced the incidence of TIMI flow grades of 2 or less, had no effect on peak CK value, and improved LVEF.[169] However, the studies included are small, and data are still not sufficient to allow a firm recommendation on the use of ATP-sensitive potassium channel openers in PPCI.

The impact of peri-PPCI beta-blockade on infarct size was investigated on a randomized basis in the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial.[170] The trial investigated whether early, prereperfusion IV beta-blocker therapy (up to three 5-mg IV boluses of metoprolol tartrate 2 minutes apart) would reduce infarct size in 270 patients with STEMI of the anterior wall presenting within 6 hours from symptom onset. The primary end point was infarct size estimated by CMRI. Infarct size calculated either in grams of infarcted tissue (25.6 ± 15.3 g vs. 32.0 ± 22.2 g; $P = .013$) or as a percentage of the left ventricle (21.2% ± 11.5% vs. 25.1% ± 13.9% of the left ventricle; $P = .029$) was significantly reduced by metoprolol. Of note, 34.9% of the initial myocardial area at risk was salvaged in the metoprolol group compared with 27.7% in the control group ($P = .028$). The LVEF was slightly but significantly higher in the metoprolol group. Thus, although important and encouraging, the results of the METOCARD-CNIC trial are probably not strong enough to warrant a change in the clinical practice of the use of beta-blockade in patients with STEMI.

In the Caldaret in Patients Undergoing Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction (CASTEMI) trial,[171] 387 patients with STEMI within the previous 6 hours were randomized to caldaret (an agent purported to reduce intracellular calcium by inhibiting Na/Ca exchanger and enhancing calcium reuptake by the sarcoplasmic reticulum) or placebo. Caldaret was not associated with reduction in infarct size or improvement in LV function as assessed by gated SPECT imaging. A subsequent publication from the same trial reported that 1 month after infarction, a significant decrease was observed in the incidence of LV dysfunction in patients receiving low and high doses of caldaret versus those receiving placebo (8.0% and 6.9%, respectively, vs. 17.5%; $P < .05$ for both comparisons).[172]

Cyclosporin A, an inhibitor of mitochondrial permeability transition pore opening, was tested in a small, randomized, placebo-controlled trial. The trial randomized 58 patients with STEMI to receive an IV bolus of 2.5 mg/kg of weight or normal saline. The release of CK was significantly reduced in the cyclosporin group compared with the control group ($P = .04$). On day 5, the absolute mass of the area of hyperenhancement (i.e., infarcted tissue) on CMRI was significantly reduced in the cyclosporin group compared with the placebo group (median, 37 vs. 46 g; $P = .04$).[173] The protective action of cyclosporin is hypothesized to involve reduced oxidative stress and calcium overload by inhibition of mitochondrial permeability transition pore opening. Nevertheless, the study was small, and differences were of borderline statistical significance. A meta-analysis of 20 experimental studies showed that cyclosporin A reduced infarct size, but considerable heterogeneity of effect was apparent across the studies. The lack of effect in porcine hearts raised concerns about the cardioprotective effects of cyclosporin A in humans.[174]

Based on the experimental evidence that complement system activation may be involved in reperfusion-associated ischemic injury, the effect of pexelizumab—a humanized monoclonal antibody that binds the C5 component of complement—on clinical outcome in patients with STEMI undergoing PPCI has been evaluated in the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial.[175] The trial randomized 5745 patients with STEMI (within 6 hours from symptom onset) to receive pexelizumab (2 mg/kg IV bolus prior to PCI followed by 0.05 mg/kg/hr infusion over the subsequent 24 hours) or placebo. No difference was observed in 30-day rate of all-cause mortality (4.06% vs. 3.92%, $P = .78$) or in the composite end point of death, cardiogenic shock, or CHF at 30 days (8.99% vs. 9.19%, $P = .81$) or at 90 days (10.24% vs. 10.16%, $P = .91$) between the pexelizumab and the placebo groups.[175] This trial showed that mortality was not affected by pexelizumab. Overall, no available evidence supports the use of complement system inhibitors in patients with STEMI undergoing PPCI.

Based on the antiinflammatory, antihypoxic, and antiapoptotic properties of erythropoietin, this agent also was used in clinical trials of patients with STEMI. Recent randomized studies[176-178] and a meta-analysis[179] did not demonstrate a reduction in infarct size by creatine kinase myocardial band (CK-MB) or CMRI. One study even suggested that the use of erythropoietin may lead to higher rates of adverse cardiovascular events or increased infarct size in older patients.[176] Although the investigation of erythropoietin impact on infarct size is ongoing, based on the available results to date, this agent has no clear role as a protective agent during PPCI.

Delcasertib, a selective inhibitor of delta-protein kinase C, was shown to reduce infarct size during ischemia/reperfusion in animal models. The Inhibition of Delta-Protein Kinase C for the Reduction of Infarct Size in Acute Myocardial Infarction (PROTECTION-AMI) trial[180] was a multicenter, double-blind randomized trial to investigate whether delta-protein kinase C reduces infarct size in patients with anterior wall STEMI undergoing PPCI. Patients with anterior STEMI were randomized to placebo or to one of three doses of delcasertib (50, 150, or 450 mg/h). No differences were found between the treatment groups in the infarct size measured by CK-MB area under the curve (AUC; the primary end point). Delcasertib also did not affect the rates of adjudicated clinical end points (death, heart failure, or serious ventricular arrhythmias).

Based on the hypothesis that hyperoxemia reduces the formation of lipid peroxide radicals, thereby altering nitric oxide synthase expression and inhibition of leukocyte adherence and plugging in the microcirculation,[181] this has been tested to reduce infarct size during PPCI procedures. However, the evidence is limited, and the data are inconsistent. The Acute Myocardial Infarction With Hyperoxemic Therapy (AMIHOT) trial[182] randomized patients with acute MI within 24 hours after primary stenting to intracoronary hyperoxemic reperfusion with aqueous oxygen or control. Although the hyperoxemic reperfusion was safe and well tolerated, it did not impart improvement in ST-segment resolution or regional wall motion by serial ECG, nor did it result in any reduction in SPECT infarct size. In post-hoc analysis, however, patients with anterior MI reperfused within 6 hours showed a greater improvement in regional wall motion and a smaller infarct size (9.0% vs. 23% of the left ventricle; $P = .03$) with hyperoxemic reperfusion. At 30 days, the incidence of MACEs was similar between the control and aqueous oxygen groups (5.2% vs. 6.7%, $P = .62$). The AMIHOT-II trial[183] included 301 patients with STEMI of the anterior wall and showed that IC delivery of supersaturated oxygen reduced scintigraphic infarct size (20% vs. 26.5%; adjusted $P = .03$) with noninferior MACE rates at 30 days compared with placebo.

Hypothermia during ischemia may reduce metabolic demand and inflammatory response.[181] A reduction in infarct size by therapeutic hypothermia has been reported if applied at the beginning or during ischemia but not during or after the reperfusion.[184,185] A pooled analysis of two small randomized trials has shown that hypothermia was associated with a 24% relative reduction (mean ± SEM, 10.7% ± 1.3% vs. 14.1% ± 1.6%, $P = .049$) in the infarct size estimated by SPECT or CMRI.[186] However, the Rapid Endovascular Catheter Core Cooling Combined With Cold Saline as an Adjunct to Percutaneous Coronary Intervention for the Treatment of Acute Myocardial Infarction (CHILL-MI) trial[187] did not show a significant reduction in the infarct size (as a percent of myocardium at risk) assessed by CMRI at 4 (± 2) days. The trial randomized 120 patients with STEMI (<6 hr) scheduled to undergo PPCI to hypothermia induced by the rapid infusion of 600 to 2000 mL cold saline and endovascular cooling or standard of care. Hypothermia was initiated before PCI and was continued for 1 hour after reperfusion. Median infarct size/myocardium at risk was 40.5%

in patients assigned to hypothermia versus 46.6% in the control group ($P = .15$). The incidence of heart failure was lower with hypothermia at 45 (± 15) days (3% vs. 14%, $P < .05$). Exploratory analysis of early anterior infarctions (0 to 4 hr) found a reduction in the infarct size/myocardium at risk end point of 33% ($P < .05$).

In summary, although there is still interest in a variety of adjunctive mechanical and/or pharmacologic interventions directed at enhancing myocardial reperfusion and reducing infarct size by limiting no-reflow phenomenon, microvascular obstruction, and reperfusion injury, available evidence is not strong enough to recommend any of these interventions for routine use as an adjunct to PPCI in patients with STEMI.

CELL-BASED THERAPY AND REGENERATIVE AGENTS AFTER STEMI

Reperfusion therapy has proven to be lifesaving in patients with STEMI; however, progression of the disease toward chronic myocardial dysfunction still remains a real challenge. Because of insufficient regeneration of lost myocardial cells, patients with STEMI may be intuitively considered prime candidates for application of cell-based cardiac repair techniques to enhance myocardial recovery after MI by replacing lost myocytes. Animal studies of MI have reported that stem cell and progenitor cell transplantation has resulted in neoangiogenesis and myogenesis and improved contractile function. Although the exact mechanisms of the beneficial effect from stem cells remain unclear, a series of putative mechanisms have been proposed (Fig. 20-22).[188]

A number of recent meta-analyses have summarized the results of these trials. One meta-analysis included 29 RCTs with 1830 patients.[189] The pooled analysis of trials showed that IC bone marrow stem cell therapy resulted in an overall improvement in LVEF of 2.70% (95% CI, 1.48 to 3.92; $P < .001$) in the short term and 3.31% (95% CI, 1.87 to 4.75; $P < .001$) over the longer term. The meta-regression suggested a dose-response relationship between quantity of CD34+ cells delivered and an increase in the LVEF ($P = .007$). Another recent meta-analysis of randomized trials has shown a sustained improvement in the LV function (Fig. 20-23) and significant reductions in the rate of recurrent MI and readmission for heart failure in patients who received IC cell therapy.[190] Along the same lines, another recent meta-analysis included 16 studies with 1641 patients (984 patients with IC bone marrow cell therapy and 657 controls). The absolute improvement in the LVEF was greater among cell-treated patients compared with controls (2.55% increase; 95% CI, 1.83 to 3.26; $P < .001$). Treatment benefit in terms of LV function improvement was more pronounced in younger patients (age < 55 years, 3.38% vs. age ≥ 55 years, 1.77%; $P = .03$). Patients with LVEF below 40% derived more benefit from cell therapy than those with LVEF of 40% or more (5.30% increase vs. 1.45% increase, $P < .001$).[191] Timing of application of cell therapy seems to be important. The Timing In Myocardial Infarction Evaluation (TIME) trial[192] showed that among patients with STEMI treated with PPCI, IC bone marrow cells infused at either 3 days or 7 days after the event had no significant effect on recovery of global or regional LV function compared with placebo. These summarized data of the existing randomized trials show a slight but significant improvement in the LVEF. However, the impact of cell therapy on clinical outcome of patients with STEMI treated with PPCI remains poorly defined.

The ability of granulocyte colony–stimulating factor (G-CSF) to mobilize stem cells from bone marrow (CD34+ mononuclear blood stem cells) and to increase their circulating levels has led to its use for stem cell mobilization (G-CSF injection) in patients with STEMI and for harvesting stem cells for IC delivery. Recent data with this agent have shown conflicting results. A meta-analysis of 10 randomized trials with 445 patients demonstrated a significant improvement of LVEF in the groups treated with G-CSF injection versus placebo with a mean

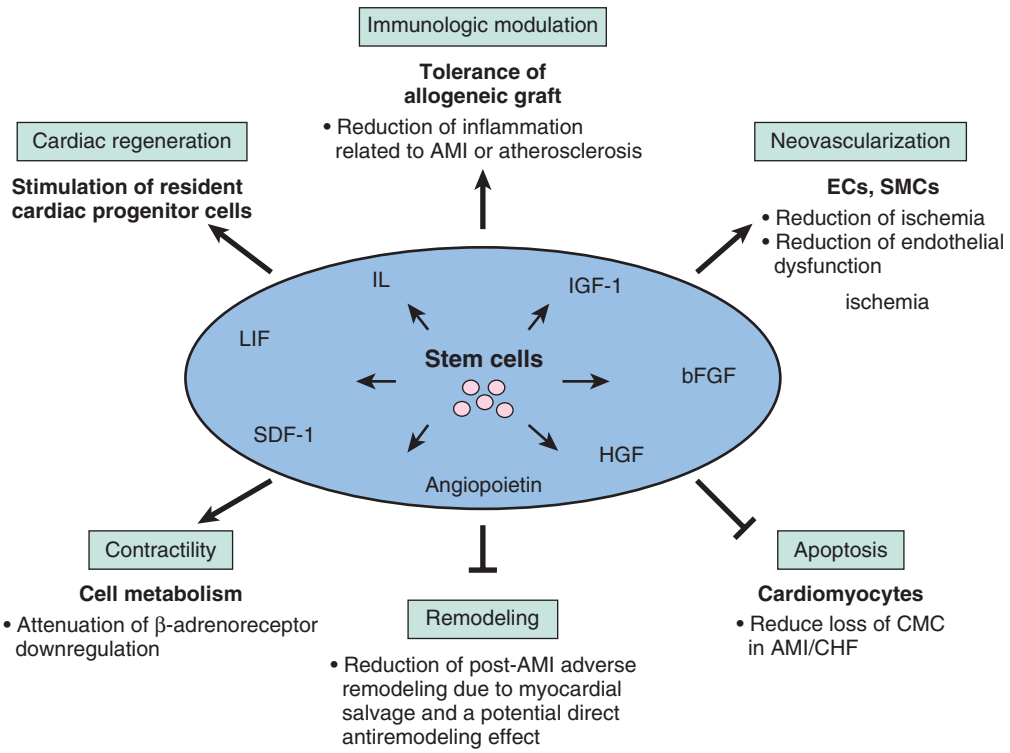


FIGURE 20-22 Paracrine effects of stem cells. Stem cells exert multiple cardioprotective effects mainly because of paracrine release of immunomodulatory, proangiogenic, and prosurvival cytokines and chemokines. *AMI,* Acute myocardial infarction; *bFGF,* basic fibroblast growth factor; *CHF,* congestive heart failure; *CMC,* cardiomyocytes; *ECs,* endothelial cells; *HGF,* hepatocyte growth factor; *IGF-1,* insulin-like growth factor 1; *IL,* interleukin; *LIF,* leukemia inhibitor factor; *SDF-1,* stromal derived factor 1; *SMCs,* smooth muscle cells. (From Takashima S, Tempel D, Duckers HJ: Current outlook of cardiac stem cell therapy towards a clinical application. *Heart* 99[23]:1772-1784, 2013.)

Study or Subgroup	Cell Therapy Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.1.1 LVEF ≤6-month follow-up								
Cao *et al* 2009	7.1	3.2	41	5	3.5	45	7.4%	2.10 (0.68 to 3.52)
Castellani *et al* 2010	0.2	2.2	5	–5.6	8.9	5	1.7%	5.80 (–2.24 to 13.84)
Ge *et al* 2006	4.8	6.8	10	–1.9	4.1	10	3.4%	6.70 (1.78 to 11.62)
Grajek *et al* 2010	2.7	7.1	31	–0.1	6.5	14	4.0%	2.80 (–1.42 to 7.02)
Hirsch *et al* 2010	3.8	7.4	67	4	5.8	60	6.3%	–0.20 (–2.50 to 2.10)
Huikuri *et al* 2008	7.1	12.3	36	1.2	11.5	36	3.0%	5.90 (0.40 to 11.40)
Janssens *et al* 2006	3.4	6.9	30	2.2	7.3	30	4.7%	1.20 (–2.39 to 4.79)
Lunde *et al* 2006	1.2	7.5	44	4.3	7.1	43	5.3%	–3.10 (–6.17 to –0.03)
Meluzin *et al* HD 2006	7	9.2	20	0	9.4	20	2.8%	7.00 (1.24 to 12.76)
Meluzin *et al* LD 2006	3	4.6	20	0	9.4	20	3.7%	3.00 (–1.59 to 7.59)
Noguiera *et al* 2009	6.9	6.6	14	2	11.3	6	1.3%	4.90 (–4.78 to 14.58)
Penicka *et al* 2007	5.8	5.4	14	7.6	4	10	4.5%	–1.80 (–5.56 to 1.96)
Piepoli *et al* 2010	8.4	4.3	17	2.2	5.6	15	4.8%	6.20 (2.71 to 9.69)
Plewka *et al* 2009	10	9	38	5	8	18	3.6%	5.00 (0.33 to 9.67)
Quyyumi *et al* 2011	2.5	9	11	1	7.8	10	2.0%	1.50 (–5.69 to 8.69)
Roncalli *et al* 2010	1.9	6.9	47	2.2	6.9	44	5.6%	–0.30 (–3.14 to 2.54)
Schachinger *et al* 2006	5.5	7.3	95	3	6.5	92	6.8%	2.50 (0.52 to 4.48)
Tendera *et al* (NS) 2009	4.4	11	46	0.5	9	20	3.3%	3.90 (–1.17 to 8.97)
Tendera *et al* (S) 2009	4.2	14.5	51	0.5	9	20	2.9%	3.70 (–1.90 to 9.30)
Traverse *et al* 2011	0.5	8.2	55	3.6	9.3	26	4.1%	–3.10 (–7.28 to 1.08)
Traverse *et al* 2010	6.2	9.8	30	9.4	10	10	2.1%	–3.20 (–10.32 to 3.92)
Turan *et al* 2012	10	10	42	2	10	20	3.1%	8.00 (2.68 to 13.32)
Wohrle *et al* 2010	1.8	5.3	28	5.7	8.4	12	3.2%	–3.90 (–9.04 to 1.24)
Wollert *et al* 2004	6.7	6.5	30	0.7	8.1	30	4.6%	6.00 (2.28 to 9.72)
Yao *et al* 2009	5.1	3.4	12	2.1	3.3	12	5.8%	3.00 (0.32 to 5.68)
Subtotal (95% CI)			**834**			**628**	**100.0%**	**2.23 (1.00 to 3.47)**
Heterogeneity: $\tau^2 = 5.07$; $\chi^2 = 61.58$, df = 24 ($P < .0001$); $I^2 = 61\%$								
Test for overall effect: Z = 3.55 ($P = .0004$)								
2.1.2 LVEF 12-month follow-up								
Cao *et al* 2009	6.9	5	41	3.9	5.5	44	12.3%	3.00 (0.77 to 5.23)
Castellani *et al* 2010	0.8	4.6	5	–7.3	14.7	4	1.1%	8.10 (–6.86 to 23.06)
Grajek *et al* 2010	0.7	7.4	27	–2.9	6.4	12	7.1%	3.60 (–0.97 to 8.17)
Lunde *et al* 2006	3	7.5	50	1.6	8	50	10.3%	1.40 (–1.64 to 4.44)
Meluzin *et al* HD 2006	7	8.9	20	0	4.5	20	7.5%	7.00 (2.63 to 11.37)
Meluzin *et al* LD 2006	4	2.3	20	0	4.5	20	12.4%	4.00 (1.79 to 6.21)
Piepoli *et al* 2010	9.5	5.4	17	3.5	5.6	15	8.5%	6.00 (2.18 to 9.82)
Plewka *et al* 2009	11	11.2	38	4.8	10.3	18	5.1%	6.20 (0.26 to 12.14)
Schachinger *et al* 2006	3.4	6.8	27	0.6	6.2	27	9.3%	2.80 (–0.67 to 6.27)
Turan *et al* 2012	11	10	42	1	10	20	5.9%	10.00 (4.68 to 15.32)
Wohrle *et al* 2010	–1.4	6.4	28	1.6	7.8	12	6.4%	–3.00 (–8.01 to 2.01)
Yao *et al* 2009	7.2	1.6	12	2.9	2	11	14.1%	4.30 (2.81 to 5.79)
Subtotal (95% CI)			**327**			**253**	**100.0%**	**3.91 (2.56 to 5.27)**
Heterogeneity: $\tau^2 = 2.21$; $\chi^2 = 20.21$, df = 11 ($P = 0.04$); $I^2 = 46\%$								
Test for overall effect: Z = 5.66 ($P < .00001$)								
2.1.3 LVEF long-term follow-up								
Cao *et al* 2009	9.2	2.9	41	5.7	3	45	24.3%	3.50 (2.25 to 4.75)
Lunde *et al* 2006	0.1	6.1	45	1.7	6	43	19.2%	–1.60 (–4.13 to 0.93)
Penicka *et al* 2007	12	6	14	8.5	6	10	11.0%	3.50 (–1.37 to 8.37)
Plewka *et al* 2009	10	7.7	38	4.7	10.1	18	10.0%	5.30 (0.03 to 10.57)
Schachinger *et al* 2006	1.1	6	26	–3.2	6	33	16.9%	4.30 (1.22 to 7.38)
Wohrle *et al* 2010	–1.7	5.8	28	2	9.4	12	8.9%	–3.70 (–9.44 to 2.04)
Wollert *et al* 2004	–2.5	11.9	30	–3.3	9.5	30	9.6%	0.80 (–4.65 to 6.25)
Subtotal (95% CI)			**222**			**191**	**100.0%**	**1.90 (–0.43 to 4.23)**
Heterogeneity: $\tau^2 = 5.93$; $\chi^2 = 19.96$, df = 6 ($P = .003$); $I^2 = 70\%$								
Test for overall effect: Z = 1.60 ($P = .11$)								

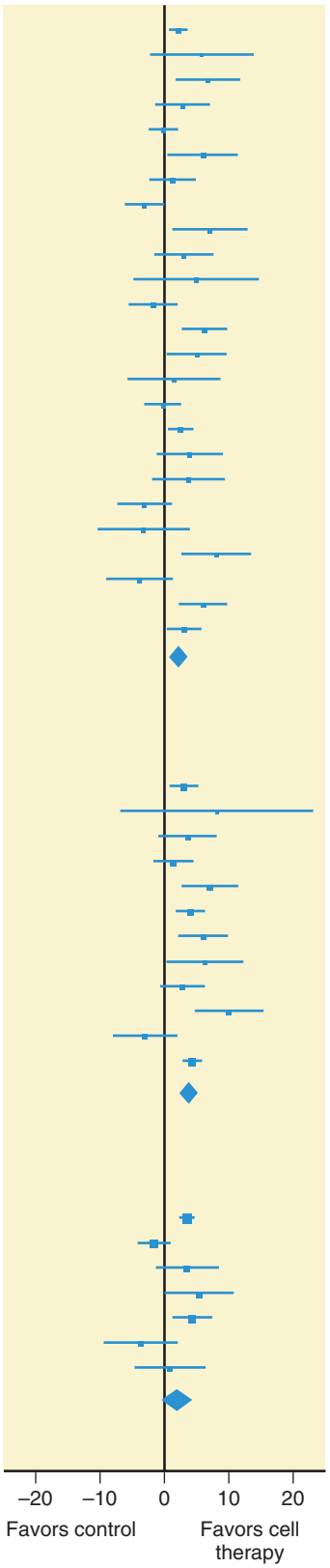


FIGURE 20-23 Forest plot of studies evaluating cell therapy and the difference in change in left ventricular ejection fraction (LVEF) from baseline to follow-up. *CI,* Confidence interval; *HD,* high dose; *LD,* low dose; *NS,* nonselected; *S,* selected; *SD,* standard deviation. (From Delewi R, Andriessen A, Tijssen JG, et al: Impact of intracoronary cell therapy on left ventricular function in the setting of acute myocardial infarction: a meta-analysis of randomised controlled clinical trials. *Heart* 99[4]:225-232, 2013.)

difference of 1.32% ($P = .36$) and no significant difference in infarct size ($P = .17$), TVR rates, or mortality at follow-up.[193] A recent Cochrane review concluded that limited evidence from small trials suggested a lack of benefit of G-CSF therapy in patients with acute MI.[194] Based on source studies and on the results of these meta-analyses, G-CSF does not represent a useful therapy in patients with STEMI undergoing PCI.

In summary, cell-based therapy for cardiac regeneration is still under investigation on multiple fronts including types of cells used, magnitude of benefit, routes and time of administration, mechanisms of action, and possible side effects that include arrhythmogenesis, oncogenic transformation, multiorgan seeding, aberrant cell differentiation, and accelerated atherosclerosis. The available evidence does not support the use of G-CSF to mobilize stem cells from bone marrow to enhance cardiac regeneration in patients with STEMI after PPCI. Further studies are needed to clarify the role of IC injection of bone marrow–derived stem cells in patients with STEMI.

SPECIAL ISSUES IN PRIMARY PERCUTANEOUS CORONARY INTERVENTION

Cardiac Arrest

Cardiac arrest is not an uncommon presentation of STEMI. Between 4% and 11% of PPCI procedures are performed in patients with STEMI after being resuscitated because of out-of-hospital cardiac arrest,[195,196] and cardiac arrest is an independent predictor of in-hospital-mortality.[196] In 2010, the International Liaison recommended that immediate angiography and subsequent PCI should be considered in patients with STEMI upon the return of spontaneous circulation after out-of-hospital cardiac arrest.[197] Current guidelines on the treatment of patients with STEMI recommend that immediate angiography and PCI should be performed in resuscitated patients whose initial ECG shows evidence of STEMI.[9,10] For comatose patients or those deeply sedated, mild therapeutic hypothermia is also recommended. In a recent study, 484 out of 4118 patients with STEMI (11.8%) had cardiac arrest. The overall in-hospital mortality in patients with cardiac arrest was 20.5%. Those who had sustained cardiac arrest before ambulance arrival had the highest unadjusted mortality (29.7%) compared with those that had cardiac arrest after ambulance arrival (12.0%), in hospital (16.1%), and in the catheterization room (23.8%, $P = .03$). Multiple logistic regression analysis showed that age (OR, 1.05; 95% CI, 1.02 to 1.08; $P = .0009$ for each year of age), female sex (OR, 2.42; 95% CI, 1.17 to 4.99; $P = .0173$), previous PCI (OR, 7.59; 95% CI, 1.72 to 33.53; $P = .0075$), asystole/electromechanical dissociation (OR, 13.43; 95% CI, 5.34 to 33.80; $P < .0001$), and patient location at arrest (OR, 5.77; 95% CI, 2.55 to 13.07; $P < .0001$ for before-ambulance arrival) were independent correlates of in-hospital mortality.[198] Several ongoing studies are investigating the cardiac arrest and its treatment.

Cardiogenic Shock

Cardiogenic shock is a serious complication and remains the major cause of death for patients with STEMI. PPCI is a class 1 recommendation in patients with STEMI who develop cardiogenic shock irrespective of time delay from STEMI onset.[9,10] Despite advances in the PPCI technique and adjunctive care, the prognosis of patients with cardiogenic shock that complicates STEMI remains grave. In a recent survey that included 1,990,486 patients aged 40 years or older treated for STEMI from 2003 to 2010, cardiogenic shock occurred in 157,892 patients (7.9%). The overall incidence of cardiogenic shock increased from 6.5% in 2003 to 10.1% in 2010 ($P_{trend} < .001$). During the same period, early mechanical revascularization rates (30.4% to 50.7%, $P_{trend} < .001$) and intraaortic balloon counterpulsation use (44.8% to 53.7%, $P_{trend} < .001$) also increased. In-hospital mortality decreased significantly (44.6% to 33.8%, $P_{trend} < .001$; adjusted OR, 0.71; 95% CI, 0.68 to 0.75). However, the average hospital costs increased from $35,892 to $45,625 ($P_{trend} < .001$) during the study period. No change was seen in the average length of stay ($P_{trend} = .394$).[199]

The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial[200] was important in establishing the place of early mechanical reperfusion in patients with STEMI complicated by cardiogenic shock. The trial randomized 302 patients with acute MI complicated by cardiogenic shock to receive early revascularization (mostly PCI, $n = 152$) or initial medical stabilization ($n = 150$). At 1 year of follow-up, an absolute 13% difference in survival rates was seen that favored patients assigned to an early revascularization approach. This benefit in survival remained almost unchanged at 3 and 6 years of follow-up (13.1% and 13.2%, respectively). The 6-year survival rates for hospital survivors were 62.4% in those assigned to early revascularization and 44.4% in those assigned to initial medical stabilization with annual rates of death of 8.3% versus 14.3%, respectively. For 1-year survivors, the annual rates of death were 8.0% versus 10.7%, again favoring patients assigned to early revascularization. The SHOCK trial demonstrated that almost two-thirds of hospital survivors with cardiogenic shock complicating acute MI who were treated with early revascularization survived to the 6-year follow-up, and the trial strongly recommended early revascularization in patients with acute MI complicated by cardiogenic shock.

The Tilarginine Acetate Injection in a Randomized International Study in Unstable MI Patients With Cardiogenic Shock (TRIUMPH) trial[201] tested the impact of nitric oxide inhibition with tilarginine, a nitric oxide synthase inhibitor, in patients with STEMI who developed cardiogenic shock, 96% of them treated with PCI. The study randomized 398 patients to tilarginine (1 mg/kg bolus and 1 mg/kg/hr in a 5-hour infusion) or placebo. The 30-day (48% vs. 42%, $P = .24$) and 6-month (58% vs. 59%, $P = .80$) all-cause mortality did not differ among patients assigned to tilarginine or placebo. The study was terminated before completion because of futility. Apart from failure of nitric oxide inhibition to improve outcome, the study showed that early mortality in patients with cardiogenic shock remains high despite recent advances in mechanical and pharmacologic therapy.

Although the evidence base for efficacy is weak, until very recently, intraaortic balloon counterpulsation has been a standard treatment in patients with STEMI complicated by cardiogenic shock. The Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial[202] randomized 600 patients with STEMI complicated by cardiogenic shock undergoing early mechanical revascularization to IABP counterpulsation (301 patients) or control (299 patients). All-cause mortality at 6 months (48.7% vs. 49.2%, $P = .91$) or 12 months (51.8% vs. 51.4%, $P = .91$) did not differ among patients assigned to intraaortic balloon counterpulsation or control. In addition, no differences were reported among patients assigned to intraaortic balloon counterpulsation or control in regard to 12-month incidence of reinfarction (9% vs. 3%, $P = .05$), recurrent revascularization (20% vs. 22%, $P = .77$), or stroke (2% vs. 1%, $P > .99$). Alternative percutaneous LV-assist devices are also under investigation in this setting.

Primary Percutaneous Coronary Intervention During Off-Hours Presentation

The relationship between the time of day at which patients with STEMI present to the hospital and outcomes from PPCI and in-hospital mortality has been addressed in a series of studies. This relationship was studied in a recent meta-analysis and in a systematic review of 48 studies of fair quality with 1,896,859 patients. Of these, 36 studies reported mortality outcomes for 1,892,424 patients with acute MI, and 30 studies reported DTB times for 70,534 patients with STEMI. In patients with acute MI, off-hour presentation was associated with higher short-term mortality (OR, 1.06; 95% CI, 1.04 to 1.09). Patients with STEMI who presented during off hours were less likely to receive PCI within 90 minutes (OR, 0.40; 95% CI, 0.35 to 0.45) and had a longer DTB time by 14.8 minutes (95% CI, 10.7 to 19.0). Differences in mortality between patients who seek medical attention during off hours and during regular hours have increased in recent years. Apart from suggesting an association between the off-hour presentation and the increased risk of mortality, the meta-analysis also suggested that

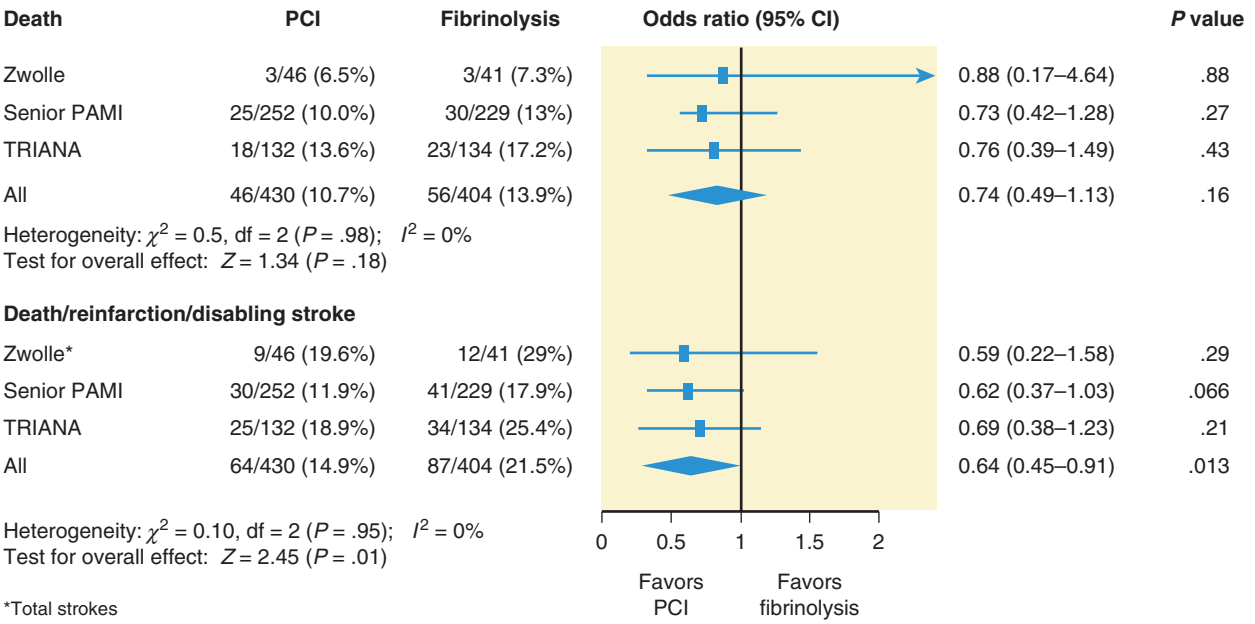


FIGURE 20-24 Odds ratios for mortality and incidence of the combined end point in the three randomized trials comparing primary percutaneous coronary intervention (PPCI) and thrombolysis performed in very old patients with ST-elevation myocardial infarction. *CI,* Confidence interval; *OR,* odds ratio. (From Bueno H, Betriu A, Heras M, et al: Primary angioplasty vs. fibrinolysis in very old patients with acute myocardial infarction: TRIANA [*TRatamiento del Infarto Agudo de miocardio eN Ancianos*] randomized trial and pooled analysis with previous studies. *Eur Heart J* 32[1]:51-60, 2011.)

increased risk of mortality may at least partially be attributed to longer DTB times in patients with STEMI who come in during off hours.[203]

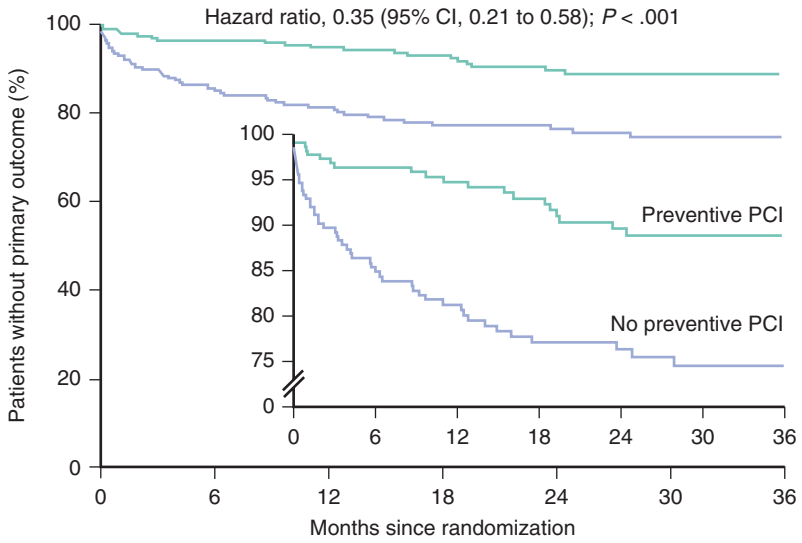
Primary Percutaneous Coronary Intervention in the Elderly

Older adult patients represent an increasing proportion of patients admitted to the hospital with STEMI, and advanced age is an important correlate of poor outcome after both PCI and thrombolysis. It is widely accepted that PPCI in older adults is more challenging for a number of reasons, including (1) more complex coronary anatomy (multivessel disease, calcified and tortuous coronary arteries with lower rates of TIMI flow grade 3 post procedure); (2) increased rate of bleeding complications; (3) increased rate of vascular complications due to a higher prevalence of peripheral vascular disease; (4) increased prevalence of comorbidities such as impaired renal function, which predisposes to contrast nephropathy; (5) delayed presentation; and (6) atypical symptoms. The optimal management of patients with STEMI is still unclear but is due at least in part to underrepresentation of elderly and very elderly patients in trials that have established the therapeutic value of PPCI. Notably, the PCAT-2 meta-analysis[53] reported that the absolute reduction of mortality with PPCI increased with advancing age, from 1% at 65 years of age and younger to 6.9% at an age of 85 years or older. Three randomized trials have assessed the efficacy of PPCI in elderly. A small study that included 87 patients 75 years of age or older showed that PPCI was superior to thrombolysis with streptokinase in reducing the composite end point of death, reinfarction, or stroke at 1 year (13% vs. 44%; $P = .001$).[204] In the Senior Primary Angioplasty in Myocardial Infarction (SENIOR-PAMI) trial,[205] 481 patients 70 years of age and older were randomized between PCI and thrombolysis. In patients 70 to 80 years of age, a trend was seen toward reduced 30-day mortality with PPCI (7.1% vs. 11.3%, $P = .17$) along with a significant reduction in the composite end point of death, reinfarction, or stroke (7.7% vs. 17.0%, $P < .01$) with PPCI compared with thrombolysis. However, none of these end points differed between the two treatment options in patients older than 80 years of age. The *Tratamiento del Infarto Agudo de Miocardio en Ancianos* (Treatment of Acute Myocardial Infarction in the Elderly, TRIANA) study[206] included 266 patients 75 years of age and older who were randomized to PPCI (134 patients) or thrombolysis (132 patients). The trial reported a trend toward reduction in the 30-day composite end point of death, reinfarction, or disabling stroke with PPCI (18.9% vs. 25.4%, $P = .21$). Nonsignificant reductions were found in the incidence of death (13.6% vs. 17.2%, $P = .43$), reinfarction (5.3% vs. 8.2%, $P = .35$), or disabling stroke (0.8% vs. 3.0%, $P = .18$). Recurrent ischemia was encountered less commonly in PPCI-treated patients (0.8% vs. 9.7%, $P = .001$). It is notable that both the SENIOR-PAMI and TRIANA trials were terminated before completion because of slow recruitment. The findings of the individual trials were reinforced by a meta-analysis of three studies (Fig. 20-24).[206] The study strongly supported the use of PPCI in older patients with STEMI.

A recent survey from the 2001 to 2010 U.S. Nationwide Inpatient Sample (NIS) database reported temporal trends in STEMI, use of PCI for STEMI, and outcomes among patients aged 65 to 79 years and 80 years and older. Among 4,017,367 patients aged 65 years and older with acute MI, 1,434,579 (35.7%) had STEMI. During the study period in patients aged 65 to 79 years and 80 or more years, STEMI decreased by 16.4% and 19%, respectively, and the use of PCI for STEMI increased by 33.5% and 22%, respectively ($P_{trend} < .001$). A significant decrease in age-adjusted in-hospital mortality was observed in patients aged 80 years and older ($P_{trend} = .02$) but not in patients aged 65 to 79 years ($P_{trend} = .886$). In multivariate analysis, intraaortic balloon pump use, acute renal failure, acute cerebrovascular disease, age 80 years and older, peripheral vascular disease, gastrointestinal bleeding, female sex, CHF, chronic lung disease, weekend admission, and multivessel PCI were independent correlates of increased in-hospital mortality among patients 65 years of age and older who underwent PCI for STEMI.[207]

Primary Percutaneous Coronary Intervention and Multivessel Intervention

Multivessel CAD occurs in approximately 50% of patients undergoing PPCI for STEMI, and its presence is associated with reduced reperfusion success and an adverse prognosis following PPCI.[208,209] The



No. at risk							
Preventive PCI	234	196	166	146	118	89	67
No preventive PCI	231	168	144	122	96	74	50

FIGURE 20-25 Kaplan-Meier curves for the primary outcome: a composite of death from cardiac causes, nonfatal myocardial infarction, or refractory angina. The inset graph shows the same data on a larger scale. All patients in the trial underwent infarct-artery percutaneous coronary intervention (PCI) immediately before randomization. *CI,* Confidence interval. (From Wald DS, Morris JK, Wald NJ, et al: Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 369[12]:1115-1123, 2013.)

increase in cardiovascular risk in patients with multivessel CAD is explained by a series of factors that include impaired function of non-infarct zones, impact of extensive atherosclerotic disease, presence of stunned and hibernating myocardium, and slow flow in the critically narrowed non–infarct-related arteries. For patients not intended to undergo CABG surgery, the revascularization strategy of nonculprit lesions in patients with STEMI consists of PCI of nonculprit lesions during the same session of PPCI, delayed planned PCI (staged approach), or PCI at a later time if driven by ischemia symptoms or strong evidence by positive ischemia tests. However, the most optimal revascularization strategy in these patients remains poorly investigated.

Prior studies of multivessel intervention during PPCI procedures have given conflicting results. The overall effect has been investigated in a series of meta-analyses. A 2011 pairwise and network meta-analysis has compared three PCI strategies in patients with STEMI and multivessel disease: *culprit vessel–only* PCI strategy; *multivessel* PCI strategy, defined as PCI of the culprit vessel, as well as one or more non–culprit vessel lesions; and *staged* PCI strategy, defined as PCI confined to a culprit vessel, after which one or more non–culprit vessel lesions are treated during staged procedures. Overall, 18 studies (four prospective and 14 retrospective) with 40,280 patients were included. The meta-analysis showed that staged PCI was associated with lower short- and long-term mortality compared with culprit and multivessel PCI strategies. Of note, multivessel PCI strategy was associated with the highest mortality rates at both short- and long-term follow-up.[210] Another recent meta-analysis that included 14 studies (11 cohort and three randomized controlled) compared the strategies of multivessel PCI with infarct-related–artery PCI only. The primary composite end point of death, MI, and revascularization was higher in the multivessel-PCI group in the short term (OR, 1.63; 95% CI, 1.12 to 2.37) and long term (OR, 1.60; 95% CI, 1.18 to 2.16). However, after excluding patients with shock, no difference was found in primary end point in the short- (OR, 1.33; 95% CI, 0.67 to 2.63) and long-term (OR, 1.39; 95% CI, 0.80 to 2.42) follow-ups. In analyses limited to RCTs, the primary end point was similar over the short term (OR, 0.79; 95% CI, 0.19 to 3.28) and was significantly lower for the multivessel-PCI group over the long term (OR, 0.55; 95% CI, 0.34 to 0.91).[211] Finally, the most recent meta-analysis included 26 studies (23 nonrandomized and three randomized) with 46,324 patients and showed that staged multivessel PCI improved short- and long-term survival and reduced the need for repeat PCI. Although overall no difference was found in in-hospital mortality with multivessel PCI or infarct-related PCI only (OR, 1.11; 95% CI, 0.98 to 1.25; $P = .10$), multivessel PCI during index catheterization was associated with increased hospital mortality (OR, 1.35; 95% CI, 1.19 to 1.54; $P < .001$). When multivessel PCI was performed as a staged procedure, hospital mortality was lower (OR, 0.35; 95% CI, 0.21 to 0.59; $P < .001$). The risk of long-term mortality was reduced by 26% ($P < .001$), and the need for repeat PCI was reduced by 35% ($P = .01$) with multivessel PCI.[212]

The Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) trial gave support for a preventive strategy, multivessel intervention at the time of PPCI. The preventive strategy consisted of same-time PCI on nonculprit coronary arteries with more than 50% diameter stenosis. The study randomized 465 patients with STEMI undergoing PPCI to a preventive PCI ($n = 234$) or no preventive PCI ($n = 231$). The trial was planned to include 600 patients, but the DSMB prematurely terminated the trial after finding a significant difference in the primary end point: a composite of death from cardiac causes, nonfatal MI, or refractory angina. During a mean follow-up of 23 months, the primary outcome occurred in 21 patients assigned to preventive PCI and in 53 patients assigned to no preventive (infarct artery only) PCI (HR, 0.35; 95% CI, 0.21 to 0.58; $P < .001$; Fig. 20-25). Hazard ratios for the three components of the primary outcome were 0.34 (95% CI, 0.11 to 1.08) for death from cardiac causes, 0.32 (95% CI, 0.13 to 0.75) for nonfatal MI, and 0.35 (95% CI, 0.18 to 0.69) for refractory angina.[213] Although the PRAMI trial offered support for a preventive PCI in patients with STEMI, limitations of this trial include the limited number of events (particularly the limited number of deaths—4 and 10 deaths per group), the choice of control group (staged PCI strategy was not included as control), the lack of validation of the criterion for applying the preventive strategy (≥50% diameter stenosis), and the premature termination of the trial that potentially overestimated the benefit.[213]

Current guidelines do not encourage performing multivessel PCI at the time of PPCI.[10] Moreover, although fractional flow reserve is

infrequently assessed in patients with STEMI, one study suggested that the test may be useful in assessing the hemodynamic significance of nonculprit lesions in patients with STEMI.[214]

Primary Percutaneous Coronary Infarction in Hospitals With and Without On-Site Coronary Artery Bypass Graft Surgery

The answer to the question of whether PPCI should be performed only in hospitals with CABG surgery capabilities or whether it should be expanded to hospitals without cardiac surgery is of importance because of the expanding number of hospitals performing PPCI and the potential for worse outcomes due to lower volumes and lack of cardiac surgery backup. Since seven studies and two meta-analyses of PPCI showed no difference for in-hospital or 30-day mortality between sites with and without on-site surgery, concerns about the risks of performing PPCI in centers without on-site surgery have abated.[215] A meta-analysis of PPCI studies for STEMI of 124,074 patients did not show an increased in-hospital mortality in centers without versus centers with on-site surgery (4.6% vs. 7.2%; OR, 0.96; 95% CI, 0.88 to 1.05). The meta-analysis showed that sites without on-site surgery had a lower occurrence of emergency CABG surgery after PPCI (OR, 0.53; 95% CI, 0.35 to 0.79).[216] Another meta-analysis identified nine PPCI studies (106,089 patients) and found no increase in in-hospital mortality (OR, 0.93; 95% CI, 0.83 to 1.05) or early CABG surgery (6.1% vs. 7.6%; OR, 0.87; 95% CI, 0.68 to 1.11) in centers without on-site surgery compared with centers with on-site surgery.[217] The message from these studies is that PPCI can be performed in hospitals without cardiac surgery on site.

Deferred Stenting

A strategy of deferred stenting—that is, stent implantation some hours after initial coronary reperfusion—has been investigated as a strategy to reduce coronary no-reflow phenomenon in patients with STEMI who undergo PPCI. The Deferred Stenting Versus Immediate Stenting to Prevent No or Slow Reflow in Acute ST-Segment Elevation Myocardial Infarction (DEFER-STEMI) trial[218] randomized 101 patients with STEMI with one or more risk factors for no-reflow to a deferred stenting strategy (4 to 16 hr after initial reperfusion) or immediate stenting strategy. Aspiration thrombectomy was performed in 85.7% and 88.5% of the patients undergoing immediate and deferred stenting, respectively. The primary outcome was the incidence of *slow to* no-reflow, defined as a TIMI flow grade of 2 or less. The median time to the second procedure in the deferred stenting group was 9 hours. The primary end point (6% vs. 29%, $P = .006$), the frequency of no-reflow (2% vs. 14%, $P = .052$) and intraprocedural thrombotic events (10% vs. 33%, $P = .010$), was achieved in fewer patients assigned to a strategy of deferred stenting compared with immediate stenting. Myocardial salvage index (proportion of initial perfusion defect salvaged) at 6 months, measured with CMRI, was greater in the deferred-stenting group (median 68% vs. 56%, $P = .031$). In this study the strategy of deferred stenting in PPCI of high-risk STEMI patients reduced the occurrence of no-reflow phenomenon and increased myocardial salvage.[218] Mechanistically, a strategy of deferred stenting may reduce distal embolization of thrombotic and/or vasopressor material compared with a strategy of immediate stenting with or without balloon predilation.

CONCLUDING REMARKS

Reperfusion therapies have dramatically improved the prognosis for patients with acute STEMI. Advances in interventional techniques, devices, and antithrombotic therapies have enhanced the effectiveness of PCI in patients with STEMI. Randomized clinical trials have clearly shown that PPCI is superior to thrombolysis as a reperfusion therapy. Its advantages are conferred by the extremely low number of contraindications, high efficacy in patients who present both early and late after symptom onset, and low number of complications. In addition, not only is PCI very helpful after failed thrombolysis, but it may also represent a valuable adjunct to initially successful pharmacologic reperfusion. Although the proportion of patients with STEMI treated with PCI has been increasing steadily in recent years, major efforts are required to make this therapy available to all patients within a short time from symptom onset. Patients with STEMI who undergo PCI benefit from pretreatment with effective antiplatelet therapies. Additional work is needed to develop new effective adjunct therapies able to promote further myocardial salvage in the setting of PPCI. Intensive experimental and clinical research aimed at myocardial cell regeneration is ongoing and offers new prospects for the improvement of prognosis and quality of life in patients with STEMI.

REFERENCES

1. Thygesen K, Alpert JS, Jaffe AS, et al: Third universal definition of myocardial infarction. *Circulation* 126(16):2020–2035, 2012.
2. DeWood MA, Stifter WF, Simpson CS, et al: Coronary arteriographic findings soon after non-Q-wave myocardial infarction. *N Engl J Med* 315(7):417–423, 1986.
3. Schmidt M, Jacobsen JB, Lash TL, et al: 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ* 344: e356, 2012.
4. McManus DD, Gore J, Yarzebski J, et al: Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. *Am J Med* 124(1):40–47, 2011.
5. Puymirat E, Simon T, Steg PG, et al: Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. *JAMA* 308(10):998–1006, 2012.
6. Ndrepepa G, Schömig A, Kastrati A: Efficacy of reperfusion with primary percutaneous coronary intervention in patients with acute ST segment elevation myocardial infarction. *Clin Res Cardiol* 100(11):1047–1048, 2011.
7. Kristensen SD, Laut KG, Fajadet J, et al: Reperfusion therapy for ST elevation acute myocardial infarction 2010/2011: current status in 37 ESC countries. *Eur Heart J* 35(29):1957–1970, 2014.
8. Harker M, Carville S, Henderson R, Gray H: Guideline Development Group: Key recommendations and evidence from the NICE guideline for the acute management of ST-segment-elevation myocardial infarction. *Heart* 100(7):536–543, 2014.
9. Steg PG, James SK, Atar D, et al: ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 33(20):2569–2619, 2012.
10. O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 127(4):e362–e425, 2013.
11. Keeley EC, Boura JA, Grines CL: Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 361(9351):13–20, 2003.
12. Fibrinolytic Therapy Trialists (FTT) Collaborative Group: Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 343:311–322, 1994.
13. Keeley EC, Grines CL: Primary coronary intervention for acute myocardial infarction. *JAMA* 291(6):736–739, 2004.
14. Grzybowski M, Clements EA, Parsons L, et al: Mortality benefit of immediate revascularization of acute ST-segment elevation myocardial infarction in patients with contraindications to thrombolytic therapy: a propensity analysis. *JAMA* 290(14): 1891–1898, 2003.
15. Abbate A, Biondi-Zoccai GG, Appleton DL, et al: Survival and cardiac remodeling benefits in patients undergoing late percutaneous coronary intervention of the infarct-related artery: evidence from a meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 51(9):956–964, 2008.
16. Schömig A, Mehilli J, Antoniucci D, et al: Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptom onset: a randomized controlled trial. *JAMA* 293(23):2865–2872, 2005.
17. Thune JJ, Hoefsten DE, Lindholm MG, et al: Simple risk stratification at admission to identify patients with reduced mortality from primary angioplasty. *Circulation* 112(13):2017–2021, 2005.
18. Aversano T, Aversano LT, Passamani E, et al: Thrombolytic therapy vs primary percutaneous coronary intervention for myocardial infarction in patients presenting to hospitals without on-site cardiac surgery: a randomized controlled trial. *JAMA* 287(15):1943–1951, 2002.
19. Nielsen PH, Maeng M, Busk M, et al: Primary angioplasty versus fibrinolysis in acute myocardial infarction: long-term follow-up in the Danish acute myocardial infarction 2 trial. *Circulation* 121(13):1484–1491, 2010.
20. Huynh T, Perron S, O'Loughlin J, et al: Comparison of primary percutaneous coronary intervention and fibrinolytic therapy in ST-segment-elevation myocardial infarction: bayesian hierarchical meta-analyses of randomized controlled trials and observational studies. *Circulation* 119(24):3101–3109, 2009.
21. Asseburg C, Vergel YB, Palmer S, et al: Assessing the effectiveness of primary angioplasty compared with thrombolysis and its relationship to time delay: a Bayesian evidence synthesis. *Heart* 93(10):1244–1250, 2007.
22. Wailoo A, Goodacre S, Sampson F, et al: Primary angioplasty versus thrombolysis for acute ST-elevation myocardial infarction: an economic analysis of the National Infarct Angioplasty project. *Heart* 96(9):668–672, 2010.
23. Concannon TW, Nelson J, Goetz J, Griffith JL: A percutaneous coronary intervention lab in every hospital? *Circ Cardiovasc Qual Outcomes* 5(1):14–20, 2012.
24. Gershlick AH, Banning AP, Myat A, et al: Reperfusion therapy for STEMI: is there still a role for thrombolysis in the era of primary percutaneous coronary intervention? *Lancet* 382(9892): 624–632, 2013.
25. Jacobs AK, Antman EM, Faxon DP, et al: Development of systems of care for ST-elevation myocardial infarction patients: executive summary. *Circulation* 116(2):217–230, 2007.
26. Bradley EH, Herrin J, Wang Y, et al: Strategies for reducing the door-to-balloon time in acute myocardial infarction. *N Engl J Med* 355(22):2308–2320, 2006.
27. Krumholz HM, Bradley EH, Nallamothu BK, et al: A campaign to improve the timeliness of primary percutaneous coronary

intervention: Door-to-Balloon: An Alliance for Quality. *JACC Cardiovasc Interv* 1(1):97–104, 2008.
28. Camp-Rogers T, Kurz MC, Brady WJ: Hospital-based strategies contributing to percutaneous coronary intervention time reduction in the patient with ST-segment elevation myocardial infarction: a review of the "system-of-care" approach. *Am J Emerg Med* 30(3):491–498, 2012.
29. Mumma BE, Kontos MC, Peng SA, Diercks DB: Association between prehospital electrocardiogram use and patient home distance from the percutaneous coronary intervention center on total reperfusion time in ST-segment-elevation myocardial infarction patients: A retrospective analysis from the National Cardiovascular Data Registry. *Am Heart J* 167(6):915–920, 2014.
30. Bagai A, Jollis JG, Dauerman HL, et al: Emergency department bypass for ST-segment-elevation myocardial infarction patients identified with a prehospital electrocardiogram: a report from the American Heart Association Mission: Lifeline program. *Circulation* 128(4):352–359, 2013.
31. Huber K, Gersh BJ, Goldstein P, et al: The organization, function, and outcomes of ST-elevation myocardial infarction networks worldwide: current state, unmet needs and future directions. *Eur Heart J* 35(23):1526–1532, 2014.
32. Jollis JG, Roettig ML, Aluko AO, et al: Implementation of a statewide system for coronary reperfusion for ST-segment elevation myocardial infarction. *JAMA* 298(20):2371–2380, 2007.
33. Henry TD, Gibson CM, Pinto DS: Moving toward improved care for the patient with ST-elevation myocardial infarction: a mandate for systems of care. *Circ Cardiovasc Qual Outcomes* 3(5):441–443, 2010.
34. Miedema MD, Newell MC, Duval S, et al: Causes of delay and associated mortality in patients transferred with ST-segment-elevation myocardial infarction. *Circulation* 124(15):1636–1644, 2011.
35. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB: The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 56(5):786–794, 1977.
36. Taher T, Fu Y, Wagner GS, et al: Aborted myocardial infarction in patients with ST-segment elevation: insights from the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3 Trial Electrocardiographic Substudy. *J Am Coll Cardiol* 44(1):38–43, 2004.
37. De Luca G, Suryapranata H, Ottervanger JP, Antman EM: Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation* 109(10):1223–1225, 2004.
38. Cannon CP, Gibson CM, Lambrew CT, et al: Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA* 283(22):2941–2947, 2000.
39. Zijlstra F, Patel A, Jones M, et al: Clinical characteristics and outcome of patients with early (<2 h), intermediate (2-4 h) and late (>4 h) presentation treated by primary coronary angioplasty or thrombolytic therapy for acute myocardial infarction. *Eur Heart J* 23(7):550–557, 2002.
40. Maeng M, Nielsen PH, Busk M, et al: Time to treatment and three-year mortality after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction-a DANish Trial in Acute Myocardial Infarction-2 (DANAMI-2) substudy. *Am J Cardiol* 105(11):1528–1534, 2010.
41. Aquaro GD, Pingitore A, Strata E, et al: Relation of pain-to-balloon time and myocardial infarct size in patients transferred for primary percutaneous coronary intervention. *Am J Cardiol* 100(1):28–34, 2007.
42. Francone M, Bucciarelli-Ducci C, Carbone I, et al: Impact of primary coronary angioplasty delay on myocardial salvage, infarct size, and microvascular damage in patients with ST-segment elevation myocardial infarction: insight from cardiovascular magnetic resonance. *J Am Coll Cardiol* 54(23):2145–2153, 2009.
43. Goldberg RJ, Spencer FA, Fox KA, et al: Prehospital Delay in Patients With Acute Coronary Syndromes (from the Global Registry of Acute Coronary Events [GRACE]). *Am J Cardiol* 103(5):598–603, 2009.
44. Spencer FA, Montalescot G, Fox KA, et al: Delay to reperfusion in patients with acute myocardial infarction presenting to acute care hospitals: an international perspective. *Eur Heart J* 31(11): 1328–1336, 2010.
45. Ting HH, Bradley EH, Wang Y, et al: Factors associated with longer time from symptom onset to hospital presentation for patients with ST-elevation myocardial infarction. *Arch Intern Med* 168(9):959–968, 2008.
46. Nallamothu BK, Bates ER, Herrin J, et al: Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NRMI)-3/4 analysis. *Circulation* 111(6):761–767, 2005.
47. Terkelsen CJ, Sorensen JT, Maeng M, et al: System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *JAMA* 304(7):763–771, 2010.
48. Rathore SS, Curtis JP, Chen J, et al: Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: national cohort study. *BMJ* 338:b1807, 2009.
49. Brodie BR, Hansen C, Stuckey TD, et al: Door-to-balloon time with primary percutaneous coronary intervention for acute myocardial infarction impacts late cardiac mortality in high-risk patients and patients presenting early after the onset of symptoms. *J Am Coll Cardiol* 47(2):289–295, 2006.
50. Nallamothu BK, Wang Y, Magid DJ, et al: Relation between hospital specialization with primary percutaneous coronary intervention and clinical outcomes in ST-segment elevation myocardial infarction: National Registry of Myocardial Infarction-4 analysis. *Circulation* 113(2):222–229, 2006.
51. Angeja BG, Gibson CM, Chin R, et al: Predictors of door-to-balloon delay in primary angioplasty. *Am J Cardiol* 89(10):1156–1161, 2002.
52. Magid DJ, Wang Y, Herrin J, et al: Relationship between time of day, day of week, timeliness of reperfusion, and in-hospital mortality for patients with acute ST-segment elevation myocardial infarction. *JAMA* 294(7):803–812, 2005.
53. Boersma E: Primary Coronary Angioplasty vs. Thrombolysis Group: Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J* 27(7):779–788, 2006.
54. Hannan EL, Zhong Y, Jacobs AK, et al: Effect of onset-to-door time and door-to-balloon time on mortality in patients undergoing percutaneous coronary interventions for ST-segment elevation myocardial infarction. *Am J Cardiol* 106(2):143–147, 2010.
55. Brodie BR, Gersh BJ, Stuckey T, et al: When is door-to-balloon time critical? Analysis from the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) and CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trials. *J Am Coll Cardiol* 56(5):407–413, 2010.
56. Gibson CM, Pride YB, Frederick PD, et al: Trends in reperfusion strategies, door-to-needle and door-to-balloon times, and in-hospital mortality among patients with ST-segment elevation myocardial infarction enrolled in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J* 156(6):1035–1044, 2008.
57. Flynn A, Moscucci M, Share D, et al: Trends in door-to-balloon time and mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Arch Intern Med* 170(20):1842–1849, 2010.
58. Menees DS, Peterson ED, Wang Y, et al: Door-to-balloon time and mortality among patients undergoing primary PCI. *N Engl J Med* 369(10):901–909, 2013.
59. Eagle KA, Goodman SG, Avezum A, et al: Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). *Lancet* 359(9304):373–377, 2002.
60. Elad Y, French WJ, Shavelle DM, et al: Primary angioplasty and selection bias inpatients presenting late (>12 h) after onset of chest pain and ST elevation myocardial infarction. *J Am Coll Cardiol* 39(5):826–833, 2002.
61. Busk M, Kaltoft A, Nielsen SS, et al: Infarct size and myocardial salvage after primary angioplasty in patients presenting with symptoms for <12 h vs. 12-72 h. *Eur Heart J* 30(11):1322–1330, 2009.
62. Ndrepepa G, Kastrati A, Mehilli J, et al: Mechanical reperfusion and long-term mortality in patients with acute myocardial infarction presenting 12 to 48 hours from onset of symptoms. *JAMA* 301(5):487–488, 2009.
63. Steg PG, Thuaire C, Himbert D, et al: DECOPI (DEsobstruction COronaire en Post-Infarctus): a randomized multi-centre trial of occluded artery angioplasty after acute myocardial infarction. *Eur Heart J* 25(24):2187–2194, 2004.
64. Hochman JS, Lamas GA, Buller CE, et al: Coronary intervention for persistent occlusion after myocardial infarction. *N Engl J Med* 355(23):2395–2407, 2006.
65. Dalby M, Bouzamondo A, Lechat P, Montalescot G: Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. *Circulation* 108(15): 1809–1814, 2003.
66. Zijlstra F: Angioplasty vs thrombolysis for acute myocardial infarction: a quantitative overview of the effects of interhospital transportation. *Eur Heart J* 24(1):21–23, 2003.
67. Dobrzycki S, Kralisz P, Nowak K, et al: Transfer with GP IIb/IIIa inhibitor tirofiban for primary percutaneous coronary intervention vs. on-site thrombolysis in patients with ST-elevation myocardial infarction (STEMI): a randomized open-label study for patients admitted to community hospitals. *Eur Heart J* 28(20): 2438–2448, 2007.
68. Widimsky P, Bilkova D, Penicka M, et al: Long-term outcomes of patients with acute myocardial infarction presenting to hospitals without catheterization laboratory and randomized to immediate thrombolysis or interhospital transport for primary percutaneous coronary intervention. Five years' follow-up of the PRAGUE-2 Trial. *Eur Heart J* 28(6):679–684, 2007.
69. Stenestrand U, Lindback J, Wallentin L: RIKS-HIA Registry: Long-term outcome of primary percutaneous coronary intervention vs prehospital and in-hospital thrombolysis for patients with ST-elevation myocardial infarction. *JAMA* 296(14):1749–1756, 2006.
70. Wang TY, Peterson ED, Ou FS, et al: Door-to-balloon times for patients with ST-segment elevation myocardial infarction requiring interhospital transfer for primary percutaneous coronary intervention: a report from the National Cardiovascular Data Registry. *Am Heart J* 161(1):76–83 e1, 2011.
71. Pinto DS, Kirtane AJ, Nallamothu BK, et al: Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. *Circulation* 114(19):2019–2025, 2006.
72. De Luca G, Cassetti E, Marino P: Percutaneous coronary intervention-related time delay, patient's risk profile, and survival benefits of primary angioplasty vs lytic therapy in ST-segment elevation myocardial infarction. *Am J Emerg Med* 27(6):712–719, 2009.
73. Pinto DS, Frederick PD, Chakrabarti AK, et al: Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. *Circulation* 124(23):2512–2521, 2011.
74. Henry TD, Atkins JM, Cunningham MS, et al: ST-segment elevation myocardial infarction: recommendations on triage of patients to heart attack centers: Is it time for a national policy for the treatment of ST-segment elevation myocardial infarction? *J Am Coll Cardiol* 47(7):1339–1345, 2006.
75. Wang TY, Magid DJ, Ting HH, et al: The quality of antiplatelet and anticoagulant medication administration among ST-segment elevation myocardial infarction patients transferred for primary percutaneous coronary intervention. *Am Heart J* 167(6):833–839, 2014.
76. Wang TY, Nallamothu BK, Krumholz HM, et al: Association of door-in to door-out time with reperfusion delays and outcomes among patients transferred for primary percutaneous coronary intervention. *JAMA* 305(24):2540–2547, 2011.
77. Nallamothu BK, Bates ER, Wang Y, et al: Driving times and distances to hospitals with percutaneous coronary intervention in the United States: implications for prehospital triage of patients with ST-elevation myocardial infarction. *Circulation* 113(9):1189–1195, 2006.
78. Kastrati A, Mehilli J, Schlotterbeck K, et al: Early administration of reteplase plus abciximab vs abciximab alone in patients with acute myocardial infarction referred for percutaneous coronary intervention: a randomized controlled trial. *JAMA* 291(8):947–954, 2004.
79. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) investigators: Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 367(9510):569–578, 2006.
80. Keeley EC, Boura JA, Grines CL: Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. *Lancet* 367(9510):579–588, 2006.
81. Ellis SG, Tendera M, de Belder MA, et al: Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med* 358(21):2205–2217, 2008.
82. Armstrong PW: WEST Steering Committee: A comparison of pharmacologic therapy with/without timely coronary intervention vs. primary percutaneous intervention early after ST-elevation myocardial infarction: the WEST (Which Early ST-elevation myocardial infarction Therapy) study. *Eur Heart J* 27(13):1530–1538, 2006.
83. Fernandez-Aviles F, Alonso JJ, Pena G, et al: Primary angioplasty vs. early routine post-fibrinolysis angioplasty for acute myocardial infarction with ST-segment elevation: the GRACIA-2 noninferiority, randomized, controlled trial. *Eur Heart J* 28(8): 949–960, 2007.
84. Fernandez-Aviles F, Alonso JJ, Castro-Beiras A, et al: Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. *Lancet* 364(9439):1045–1053, 2004.
85. Scheller B, Hennen B, Hammer B, et al: Beneficial effects of immediate stenting after thrombolysis in acute myocardial infarction. *J Am Coll Cardiol* 42(4):634–641, 2003.
86. Di Mario C, Dudek D, Piscione F, et al: Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised, multicentre trial. *Lancet* 371(9612):559–568, 2008.
87. Cantor WJ, Fitchett D, Borgundvaag B, et al: Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Engl J Med* 360(26):2705–2718, 2009.
88. Borgia F, Goodman SG, Halvorsen S, et al: Early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST-segment elevation myocardial infarction: a meta-analysis. *Eur Heart J* 31(17):2156–2169, 2010.
89. Desch S, Eitel I, Rahimi K, et al: Timing of invasive treatment after fibrinolysis in ST elevation myocardial infarction–a meta-analysis of immediate or early routine versus deferred or ischemia-guided randomised controlled trials. *Heart* 96(21): 1695–1702, 2010.
90. D'Souza SP, Mamas MA, Fraser DG, Fath-Ordoubadi F: Routine early coronary angioplasty versus ischaemia-guided angioplasty after thrombolysis in acute ST-elevation myocardial infarction: a meta-analysis. *Eur Heart J* 32(8):972–982, 2011.
91. Armstrong PW, Gershlick AH, Van de Werf F, Group SS: Fibrinolysis or primary PCI in myocardial infarction. *N Engl J Med* 369(3):280–281, discussion page 281, 2013.
92. Dianati Maleki N, Van de Werf F, Goldstein P, et al: Aborted myocardial infarction in ST-elevation myocardial infarction: insights from the STrategic Reperfusion Early After Myocardial infarction trial. *Heart* 100(19):1543–1549, 2014.

93. Brosius FC, 3rd, Roberts WC: Significance of coronary arterial thrombus in transmural acute myocardial infarction. A study of 54 necropsy patients. *Circulation* 63(4):810–816, 1981.
94. Richardson SG, Allen DC, Morton P, et al: Pathological changes after intravenous streptokinase treatment in eight patients with acute myocardial infarction. *Br Heart J* 61(5):390–395, 1989.
95. Wijeysundera HC, Vijayaraghavan R, Nallamothu BK, et al: Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomized trials. *J Am Coll Cardiol* 49(4):422–430, 2007.
96. Schömig A, Ndrepepa G, Mehilli J, et al: A randomized trial of coronary stenting versus balloon angioplasty as a rescue intervention after failed thrombolysis in patients with acute myocardial infarction. *J Am Coll Cardiol* 44(10):2073–2079, 2004.
97. Sutton AG, Campbell PG, Graham R, et al: A randomized trial of rescue angioplasty versus a conservative approach for failed fibrinolysis in ST-segment elevation myocardial infarction: the Middlesbrough Early Revascularization to Limit INfarction (MERLIN) trial. *J Am Coll Cardiol* 44(2):287–296, 2004.
98. Gershlick AH, Stephens-Lloyd A, Hughes S, et al: Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 353(26):2758–2768, 2005.
99. Carver A, Rafelt S, Gershlick AH, et al: Longer-term follow-up of patients recruited to the REACT (Rescue Angioplasty Versus Conservative Treatment or Repeat Thrombolysis) trial. *J Am Coll Cardiol* 54(2):118–126, 2009.
100. De Luca G, Suryapranata H, Stone GW, et al: Coronary stenting versus balloon angioplasty for acute myocardial infarction: a meta-regression analysis of randomized trials. *Int J Cardiol* 126(1):37–44, 2008.
101. Mehta RH, Harjai KJ, Cox DA, et al: Comparison of coronary stenting versus conventional balloon angioplasty on five-year mortality in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol* 96(7):901–906, 2005.
102. Joner M, Finn AV, Farb A, et al: Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 48(1):193–202, 2006.
103. De Luca G, Dirksen MT, Spaulding C, et al: Drug-eluting vs bare-metal stents in primary angioplasty: a pooled patient-level meta-analysis of randomized trials. *Arch Intern Med* 172(8):611–621, discussion 621–622, 2012.
104. Kalesan B, Pilgrim T, Heinimann K, et al: Comparison of drug-eluting stents with bare metal stents in patients with ST-segment elevation myocardial infarction. *Eur Heart J* 33(8):977–987, 2012.
105. Windecker S, Bax JJ, Myat A, et al: Future treatment strategies in ST-segment elevation myocardial infarction. *Lancet* 382(9892):644–657, 2013.
106. Raber L, Kelbaek H, Ostojic M, et al: Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. *JAMA* 308(8):777–787, 2012.
107. Raber L, Kelbaek H, Taniwaki M, et al: Biolimus-eluting stents with biodegradable polymer versus bare-metal stents in acute myocardial infarction: two-year clinical results of the COMFORTABLE AMI Trial. *Circ Cardiovasc Interv* 7(3):355–364, 2014.
108. Sabate M, Cequier A, Iñiguez A, et al: Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet* 380(9852):1482–1490, 2012.
109. Palmerini T, Biondi-Zoccai G, Della Riva D, et al: Clinical outcomes with drug-eluting and bare-metal stents in patients with ST-segment elevation myocardial infarction: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol* 62(6):496–504, 2013.
110. Belkacemi A, Agostoni P, Nathoe HM, et al: First results of the DEB-AMI (drug eluting balloon in acute ST-segment elevation myocardial infarction) trial: a multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug-eluting stent in primary percutaneous coronary intervention with 6-month angiographic, intravascular, functional, and clinical outcomes. *J Am Coll Cardiol* 59(25):2327–2337, 2012.
111. Palmerini T, Biondi-Zoccai G, Della Riva D, et al: Clinical outcomes with bioabsorbable polymer- versus durable polymer-based drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol* 63(4):299–307, 2014.
112. Loubeyre C, Morice MC, Lefevre T, et al: A randomized comparison of direct stenting with conventional stent implantation in selected patients with acute myocardial infarction. *J Am Coll Cardiol* 39(1):15–21, 2002.
113. Mockel M, Vollert J, Lansky AJ, et al: Comparison of direct stenting with conventional stent implantation in acute myocardial infarction. *Am J Cardiol* 108(12):1697–1703, 2011.
114. Dziewierz A, Siudak Z, Rakowski T, et al: Impact of direct stenting on outcome of patients with St-elevation myocardial infarction transferred for primary percutaneous coronary intervention (from the EUROTRANSFER registry). *Catheter Cardiovasc Interv* 84(6):925–931, 2014.
115. Jolly SS, Yusuf S, Cairns J, et al: Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet* 377(9775):1409–1420, 2011.
116. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al: Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *J Am Coll Cardiol* 60(24):2481–2489, 2012.
117. Bernat I, Horak D, Stasek J, et al: ST-segment elevation myocardial infarction treated by radial or femoral approach in a multicenter randomized clinical trial: the STEMI-RADIAL trial. *J Am Coll Cardiol* 63(10):964–972, 2014.
118. Wimmer NJ, Cohen DJ, Wasfy JH, et al: Delay in reperfusion with transradial percutaneous coronary intervention for ST-elevation myocardial infarction: Might some delays be acceptable? *Am Heart J* 168(1):103–109, 2014.
119. Valgimigli M, Saia F, Guastaroba P, et al: Transradial versus transfemoral intervention for acute myocardial infarction: a propensity score-adjusted and -matched analysis from the REAL (REgistro regionale AngiopLastiche dell'Emilia-Romagna) multicenter registry. *JACC Cardiovasc Interv* 5(1):23–35, 2012.
120. Baklanov DV, Kaltenbach LA, Marso SP, et al: The prevalence and outcomes of transradial percutaneous coronary intervention for ST-segment elevation myocardial infarction: analysis from the National Cardiovascular Data Registry (2007 to 2011). *J Am Coll Cardiol* 61(4):420–426, 2013.
121. Stone GW, Webb J, Cox DA, et al: Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. *JAMA* 293(9):1063–1072, 2005.
122. Kumbhani DJ, Bavry AA, Desai MY, et al: Role of aspiration and mechanical thrombectomy in patients with acute myocardial infarction undergoing primary angioplasty: an updated meta-analysis of randomized trials. *J Am Coll Cardiol* 62(16):1409–1418, 2013.
123. Svilaas T, Vlaar PJ, van der Horst IC, et al: Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med* 358(6):557–567, 2008.
124. Sardella G, Mancone M, Bucciarelli-Ducci C, et al: Thrombus aspiration during primary percutaneous coronary intervention improves myocardial reperfusion and reduces infarct size: the EXPIRA (thrombectomy with export catheter in infarct-related artery during primary percutaneous coronary intervention) prospective, randomized trial. *J Am Coll Cardiol* 53(4):309–315, 2009.
125. Frobert O, Lagerqvist B, Olivecrona GK, et al: Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 369(17):1587–1597, 2013.
126. Kumbhani DJ, Bavry AA, Desai MY, et al: Aspiration thrombectomy in patients undergoing primary angioplasty: Totality of data to 2013. *Catheter Cardiovasc Interv* 84(6):973–977, 2014.
127. Stone GW, Webb J, Cox DA, et al: Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. *JAMA* 293(9):1063–1072, 2005.
128. Gick M, Jander N, Bestehorn HP, et al: Randomized evaluation of the effects of filter-based distal protection on myocardial perfusion and infarct size after primary percutaneous catheter intervention in myocardial infarction with and without ST-segment elevation. *Circulation* 112(10):1462–1469, 2005.
129. Kelbaek H, Terkelsen CJ, Helqvist S, et al: Randomized comparison of distal protection versus conventional treatment in primary percutaneous coronary intervention: the drug elution and distal protection in ST-elevation myocardial infarction (DEDICATION) trial. *J Am Coll Cardiol* 51(9):899–905, 2008.
130. Montalescot G, Zeymer U, Silvain J, et al: Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. *Lancet* 378(9792):693–703, 2011.
131. Silvain J, Beygui F, Barthelemy O, et al: Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. *BMJ* 344:e553, 2012.
132. Stone GW, Witzenbichler B, Guagliumi G, et al: Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 358(21):2218–2230, 2008.
133. Stone GW, Witzenbichler B, Guagliumi G, et al: Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. *Lancet* 377(9784):2193–2204, 2011.
134. Stone GW, Clayton T, Deliargyris EN, et al: Reduction in cardiac mortality with bivalirudin in patients with and without major bleeding: The HORIZONS-AMI trial (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction). *J Am Coll Cardiol* 63(1):15–20, 2014.
135. Dangas GD, Mehran R, Nikolsky E, et al: Effect of switching antithrombin agents for primary angioplasty in acute myocardial infarction: the HORIZONS-SWITCH analysis. *J Am Coll Cardiol* 57(23):2309–2316, 2011.
136. Steg PG, van 't Hof A, Hamm CW, et al: Bivalirudin started during emergency transport for primary PCI. *N Engl J Med* 369(23):2207–2217, 2013.
137. Schulz S, Richardt G, Laugwitz KL, et al: Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. *Eur Heart J* 35(34):2285–2294, 2014.
138. Shahzad A, Kemp I, Mars C, et al: Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet* 384(9957):1849–1858, 2014.
139. Sabatine MS, Cannon CP, Gibson CM, et al: Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA* 294(10):1224–1232, 2005.
140. Mehta SR, Tanguay JF, Eikelboom JW, et al: Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet* 376(9748):1233–1243, 2010.
141. Bellemain-Appaix A, O'Connor SA, Silvain J, et al: Association of clopidogrel pretreatment with mortality, cardiovascular events, and major bleeding among patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *JAMA* 308(23):2507–2516, 2012.
142. Wiviott SD, Braunwald E, McCabe CH, et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 357(20):2001–2015, 2007.
143. Montalescot G, Wiviott SD, Braunwald E, et al: Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet* 373(9665):723–731, 2009.
144. Steg PG, James S, Harrington RA, et al: Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation* 122(21):2131–2141, 2010.
145. Montalescot G, Antoniucci D, Kastrati A, et al: Abciximab in primary coronary stenting of ST-elevation myocardial infarction: a European meta-analysis on individual patients' data with long-term follow-up. *Eur Heart J* 28(4):443–449, 2007.
146. De Luca G, Gibson CM, Bellandi F, et al: Early glycoprotein IIb-IIIa inhibitors in primary angioplasty (EGYPT) cooperation: an individual patient data meta-analysis. *Heart* 94(12):1548–1558, 2008.
147. Mehilli J, Kastrati A, Schulz S, et al: Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. *Circulation* 119(14):1933–1940, 2009.
148. ten Berg JM, van 't Hof AW, Dill T, et al: Effect of early, prehospital initiation of high bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short- and long-term clinical outcome. *J Am Coll Cardiol* 55(22):2446–2455, 2010.
149. Gu YL, Kampinga MA, Wieringa WG, et al: Intracoronary versus intravenous administration of abciximab in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with thrombus aspiration: the comparison of intracoronary versus intravenous abciximab administration during emergency reperfusion of ST-segment elevation myocardial infarction (CICERO) trial. *Circulation* 122(25):2709–2717, 2010.
150. Thiele H, Wohrle J, Hambrecht R, et al: Intracoronary versus intravenous bolus abciximab during primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction: a randomised trial. *Lancet* 379(9819):923–931, 2012.
151. Eitel I, Wohrle J, Suenkel H, et al: Intracoronary compared with intravenous bolus abciximab application during primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: cardiac magnetic resonance substudy of the AIDA STEMI trial. *J Am Coll Cardiol* 61(13):1447–1454, 2013.
152. Yusuf S, Mehta SR, Chrolavicius S, et al: Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 295(13):1519–1530, 2006.
153. Ndrepepa G, Tiroch K, Fusaro M, et al: 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. *J Am Coll Cardiol* 55(21):2383–2389, 2010.
154. Thuny F, Lairez O, Roubille F, et al: Post-conditioning reduces infarct size and edema in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 59(24):2175–2181, 2012.
155. Sorensson P, Saleh N, Bouvier F, et al: Effect of postconditioning on infarct size in patients with ST elevation myocardial infarction. *Heart* 96(21):1710–1715, 2010.
156. Botker HE, Kharbanda R, Schmidt MR, et al: Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet* 375(9716):727–734, 2010.
157. Limalanathan S, Andersen GO, Klow NE, et al: Effect of ischemic postconditioning on infarct size in patients with ST-elevation myocardial infarction treated by primary PCI results of the POSTEMI (POstconditioning in ST-Elevation Myocardial Infarction) randomized trial. *J Am Heart Assoc* 3(2):e000679, 2014.
158. Khalili H, Patel VG, Mayo HG, et al: Surrogate and clinical outcomes following ischemic postconditioning during primary

percutaneous coronary intervention of St-segment elevation myocardial infarction: A meta-analysis of 15 randomized trials. *Catheter Cardiovasc Interv* 84(6):978–986, 2014.
159. Khan AR, Bin Abdulhak AA, Alastal Y, et al: Cardioprotective role of ischemic postconditioning in acute myocardial infarction: a systematic review and meta-analysis. *Am Heart J* 168(4): 512–521 e4, 2014.
160. Patel MR, Smalling RW, Thiele H, et al: Intra-aortic balloon counterpulsation and infarct size in patients with acute anterior myocardial infarction without shock: the CRISP AMI randomized trial. *JAMA* 306(12):1329–1337, 2011.
161. Wohrle J, Merkle N, Kunze M, et al: Effect of bivalirudin compared with unfractionated heparin plus abciximab on infarct size and myocardial recovery after primary percutaneous coronary intervention: the HORIZONS-AMI CMRI substudy. *Catheter Cardiovasc Interv* 79(7):1083–1089, 2012.
161a. Stone GW, Maehara A, Witzenbichler B, et al: Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. *JAMA* 307(17):1817–1826, 2012.
162. Mukamal KJ, Mittleman MA, Maclure M, et al: Recent aspirin use is associated with smaller myocardial infarct size and lower likelihood of Q-wave infarction. *Am Heart J* 137(6):1120–1128, 1999.
163. Roubille F, Lairez O, Mewton N, et al: Cardioprotection by clopidogrel in acute ST-elevated myocardial infarction patients: a retrospective analysis. *Basic Res Cardiol* 107(4):275, 2012.
164. Sugidachi A, Yamaguchi S, Jakubowski JA, et al: Selective blockade of P2Y12 receptors by prasugrel inhibits myocardial infarction induced by thrombotic coronary artery occlusion in rats. *J Cardiovasc Pharmacol* 58(3):329–334, 2011.
165. Desmet W, Bogaert J, Dubois C, et al: High-dose intracoronary adenosine for myocardial salvage in patients with acute ST-segment elevation myocardial infarction. *Eur Heart J* 32(7): 867–877, 2011.
166. Singh M, Shah T, Khosla K, et al: Safety and efficacy of intracoronary adenosine administration in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: a meta-analysis of randomized controlled trials. *Ther Adv Cardiovasc Dis* 6(3):101–114, 2012.
167. Siddiqi N, Neil C, Bruce M, et al: Intravenous sodium nitrite in acute ST-elevation myocardial infarction: a randomized controlled trial (NIAMI). *Eur Heart J* 35(19):1255–1262, 2014.
168. Kitakaze M, Asakura M, Kim J, et al: Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials. *Lancet* 370(9597):1483–1493, 2007.
169. Iwakura K, Ito H, Okamura A, et al: Nicorandil treatment in patients with acute myocardial infarction: a meta-analysis. *Circ J* 73(5):925–931, 2009.
170. Ibanez B, Macaya C, Sánchez-Brunete V, et al: Effect of early metoprolol on infarct size in ST-segment-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial. *Circulation* 128(14):1495–1503, 2013.
171. Bar FW, Tzivoni D, Dirksen MT, et al: Results of the first clinical study of adjunctive CAldaret (MCC-135) in patients undergoing primary percutaneous coronary intervention for ST-Elevation Myocardial Infarction: the randomized multicentre CASTEMI study. *Eur Heart J* 27(21):2516–2523, 2006.
172. Tzivoni D, Balkin J, Bar FW, et al: Effect of caldaret on the incidence of severe left ventricular dysfunction in patients with ST-elevation myocardial infarction undergoing primary coronary intervention. *Am J Cardiol* 103(1):1–4, 2009.
173. Piot C, Croisille P, Staat P, et al: Effect of cyclosporine on reperfusion injury in acute myocardial infarction. *N Engl J Med* 359(5):473–481, 2008.
174. Lim WY, Messow CM, Berry C: Cyclosporin variably and inconsistently reduces infarct size in experimental models of reperfused myocardial infarction: a systematic review and meta-analysis. *Br J Pharmacol* 165(7):2034–2043, 2012.
175. Armstrong PW, Granger CB, Adams PX, et al: Pexelizumab for acute ST-elevation myocardial infarction in patients undergoing primary percutaneous coronary intervention: a randomized controlled trial. *JAMA* 297(1):43–51, 2007.
176. Najjar SS, Rao SV, Melloni C, et al: Intravenous erythropoietin in patients with ST-segment elevation myocardial infarction: REVEAL: a randomized controlled trial. *JAMA* 305(18):1863–1872, 2011.
177. Voors AA, Belonje AM, Zijlstra F, et al: A single dose of erythropoietin in ST-elevation myocardial infarction. *Eur Heart J* 31(21):2593–2600, 2010.
178. Ludman AJ, Yellon DM, Hasleton J, et al: Effect of erythropoietin as an adjunct to primary percutaneous coronary intervention: a randomised controlled clinical trial. *Heart* 97(19):1560–1565, 2011.
179. Gao D, Ning N, Niu X, et al: Erythropoietin treatment in patients with acute myocardial infarction: a meta-analysis of randomized controlled trials. *Am Heart J* 164(5):715–727 e1, 2012.
180. Lincoff AM, Roe M, Aylward P, et al: Inhibition of delta-protein kinase C by delcasertib as an adjunct to primary percutaneous coronary intervention for acute anterior ST-segment elevation myocardial infarction: results of the PROTECTION AMI Randomized Controlled Trial. *Eur Heart J* 35(37):2516–2523, 2014.
181. Frohlich GM, Meier P, White SK, et al: Myocardial reperfusion injury: looking beyond primary PCI. *Eur Heart J* 34(23):1714–1722, 2013.
182. O'Neill WW, Martin JL, Dixon SR, et al: Acute Myocardial Infarction with Hyperoxemic Therapy (AMIHOT): a prospective, randomized trial of intracoronary hyperoxemic reperfusion after percutaneous coronary intervention. *J Am Coll Cardiol* 50(5):397–405, 2007.
183. Stone GW, Martin JL, de Boer MJ, et al: Effect of supersaturated oxygen delivery on infarct size after percutaneous coronary intervention in acute myocardial infarction. *Circ Cardiovasc Interv* 2(5):366–375, 2009.
184. Gotberg M, Olivecrona GK, Engblom H, et al: Rapid short-duration hypothermia with cold saline and endovascular cooling before reperfusion reduces microvascular obstruction and myocardial infarct size. *BMC Cardiovasc Disord* 8:7, 2008.
185. Maeng M, Mortensen UM, Kristensen J, et al: Hypothermia during reperfusion does not reduce myocardial infarct size in pigs. *Basic Res Cardiol* 101(1):61–68, 2006.
186. Erlinge D, Gotberg M, Grines C, et al: A pooled analysis of the effect of endovascular cooling on infarct size in patients with ST-elevation myocardial infarction. *EuroIntervention* 8(12): 1435–1440, 2013.
187. Erlinge D, Gotberg M, Lang I, et al: Rapid endovascular catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. The CHILL-MI trial: a randomized controlled study of the use of central venous catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. *J Am Coll Cardiol* 63(18):1857–1865, 2014.
188. Takashima S, Tempel D, Duckers HJ: Current outlook of cardiac stem cell therapy towards a clinical application. *Heart* 99(23): 1772–1784, 2013.
189. Zimmet H, Porapakkham P, Porapakkham P, et al: Short- and long-term outcomes of intracoronary and endogenously mobilized bone marrow stem cells in the treatment of ST-segment elevation myocardial infarction: a meta-analysis of randomized control trials. *Eur J Heart Fail* 14(1):91–105, 2012.
190. Delewi R, Andriessen A, Tijssen JG, et al: Impact of intracoronary cell therapy on left ventricular function in the setting of acute myocardial infarction: a meta-analysis of randomised controlled clinical trials. *Heart* 99(4):225–232, 2013.
191. Delewi R, Hirsch A, Tijssen JG, et al: Impact of intracoronary bone marrow cell therapy on left ventricular function in the setting of ST-segment elevation myocardial infarction: a collaborative meta-analysis. *Eur Heart J* 35(15):989–998, 2014.
192. Traverse JH, Henry TD, Pepine CJ, et al: Effect of the use and timing of bone marrow mononuclear cell delivery on left ventricular function after acute myocardial infarction: the TIME randomized trial. *JAMA* 308(22):2380–2389, 2012.
193. Zohlnhofer D, Dibra A, Koppara T, et al: Stem cell mobilization by granulocyte colony-stimulating factor for myocardial recovery after acute myocardial infarction: a meta-analysis. *J Am Coll Cardiol* 51(15):1429–1437, 2008.
194. Moazzami K, Roohi A, Moazzami B: Granulocyte colony stimulating factor therapy for acute myocardial infarction. *Cochrane Database Syst Rev* (5):CD008844, 2013.
195. Henry TD, Sharkey SW, Burke MN, et al: A regional system to provide timely access to percutaneous coronary intervention for ST-elevation myocardial infarction. *Circulation* 116(7):721–728, 2007.
196. Lettieri C, Savonitto S, De Servi S, et al: Emergency percutaneous coronary intervention in patients with ST-elevation myocardial infarction complicated by out-of-hospital cardiac arrest: early and medium-term outcome. *Am Heart J* 157(3):569–575 e1, 2009.
197. Hazinski MF, Nolan JP, Billi JE, et al: Part 1: Executive summary: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation* 122(16 Suppl 2):S250–S275, 2010.
198. Kunadian V, Bawamia B, Maznyczka A, et al: Outcomes following primary percutaneous coronary intervention in the setting of cardiac arrest: A registry database study. *Eur Heart J Acute Cardiovasc Care* 2014. [Epub ahead of print].
199. Kolte D, Khera S, Aronow WS, et al: Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. *J Am Heart Assoc* 3(1):e000590, 2014.
200. Hochman JS, Sleeper LA, Webb JG, et al: Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *JAMA* 295(21):2511–2515, 2006.
201. Alexander JH, Reynolds HR, Stebbins AL, et al: Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: the TRIUMPH randomized controlled trial. *JAMA* 297(15):1657–1666, 2007.
202. Thiele H, Zeymer U, Neumann FJ, et al: Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. *Lancet* 382(9905):1638–1645, 2013.
203. Sorita A, Ahmed A, Starr SR, et al: Off-hour presentation and outcomes in patients with acute myocardial infarction: systematic review and meta-analysis. *BMJ* 348:f7393, 2014.
204. de Boer MJ, Ottervanger JP, van 't Hof AW, et al: Reperfusion therapy in elderly patients with acute myocardial infarction: a randomized comparison of primary angioplasty and thrombolytic therapy. *J Am Coll Cardiol* 39(11):1723–1728, 2002.
205. Grines CL: *A prospective randomized trial of primary angioplasty and thrombolytic therapy in elderly patients with acute myocardial infarction (SENIOR-PAMI). Presented at Transcatheter Cardiovascular Therapeutics*, Washington, DC, 2005.
206. Bueno H, Betriu A, Heras M, et al: Primary angioplasty vs. fibrinolysis in very old patients with acute myocardial infarction: TRIANA (TRatamiento del Infarto Agudo de miocardio eN Ancianos) randomized trial and pooled analysis with previous studies. *Eur Heart J* 32(1):51–60, 2011.
207. Khera S, Kolte D, Palaniswamy C, et al: ST-elevation myocardial infarction in the elderly–temporal trends in incidence, utilization of percutaneous coronary intervention and outcomes in the United States. *Int J Cardiol* 168(4):3683–3690, 2013.
208. Dziewierz AS, Rakowski Z, Zasada T, et al: Impact of multivessel coronary artery disease and noninfarct-related artery revascularization on outcome of patients with ST-elevation myocardial infarction transferred for primary percutaneous coronary intervention (from the EUROTRANSFER Registry). *Am J Cardiol* 106(3):342–347, 2010.
209. Sorajja P, Gersh BJ, Cox DA, et al: Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. *Eur Heart J* 28(14):1709–1716, 2007.
210. Vlaar PJ, Mahmoud KD, Holmes DR, Jr, et al: Culprit vessel only versus multivessel and staged percutaneous coronary intervention for multivessel disease in patients presenting with ST-segment elevation myocardial infarction: a pairwise and network meta-analysis. *J Am Coll Cardiol* 58(7):692–703, 2011.
211. Bagai A, Thavendiranathan P, Sharieff W, et al: Non-infarct-related artery revascularization during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a systematic review and meta-analysis. *Am Heart J* 166(4):684–693 e1, 2013.
212. Bainey KR, Mehta SR, Lai T, Welsh RC: Complete vs culprit-only revascularization for patients with multivessel disease undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a systematic review and meta-analysis. *Am Heart J* 167(1):1–14 e2, 2014.
213. Wald DS, Morris JK, Wald NJ, et al: Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 369(12): 1115–1123, 2013.
214. Ntalianis A, Sels JW, Davidavicius G, et al: Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv* 3(12):1274–1281, 2010.
215. Dehmer GJ, Blankenship JC, Cilingiroglu M, et al: SCAI/ACC/AHA Expert Consensus Document: 2014 Update on Percutaneous Coronary Intervention Without On-Site Surgical Backup. *J Am Coll Cardiol* 63(23):2624–2641, 2014.
216. Singh M, Holmes DR, Jr, Dehmer GJ, et al: Percutaneous coronary intervention at centers with and without on-site surgery: a meta-analysis. *JAMA* 306(22):2487–2494, 2011.
217. Zia MI, Wijeysundera HC, Tu JV, et al: Percutaneous coronary intervention with vs without on-site cardiac surgery backup: a systematic review and meta-analysis. *Can J Cardiol* 27(5):664, e9–e16, 2011.
218. Carrick D, Oldroyd KG, McEntegart M, et al: A randomized trial of deferred stenting versus immediate stenting to prevent no- or slow-reflow in acute ST-segment elevation myocardial infarction (DEFER-STEMI). *J Am Coll Cardiol* 63(20):2088–2098, 2014.

21 Interventions in Cardiogenic Shock

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KEY POINTS

- Cardiogenic shock (CS) remains the leading cause of death among patients hospitalized with acute myocardial infarction (AMI).
- Left ventricular (LV) dysfunction accounts for the majority of CS in AMI patients. Early restoration of perfusion to the territory supplied by the infarct-related artery is of paramount importance in preventing CS and changing outcomes once it has developed.
- The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial and registry demonstrated the mortality benefit of early, immediate revascularization compared with medical stabilization.
- Major predictors of improved outcomes with percutaneous coronary intervention (PCI) in CS are time to reperfusion, achievement of vessel patency, and increase in thrombolysis in myocardial infarction (TIMI) flow grade.
- The majority of patients who present with CS have multivessel disease. Interventions on non–infarct-related artery (IRA) lesions may be beneficial. Patients with coronary anatomy not deemed suitable for PCI should be surgically revascularized.
- CS is a treatable illness with a reasonable chance of recovery in the primary PCI era. An early invasive approach can increase both short- and long-term survival, and survivors often regain an excellent quality of life.

BACKGROUND

The combination of a systolic blood pressure less than 90 mm Hg, elevated intracardiac filling pressures, and target organ damage due to cardiac dysfunction defines CS.[1] Early case series of CS revealed an in-hospital mortality approaching 80%.[2] Advances in intravenous (IV) drug therapy, systems of care, newer circulatory support devices, and more aggressive attempts at coronary revascularization have all led to an improvement in survival, but CS continues to have an in-hospital mortality approaching 50%. To understand which therapies might benefit patients with CS, it is necessary to review the pathophysiology and examine in detail the trials of drugs, circulatory support devices, and PCI.

PATHOPHYSIOLOGY

CS is a state of end-organ hypoperfusion caused by cardiac failure. Manifestations may include cold extremities, decreased urine output (less than 30 mL/hr), alteration in mental status, or both in the setting of low systemic arterial blood pressure. Hemodynamically, CS is characterized by low cardiac output and systemic arterial hypotension in the setting of normal or elevated LV filling pressure.

LV pump failure is the primary insult in most forms of CS. LV dysfunction may reflect new irreversible injury, reversible ischemia, damage from prior infarction, or a combination of these. Ventricular pump failure is caused by both systolic and diastolic dysfunction (Fig. 21-1). *Systolic dysfunction* results in a decreased stroke volume and resultant decreased cardiac output, which clinically presents as a lower blood pressure. The body's response is to attempt to raise the blood pressure by increasing the heart rate and peripheral vasoconstriction, which although temporarily effective also leads to increased myocardial work. The combination of the decreasing blood pressure, higher heart rate, and increased myocardial work leads to decreased coronary perfusion that is dependent on diastolic blood pressure and the diastolic filling period, which shortens as the heart rate increases. This decreased coronary perfusion leads to further myocardial ischemia. The lower blood pressure also triggers the renin-angiotensin-aldosterone system (RAAS), which results in fluid retention and peripheral vasoconstriction. These two effects, combined with the aforementioned tachycardia, further increase myocardial workload and contribute to worsening myocardial dysfunction. Finally, *diastolic dysfunction* leads to an increased LV end-diastolic pressure (LVEDP), which causes pulmonary congestion and hypoxia. The elevation in LVEDP and the lower diastolic blood pressure also contribute to lower coronary perfusion pressure. Both the hypoxia and the lower coronary perfusion pressure result in further myocardial ischemia.

Right ventricular (RV) dysfunction may also cause or contribute to CS. Predominant RV failure is rare and represents only 5% of cases of shock complicating AMI. RV failure may limit LV filling via a decrease in cardiac output, ventricular interdependence, or both. Shock caused by isolated RV dysfunction carries nearly as high a mortality risk as shock caused by LV failure. Additionally, the benefit of revascularization was similar in the SHOCK trial and in the registry in patients with primarily RV dysfunction versus primarily LV dysfunction.[3]

Mechanical complications such as ventricular septal rupture and papillary muscle rupture may lead to CS without severe reduction in LV function.[4,5] Ultimately, most patients with CS complicating AMI develop shock after presenting at the hospital. In some, medication use contributes to the development of shock. Classes of medications used to treat AMI that have been associated with shock include beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, nitrates, diuretics, and morphine.

CLINICAL PRESENTATION

Whereas severe cardiac dysfunction that might lead to CS has many causes, by far the most common cause of CS in hospitalized inpatients in the United States is coronary artery disease (CAD).[6] The incidence and mortality of patients with CS in the setting of AMI remained unchanged during the 1980s and 1990s despite a progressive decline in the overall mortality of AMI, the development of the coronary care unit and early defibrillation in the 1970s, the routine use of aspirin and beta-blockers in the 1980s, and the introduction of reperfusion therapy with thrombolytics in the early 1990s.[7-10] The mortality associated with an acute coronary syndrome (ACS) and CS started to improve with attempts at percutaneous revascularization (Figs. 21-2 and 21-3).[11,12]

The Shock Trial and the Shock Registry

The SHOCK trial is the largest randomized trial to compare early, immediate revascularization, accomplished by either PCI or coronary artery bypass grafting (CABG), and initial medical stabilization in the setting of CS complicating AMI, which includes reperfusion therapy with thrombolytics.[13,14] The SHOCK trial and its registry provide insight into the etiology, risk factors, hemodynamic profile, clinical

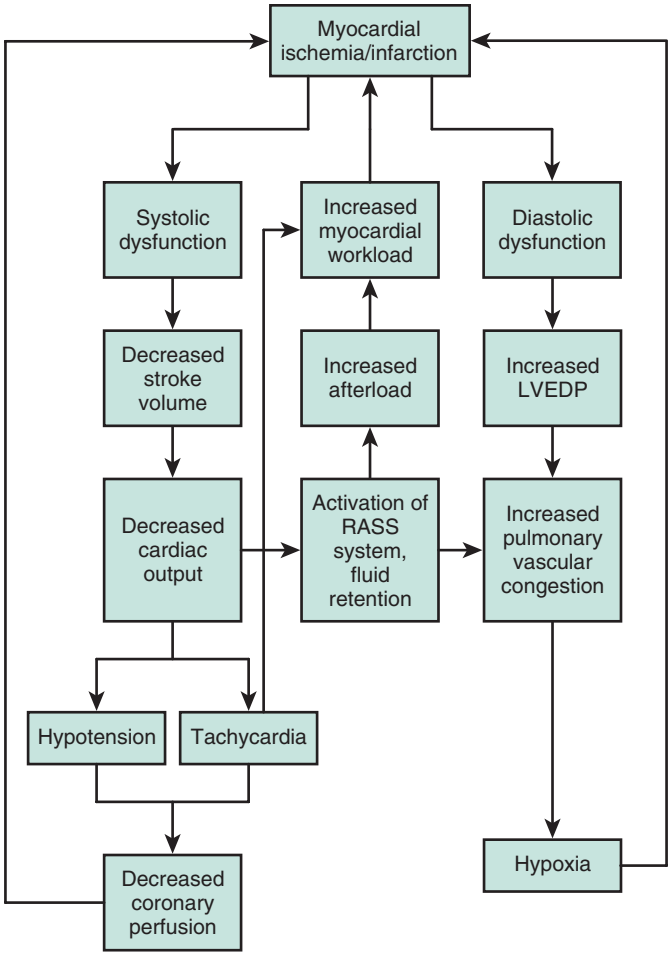


FIGURE 21-1 Progression of myocardial infarction to cardiogenic shock. *LVEDP,* Left ventricular end-diastolic pressure.

features, timing, and prognosis of CS complicating AMI. Eligible patients had to have an ST-segment elevation myocardial infarction (STEMI) complicated by shock caused by LV failure (mechanical and iatrogenic causes excluded), clinical and hemodynamic confirmation of CS, and shock developing within 36 hours of infarction. Intraaortic balloon pump (IABP) counterpulsation was permitted in both arms. Randomization had to occur within 12 hours of the diagnosis of shock. Patients with severe systemic illness, mechanical complications of MI, dilated cardiomyopathy (DCM), and severe valvular heart disease were excluded. A total of 302 patients were randomized in the SHOCK trial; a simultaneous registry prospectively enrolled patients who did *not* fulfill the eligibility criteria for entry into the trial. The SHOCK trial and registry included patients with mechanical

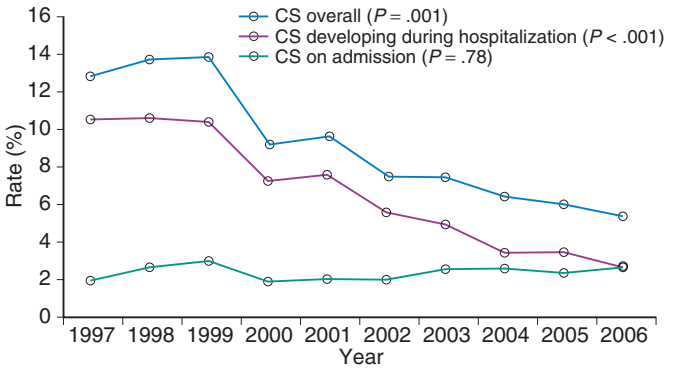


FIGURE 21-2 Temporal trends of cardiogenic shock (CS) from 1997 to 2006. These demonstrate a reduction in the overall incidence and development of CS during hospitalization in patients presenting with an acute coronary syndrome. (Redrawn from Jeger RV, Radovanovic D, Hunziker PR, et al: AMIS Plus Registry investigators: ten-year trends in the incidence and treatment of cardiogenic shock. *Ann Intern Med* 149:618-626, 2008.)

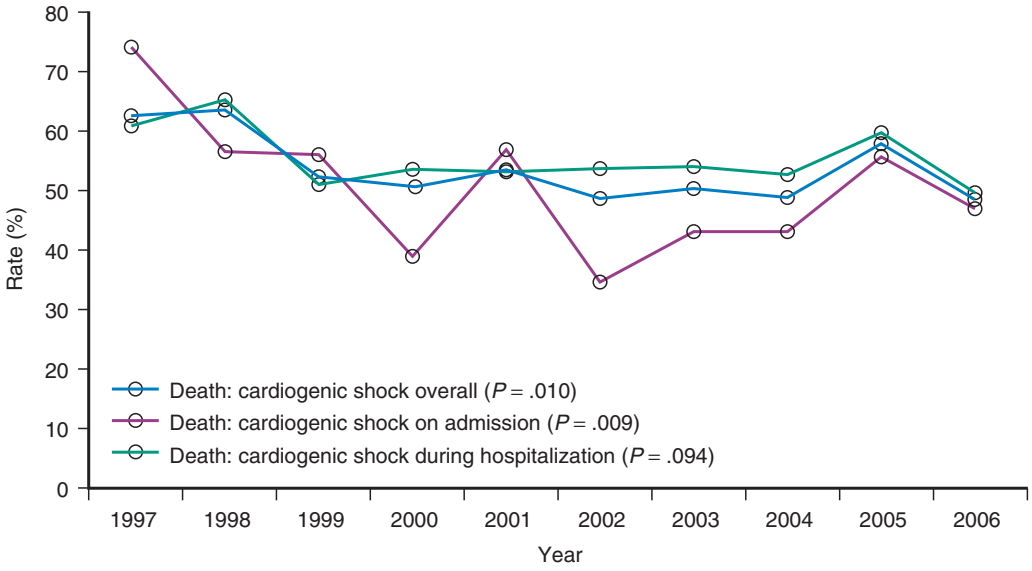


FIGURE 21-3 Temporal trends in mortality in patients with an acute coronary syndrome and cardiogenic shock (CS) from 1997 to 2006. The data demonstrate a reduction in the rate of death in CS overall, in patients with CS on admission, and in those developing CS during hospitalization. (Redrawn from Jeger RV, Radovanovic D, Hunziker PR, et al: AMIS Plus Registry investigators: ten-year trends in the incidence and treatment of cardiogenic shock. *Ann Intern Med* 149:618-626, 2008.)

complications of AMI, those with shock secondary to medications, those who presented more than 36 hours after infarction or who were not randomized within 12 hours of shock, and patients with shock diagnosed on clinical grounds alone (no hemodynamic confirmation). A total of 1190 patients were enrolled in this prospective, nonrandomized registry.

Etiology

Among all of the patients enrolled in the SHOCK trial and registry, 78.5% had predominant LV failure, most often with electrocardiography (ECG) findings consistent with recent anterior MI (58%). Shock complicating inferior MI was less common (34.4%) and was associated with a prior MI in one third of patients and a mechanical cause of shock in the remainder. Mechanical complications accounted for a minority of causes of CS. Severe mitral regurgitation was found in 6.9% of cases, ventricular septal rupture in 3.4%, RV infarction in 2.8%, and tamponade and rupture in 1.4%. Additionally, a minority of cases may be iatrogenic, induced by medications such as beta-blockers, calcium channel blockers, ACE inhibitors, diuretics, nitrates, and morphine. Risk factors for the development of CS in the context of AMI include older age, anterior MI, hypertension, diabetes mellitus, multivessel CAD, prior MI or angina, prior diagnosis of heart failure, STEMI, and left bundle branch block (LBBB).

Clinical Manifestations

Variability exists in the clinical manifestations of CS caused by LV failure in the setting of AMI.[15] Although the majority of patients with CS from predominant LV failure have classic findings of peripheral hypoperfusion and pulmonary congestion in the setting of arterial hypotension, approximately 25% of patients manifest hypotension and hypoperfusion in the *absence* of clinical pulmonary congestion. Consequently, the absence of pulmonary congestion on physical evaluation should not be considered a surrogate for low risk; clearly, LV compromise can coexist with a normal initial pulmonary evaluation. CS is diagnosed at presentation in only a minority of patients, but the majority of patients who ultimately develop shock following AMI do so within the first 24 hours. In a report from the SHOCK trial and registry that included CS patients with predominant LV failure, only 9% of the patients were diagnosed at presentation (median delay from MI symptom onset to hospital admission was 1.25 hr).[16] About half of the patients (46.6%) who developed CS did so within 6 hours of infarct onset. By 24 hours, 74.1% of the patients who developed CS were diagnosed, and late shock (onset >24 hr) occurred in 25.9% of the study patients. By implication, then, often a therapeutic window exists that could allow for intervention either before CS develops or early in its course. However, the median time from hospital admission to shock onset was only 4.6 hours, which indicates that this window is relatively narrow for many patients. Other studies have shown a higher incidence of late shock. These studies included CS caused by the mechanical complications of MI, which usually manifest later than CS caused by LV failure.[17] Angiographic data from patients enrolled in the SHOCK trial revealed extensive, severe CAD in the majority. Almost two thirds had three-vessel coronary disease, and 21% had left main CAD. The left anterior descending (LAD) coronary artery was the culprit vessel in 49% of the cases, and the right coronary artery (RCA) was the problem in 29%.[18] The mortality rates from CS in the modern era (50% to 60%) are lower than many clinicians believe and are far lower than the historic figures of 80% to 90%. However, mortality rates can range from 10% to 80%, depending on demographic, clinical, and hemodynamic factors. Specific factors include age, clinical signs of peripheral hypoperfusion, anoxic brain damage, left ventricular ejection fraction (LVEF), and stroke. Female sex does not appear to be an independent predictor of poor outcome, although hemodynamic data are predictive of short-term mortality but not long-term mortality; however, early revascularization remains the strongest predictor of outcome.

TABLE 21-1 Sensitiving and Specificity of Physical Exam Findings in Predicting a Pulmonary Capillary Wedge Pressure Greater Than 22 mm Hg

	Sensitivity (%)	Specificity (%)
Elevated jugular venous pressure	67	74
Rales	15	85
Ascites	21	88
Pedal edema	48	69
Orthopnea	40	60
Hepatomegaly	15	92

ESCAPE investigators: Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA* 294:1625-1633, 2005.

TREATMENT

Role of Right Heart Catheterization

With severe acute heart failure, it is sometimes difficult to accurately predict hemodynamic status or response to medical interventions.[19,20] For this reason, early right heart catheterization with a "leave-in" Swan-Ganz catheter may be considered in patients who are thought to be in CS. Not only does this allow for the quick and accurate diagnosis of a cardiac etiology, it also allows for subsequent tailored medical therapy. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial examined the role of routine right heart catheterization in acute decompensated heart failure patients and did not reveal a mortality difference between patients treated with invasive monitoring compared with those treated without invasive monitoring.[21] However, this study did not enroll all patients at each site who presented with acute decompensated heart failure, and it is possible that physicians may not have enrolled the sickest patients because of the possibility of randomization to no invasive monitoring. This study also confirmed the lack of sensitivity of physical exam findings at predicting the hemodynamic state of the CS patient (Table 21-1).

In addition to helping diagnose the etiology of shock and helping to tailor medical interventions, an invasive monitoring approach also allows for prediction of in-hospital outcomes. Both pulmonary capillary wedge pressure (PCWP) and cardiac output (CO) were shown to have independent prognostic valve in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial.[22] Another invasively derived parameter, the *cardiac power output* (CPO: mean arterial pressure [MAP] × CO ÷ 451) has been shown to be a powerful predictor of in-hospital mortality. In the SHOCK trial, CPO was the strongest independent hemodynamic predictor of in-hospital mortality (Fig. 21-4).[23] Based on these results, patients with a CPO of fewer than 0.53 have an in-hospital mortality that approaches 60%. Hemodynamics can help guide medical therapy and can help the clinician make decisions as to which patients might benefit from more aggressive treatment.

Inotropes

One of the first lines of medical treatment in a patient with CS is the initiation of IV inotropes and vasopressors despite the lack of evidence supporting this practice.[24] Frequently, the use of these medications may help to stabilize the hemodynamic state while further investigations and/or interventions can proceed (coronary revascularization, valve surgery, workup for ventricular assist devices, and/or orthotopic heart transplantation).

Two types of inotropes are currently available, phosphodiesterase inhibitors (milrinone) and catecholamines (dobutamine). Both work by increasing intracellular cyclic adenosine monophosphate (cAMP) but via two different mechanisms: *catecholamines* bind to extracellular

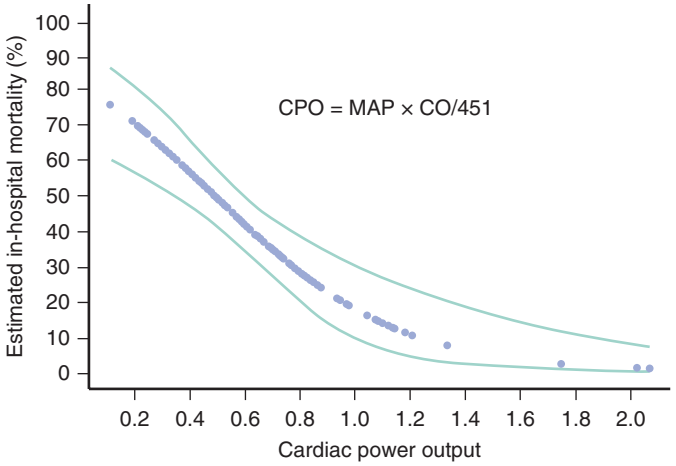
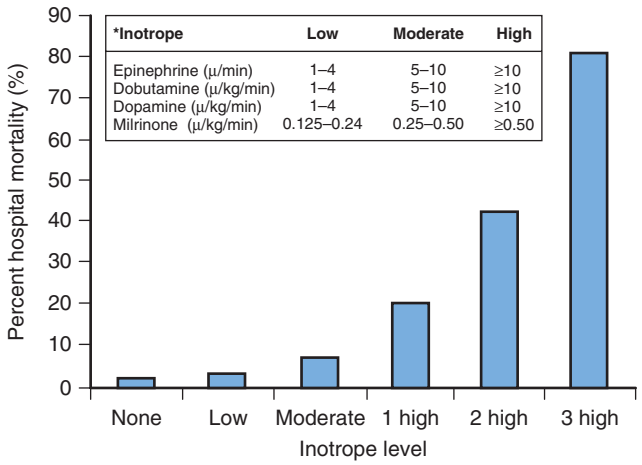


FIGURE 21-4 Cardiac power output (CPO) and in-hospital mortality. *CO,* Cardiac output; *MAP,* mean arterial pressure. (Fincke, R, Hochman JS, Lowe, AM, et al: Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. *J Am Coll Cardiol* 44:340-348, 2004.)



*Inotrope	Low	Moderate	High
Epinephrine (μ/min)	1–4	5–10	≥10
Dobutamine (μ/kg/min)	1–4	5–10	≥10
Dopamine (μ/kg/min)	1–4	5–10	≥10
Milrinone (μ/kg/min)	0.125–0.24	0.25–0.50	≥0.50

FIGURE 21-5 Mortality based on inotrope requirements. (Samuels LE, Kaufman MS, Thomas MP, et al: Doses and types of vasopressors and inotropes and increasing mortality. *J Card Surg* 14:288-293, 1999.)

adrenergic surface receptors and increase the production of cAMP, whereas *phosphodiesterase inhibitors* block the intracellular degradation of cAMP to adenosine monophosphate (AMP). Despite the widespread use of inotropes, both the Acute Decompensated Heart Failure National Registry (ADHERE) and the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study have examined the role of inotropes in severe heart failure and have shown that patients on long-term inotrope therapy have increased mortality.[25,26] These findings have led to a decrease in the use of inotropes routinely, although these medications are still frequently used in rapidly deteriorating CS patients.

When inotropes fail to stabilize the patient, the use of vasopressors such as dopamine, norepinephrine, and/or epinephrine can be used to maintain perfusion pressure, but the use of these medications has also not been proven to improve symptoms or survival. Comparative studies between these vasopressors have yielded mixed results. Prevailing dogma was that the use of dopamine was superior to the use of norepinephrine in patients with CS because of the greater action of dopamine on the β-receptors compared with the peripheral α-receptors.[27] This was thought to promote cardiac contractility and to not appreciably increase peripheral vasoconstriction, and thus afterload, when compared with the greater effect of norepinephrine on the peripheral α-receptors. However, in the Sepsis Occurrence in Acutely Ill Patients II (SOAP II trial), which compared dopamine with norepinephrine in the treatment of shock, the subset of CS patients treated with dopamine had a significantly higher mortality than the patients treated with norepinephrine.[28] These data are clouded by the fact that patients treated with norepinephrine were also more likely to receive concomitant treatment with dobutamine. It is possible that instead of the beneficial effects of one vasopressor over another, the use of a potent inotrope is responsible for the difference in survival.

Whereas there may be a paucity of data on the best use of inotropes and vasopressors in CS, the amount and types of IV drugs has long been shown to have a strong correlation with increased mortality (Fig. 21-5). Once a patient is on more than one inotrope or vasopressor, their in-hospital mortality is greater than 40%.[29] Likewise, trials comparing the use of surgical ventricular assist devices with ideal medical therapy (mostly inotropes and vasopressors) have also shown that medical therapy is inferior to definitive surgical LV-assist device implantation.[30] The use of inotropes and vasopressors should be limited to patients who can be stabilized while a precipitating cause is found and treated. Longer treatment or the use of these medications in end-stage heart failure patients without a reversible cause increases mortality and is inferior to mechanical surgical circulatory support.

Mechanical Support

Intraaortic balloon pump (IABP) counterpulsation has long been the mainstay of mechanical therapy for CS. Use of IABP improves coronary and peripheral perfusion and augments LV performance. The use of the IABP in CS was first described by Adrian Kantrowitz and colleagues in 1968,[31] and its use increased in the 1980s and 1990s, when studies on the use of IABP and thrombolysis in AMI revealed increased patency of the infarct-related artery and improved thrombolysis in myocardial infarction (TIMI) flow grade.[32,33] Despite the improvement in hemodynamics, no large randomized trial has shown any mortality advantage to the use of the IABP in CS, especially in the current PCI era. A large meta-analysis of several randomized trials and cohort studies on the use of IABP in STEMI complicated by CS showed no survival benefit to the use of the IABP.[34] Because of the conflicting prior data with the use of IABP during the thrombolysis era and the equivocal meta-analysis results, two subsequent large randomized trials of the IABP were conducted. The Intraaortic Balloon Pump in Cardiogenic Shock II (IABP–SHOCK II) trial randomized 595 patients who presented with an acute MI and CS to IABP and early revascularization versus early revascularization alone and revealed that the use of IABP does not decrease 12-month all-cause mortality.[35] In addition to not changing the mortality of patients in CS, the use of IABP in reducing infarct size was also questioned by the Counterpulsation to Reduce Infarct Size Pre-PCI for Acute Myocardial Infarction (CRISP-AMI) trial.[36] This trial randomized patients with STEMI to an IABP prior to PCI versus PCI alone to examine whether the use of the IABP would reduce infarct size, but it revealed no difference between the two groups in LV mass as measured by cardiac magnetic resonance imaging (CMRI). One good outcome in these two trials was that the use of IABP, although of questionable therapeutic benefit, was also not associated with significant side effects or complications. Small randomized trials of the use of IABP versus extracorporeal membrane oxygenation (ECMO) and peripheral LV-assist devices (TandemHeart [CardiacAssist, Pittsburgh, PA] and Impella [Abiomed, Danvers, MA]) have shown that the use of IABP is frequently safer than more invasive modalities and that the use of the IABP confers some hemodynamic benefit.[37] Based on the relative safety profile and the hemodynamic benefits, it is reasonable to use the IABP as part of a stepwise algorithm to treat CS patients who are not responsive to inotropes and to do so

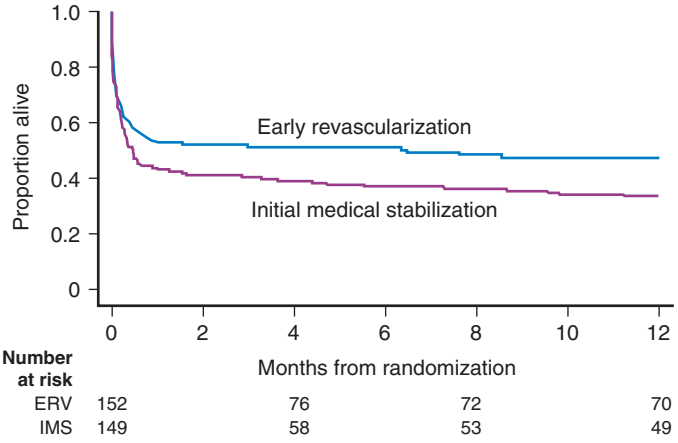


FIGURE 21-6 Survival rates among patients undergoing early revascularization (ERV) or initial medical stabilization (IMS) in the SHOCK trial. Both 6-month and 12-month survival rates were significantly higher in those randomized to early revascularization. (Redrawn from Hochman JS, Sleeper LA, White HD, et al, SHOCK investigators: One-year survival following early revascularization for cardiogenic shock. *JAMA* 285:190-192, 2001.)

prior to the initiation of more invasive mechanical circulatory support.[38] Further discussion of the role of ventricular-assist devices in the setting of AMI is discussed elsewhere in this textbook.

Reperfusion in Cardiogenic Shock

The only way to prevent CS in the setting of AMI appears to be very early reperfusion therapy. In a randomized trial of early, in-ambulance thrombolysis versus primary PCI (PPCI), the incidence of CS was 0% among patients assigned to prehospital thrombolysis and only 0.5% in the group randomized within 2 hours from symptom onset.[39] However, reperfusion with thrombolytics is inferior to revascularization with PCI in achieving sustained TIMI grade 3 flow in the infarct-related artery. The survival benefit of early revascularization in CS, reported in several observational studies, was demonstrated convincingly in the randomized SHOCK trial, which demonstrated lower 6-month and 12-month mortality rates with a strategy of early emergency revascularization compared with initial medical stabilization, which included IABP placement and thrombolytic therapy.[40-42] A 13% absolute increase was reported in 1-year survival in patients assigned to early revascularization (Fig. 21-6).[43] This corresponds to a number needed to treat (NNT) of fewer than eight patients to save one life. Numerous registry studies have confirmed the survival advantage of early revascularization in CS, whether percutaneous or surgical, both in the young and in older adults. Although thrombolytic therapy is less effective, in the absence of contraindications, thrombolytics should be administered when immediate revascularization is not possible. Ideally, such patients should have IABP and should be transferred immediately to a facility that offers revascularization.

Percutaneous Coronary Intervention in Cardiogenic Shock

Multiple trials have demonstrated the superiority of emergency revascularization with PCI compared with fibrinolytics in achieving sustained TIMI grade 3 flow in STEMI, with improvement in mortality rates and preservation of LV function. In the SHOCK trial, PCI was the most frequent mode of revascularization, with 84 of 132 patients randomized to immediate revascularization with PCI.[44] Success with PCI—defined as the combination of a residual stenosis less than 50%, a greater than 20% reduction in stenosis, and TIMI grade 2 or 3 flow—was achieved in 76% of patients. Overall survival in the patients selected for PCI was 54% at 30 days and 50% at 1 year. Thirty-day survival was 65% after successful PCI, but it was only 20% if PCI was unsuccessful ($P > .001$). At 1 year, these values were 61% and 15%, respectively ($P > .001$). Post-PCI patency and TIMI grade 3 flow in the infarct-related artery was strongly associated with survival, even after adjustment for important clinical and hemodynamic characteristics. No patient who had an occluded infarct-related artery (TIMI flow grade 0 or 1) after PCI survived. Among CS patients undergoing PCI, age, time from symptom onset to PCI, and post-PCI flow grade are independent predictors of mortality. Of note, revascularization provided benefit at every level of risk.

In the SHOCK trial, the success rate of PCI was relatively low (76%) and not unexpected, given that most patients had diffuse disease and occluded arteries and were hemodynamically unstable. This study predates the era of widespread stenting and adjunctive antiplatelet therapies in the setting of AMI. The majority of these patients underwent balloon angioplasty. Stents were used in 34% of patients, mainly to salvage a failed balloon PCI; the stents were largely first-generation devices implanted without the benefit of current adjunctive therapies. The culprit-artery stenting rate increased during the study from 0% in 1993 to 10% in 1996 and to 74% by 1998 ($P > .001$). PCI was more often successful in stented patients than in unstented patients (93% vs. 67%, $P < .013$), although 1-year survival was similar (54% vs. 48%, $P < .82$). This discrepancy between the success rate and the mortality rate for PCI is probably a result of bias because most stenting was performed following unsuccessful balloon angioplasty. The use of glycoprotein (GP) IIb/IIIa inhibitors (abciximab) also increased during the study period from 0% in 1993 to over 80% by 1998. Although the use of stents and GP IIb/IIIa inhibitors did not improve the mortality rate in the SHOCK trial, more recent data from multiple registries demonstrated that increased use of routine stenting and GP IIb/IIIa inhibitors were independent predictors of procedural success rates, TIMI grade 3 flow, and mortality in patients undergoing PCI for CS.[45] Although 81% of patients in the SHOCK trial had multivessel disease, most patients with PCI underwent single-vessel procedures (87%). During the study period, an increase was reported in the frequency of multivessel procedures from 0% to 23% ($P = .018$). One-year survival was 55% after single-vessel PCI but only 20% after a single-stage multivessel procedure. More recent data demonstrated no mortality difference between those undergoing only culprit-vessel PCI and those undergoing multivessel PCI in CS despite a high percentage of use of stenting and GP IIb/IIIa inhibitors.[46] Although PCI of the culprit lesion alone has been advocated in the management of AMI, the prevalence of multivessel disease and the possibility of ischemia far from the infarct zone and of progressive deterioration in LV function may argue for a strategy of more complete revascularization with multivessel PCI or surgery. As in STEMI without shock, earlier revascularization is better in CS. Presentation 0 to 6 hours after symptom onset was associated with lower mortality rates among CS patients undergoing primary PCI in the *Arbeitsgemeinschaft Leitende Kardiologische Krankenhausarzte* (ALKK) registry, in which door-to-angiography times were less than 90 minutes in approximately three fourths of patients.[45] In the SHOCK trial, long-term mortality rates appeared to increase as time to revascularization increased from 0 to 8 hours. However, a survival benefit was seen as long as revascularization was performed within 48 hours after MI and 18 hours after shock onset. The initial misperception that older patients do not benefit from PCI arose from the interaction between treatment effect and age in the SHOCK trial. The apparent lack of benefit for older adults in the trial was likely caused by imbalances between groups in the baseline ejection fraction. Several studies, including the SHOCK trial and registry, have shown the consistent benefit of revascularization in older patients, which suggests that clinicians are capable of identifying older patients who are most appropriate for revascularization.[47] The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend early revascularization in CS for those younger than 75 years of age (class I) and for suitable candidates over 75 years of age (class IIa).[48] In a certain

group of patients, however, additional treatment is futile, particularly when irreversible multiple end-organ failure or anoxic brain damage has occurred.

MULTIVESSEL DISEASE

The optimal revascularization strategy (i.e., percutaneous or surgical revascularization, single or multivessel PCI) for patients with multivessel CAD and CS is not clear. This is of particular importance because multivessel disease is common; 87% of patients in the SHOCK trial had multivessel disease. Both percutaneous and surgical methods of revascularization were permitted in the SHOCK trial. Thirty-seven percent of patients assigned to the early revascularization strategy underwent CABG at a median of 2.7 hours after randomization.[49] Despite a higher prevalence of triple-vessel or left main CAD and diabetes mellitus in patients who underwent CABG compared with those who underwent PCI, survival and quality of life were similar. The coronary anatomy may be most amenable to CABG in some patients. Immediate CABG is the preferred method of revascularization when severe triple-vessel or left main CAD is present and should be performed, as needed, when ventricular septal rupture or severe mitral regurgitation exists. In the SHOCK trial, the rate of multivessel PCI increased over the study period, which perhaps suggests that operators had gained experience with PCI in patients with CS. However, this small subset had a worse adjusted outcome than those who had single-vessel PCI.

Although current ACC/AHA guidelines suggest avoiding PCI in non–infarct-related arteries, unless the patient is in CS, recent trial data suggest a possible benefit for complete revascularization even in patients who are not in CS. The Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) trial[50] examined the role of multivessel PCI in both infarct and nonculprit arteries and showed that those patients randomized to the preventative PCI group of more complete revascularization had a significantly reduced risk of adverse cardiovascular events (hazard ratio [HR], 0.35; 95% confidence interval [CI], 0.21 to 0.58; $P < .001$). Although promising, the PRAMI trial was relatively small (465 patients), and follow-up was limited to 23 months because of early discontinuation of the trial. Another criticism of the trial has been that revascularization in the nonculprit lesions occurred without any further testing for ischemia, which is the most commonly used practice. Large trials of multivessel PCI in both CS and non-CS patients are ongoing.

Based on the current trial data and the ACC/AHA guidelines, PCI of the infarct-related artery is recommended in the case of single-vessel or double-vessel disease or moderate triple-vessel disease and when CABG is not possible for patients with more extensive disease. Staged multivessel PCI may be performed if surgery is not an option, and a single-stage procedure may be considered if the patient remains in shock after PCI of the infarct-related artery and if the other vessels have a flow-limiting lesion and supply a large region at risk.

LONG-TERM SURVIVAL AND QUALITY OF LIFE

Long-term survival data from the SHOCK trial revealed persistence of treatment benefit with remarkable 3- and 6-year survival rates in the early revascularization group of 41.4% and 32.8%, respectively, with persistence of treatment benefit (Fig. 21-7).[51] These findings are consistent with the 11-year survival rate of 55% observed in the GUSTO-I trial with 30-day CS survivors.[52] Furthermore, in GUSTO-I, annual mortality rates after 1 year (2% to 4%) were similar for those with shock and those without.

In survivors, quality of life is at least as important as long-term survival. At 2 weeks after discharge, 75.9% of patients assigned to revascularization and 62.5% assigned to medical stabilization in the SHOCK trial were in New York Heart Association (NYHA) functional classes I or II.[53] Among patients who were in NYHA functional class III to IV at 2 weeks, 55% of survivors improved to class I or II by 1 year. Similarly, in a series of patients with CS treated with early revascularization, 80% of survivors were completely asymptomatic at a median of 18 months, and all were in NYHA functional class I or II.[54] Bicycle exercise testing in a subgroup showed age-appropriate exercise capacity in all. Finally, in a series of patients treated with circulatory support, nearly all performed activities of daily living 1 year after the event, and some had even returned to full-time employment.[55]

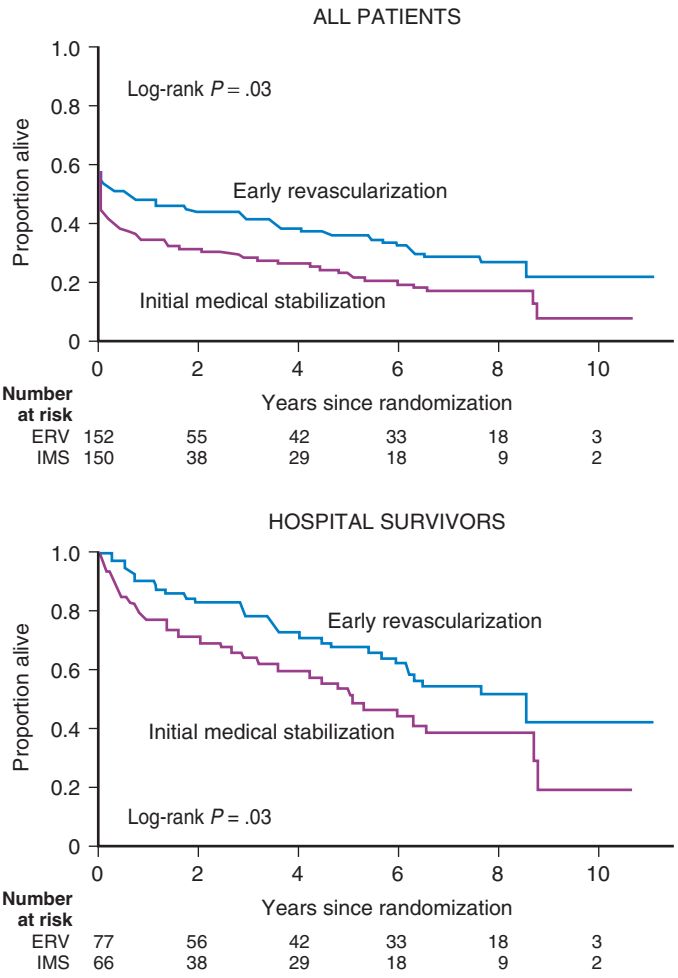


FIGURE 21-7 Long-term survival rates by Kaplan-Meier analysis of patients undergoing early revascularization (ERV) or initial medical stabilization (IMS) in the SHOCK trial. The mortality benefit of immediate revascularization persisted during the 6 years of mean follow-up. (Redrawn from Hochman JS, Sleeper LA, Webb JG, et al, for the SHOCK investigators: Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *JAMA* 295:2511-2515, 2006.)

CONCLUSION

CS is a treatable illness with a reasonable chance for recovery, although the literature has traditionally focused on the very high mortality associated with this diagnosis. It is important to recognize that although patients with CS are at very high risk for early death, great potential exists for salvage. Revascularization is associated with some benefit at every level of risk. An early invasive approach can increase short-term and long-term survival and results in patients regaining an excellent quality of life.

REFERENCES

1. Hollenberg SM, Davinsky CJ, Parillo JE: Cardiogenic shock. *Ann Intern Med* 131:47–59, 1999.
2. Goldberg RJ, Gore JM, Alpert JS, et al: Cardiogenic shock after acute myocardial infarction—incidence and mortality from a community wide perspective 1975-1988. *N Eng J Med* 325:1117–1122, 1991.
3. Jacobs AK, Leopold JA, Bates E, et al: Cardiogenic shock caused by right ventricular infarction: a report from the SHOCK registry. *J Am Coll Cardiol* 41:1273–1279, 2003.
4. Menon V, Webb JG, Hillis LD, et al: Outcome and profile of ventricular septal rupture with cardiogenic shock after myocardial infarction: a report from the SHOCK trial registry. *J Am Coll Cardiol* 36(3 Suppl A):1110–1116, 2000.
5. Thompson CR, Buller CE, Sleeper LA, et al: Cardiogenic shock due to acute severe mitral regurgitation complicating acute myocardial infarction: a report from the SHOCK trial registry. *J Am Coll Cardiol* 36(3 Suppl A):1104–1109, 2000.
6. Becker RC, Gore JM, Lambrew C, et al: A composite view of cardiac rupture in the United States National Registry of Myocardial Infarction. *J Am Coll Cardiol* 27:1321–1326, 1996.
7. Goldberg RJ, Samad NA, Yarzebski J, et al: Temporal trends in cardiogenic shock complicating acute myocardial infarction. *N Engl J Med* 340:1162–1168, 1999.
8. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi ne'll infarto Miocardico (GISSI). *Lancet* 1:397–401, 1986.
9. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group: Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction. ISIS-2. *Lancet* 2:349–360, 1988.
10. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group: Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. *Lancet* 343:311–322, 1994.
11. AMIS Plus Registry investigators: Ten-year trends in the incidence and treatment of cardiogenic shock. *Ann Intern Med* 149: 618–626, 2008.
12. Babaev A, Frederick PD, Pasta DJ, et al: Trends in the management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA* 294:448–454, 2005.
13. Hochman JS, Sleeper LA, Webb JG, et al: Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med* 341: 625–634, 1999.
14. Hochman JS, Buller CE, Sleeper LA, et al: Cardiogenic shock complicating acute myocardial infarction–etiologies, management and outcome: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? *J Am Coll Cardiol* 36(3 Suppl A):1063–1070, 2000.
15. Menon V, White H, LeJemtel T, et al: The clinical profile of patients with suspected cardiogenic shock due to predominant left ventricular failure: a report from the SHOCK trial registry. SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK? *J Am Coll Cardiol* 36(3 Suppl A):1071–1076, 2000.
16. Webb JG, Sleeper LA, Buller CE, et al: Implications of the timing of onset of cardiogenic shock after acute myocardial infarction: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK? *J Am Coll Cardiol* 36:1084–1090, 2000.
17. Lindholm MG, Køber L, Boesgaard S, et al: Cardiogenic shock complicating acute myocardial infarction: prognostic impact of early and late shock development. *Eur Heart J* 24:258–265, 2003.
18. SHOCK Investigators: Correlates of one-year survival inpatients with cardiogenic shock complicating acute myocardial infarction: angiographic findings from the SHOCK trial. *J Am Coll Cardiol* 42:1373–1379, 2003.
19. Stevenson LW, Perloff JK: The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA* 261:884–888, 1989.
20. Chakko S, Woska D, Martinez H, et al: clinical radiographic, and hemodynamic correlations in chronic congestive heart failure: conflicting results may lead to inappropriate care. *Am J Med* 90: 353–359, 1991.
21. ESCAPE Investigators and ESCAPE Study Coordinators: Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA* 294:1625–1633, 2005.
22. Hasdai D, Holmes DR, Califf RM, et al: Cardiogenic shock complicating acute myocardial infarction: predictors of death. *Am Heart J* 138:21–31, 1999.
23. SHOCK Investigators: Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. *J Am Coll Cardiol* 44:340–348, 2004.
24. Hunt SA, Abraham W, Chin MH, et al: ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. *Circulation* 112:1825–1852, 2005.
25. Abraham WT, Kirkwood KF, Fonarow GC, et al: In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol* 46:57–64, 2005.
26. Cuffe MS, Califf RM, Adams KF, et al: Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial (OPTIME-CHF). *JAMA* 287:1578–1580, 2002.
27. Loeb HS, Winslow EB, Rahimtoola SH, et al: Acute hemodynamic effects of dopamine in patients with shock. *Circulation* 44:163–173, 1971.
28. De Backer D, Biston P, Devriendt J, et al: Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 362:779–789, 2010.
29. Samuels LE, Kaufman MS, Thomas MP, et al: Doses and types of vasopressors and inotropes and increasing mortality. *J Card Surg* 14:288–293, 1999.
30. Rose EA, Gelijns AC, Moskowitz AJ, et al: Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med* 345:1435–1443, 2001.
31. Kantrowitz A, Tjonneland S, Freed PS, et al: Initial clinical experience with intraaortic balloon pumping in cardiogenic shock. *JAMA* 203:113–118, 1968.
32. Ohman EM, George BS, White CJ, et al: Use of aortic counterpulsation to improve sustained coronary artery patency during acute myocardial infarction. Results of a randomized trial. The Randomized IABP study group. *Circulation* 90:792–799, 1994.
33. Kono T, Morita H, Nishina T, et al: Aortic counterpulsation may improve late patency of the occluded coronary artery in patients with early failure of thrombolytic therapy. *J Am Coll Card* 28:876–881, 1996.
34. Sjauw KD, Engström AE, Vis MM, et al: A systematic review and meta-analysis of intraaortic balloon pump therapy in ST elevation myocardial infarction: Should we change the guidelines? *Eur Heart J* 30:459–468, 2009.
35. Thiele H, Zeymer U, Neumann FJ, et al: Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. *Lancet* 382:1638–1645, 2013.
36. Patel MR, Smalling RW, Thiele H, et al: Intra-aortic balloon counterpulsation and infarct size in patients with acute anterior myocardial infarction without shock: the CRISP AMI randomized trial. *JAMA* 306:1329–1337, 2011.
37. Seyfarth M, Sibbing D, Bauer I, et al: A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intraaortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. *J Am Coll Cardiol* 52:1584–1588, 2008.
38. Shreenivas S, Wilensky R: Percutaneous circulatory support during percutaneous coronary intervention. *Interv Cardiol* 4:449–460, 2012.
39. Steg PG, Bonnefoy E, Chabaud S, et al: Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. *Circulation* 108:851–2856, 2003.
40. Lee L, Bates ER, Pitt B, et al: Percutaneous transluminal coronary angioplasty improves survival in acute myocardial infarction complicated by cardiogenic shock. *Circulation* 78:1345–1351, 1988.
41. Verna E, Repetto S, Boscarini M, et al: Emergency coronary angioplasty in patients with severe left ventricular dysfunction or cardiogenic shock after acute myocardial infarction. *Eur Heart J* 10:958–966, 1989.
42. Moosvi AR, Khaja F, Villanueva L, et al: Early revascularization improves survival in cardiogenic shock complicating acute myocardial infarction. *J Am Coll Cardiol* 19:907–914, 1992.
43. SHOCK Investigators: One-year survival following early revascularization for cardiogenic shock. *JAMA* 285:190–192, 2001.
44. SHOCK Investigators: Percutaneous coronary intervention for cardiogenic shock in the SHOCK trial. *J Am Coll Cardiol* 42:1380–1386, 2003.
45. Zeymer U, Vogt A, Zahn R, et al: Predictors of in-hospital mortality in 1333 patients with acute myocardial infarction complicated by cardiogenic shock treated with primary percutaneous coronary intervention (PCI): Results of the primary PCI registry of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausarzte (ALKK). *Eur Heart J* 25:322–328, 2004.
46. Claessen B, Vis MM, Koch KT, et al: Multivessel versus culprit only intervention in patients with multivessel disease complicated with cardiogenic shock. *J Am Coll Cardiol* 5(Suppl 1):A 185. E1734, 2010. (abstract).
47. Dzavik V, Sleeper LA, Cocke TP, et al: Early revascularization is associated with improved survival in elderly patients with acute myocardial infarction complicated by cardiogenic shock: a report from the SHOCK trial registry. *Eur Heart J* 24:828–837, 2003.
48. Ryan TJ, Antman EM, Brooks NH, et al: 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol* 34:890–911, 1999.
49. White HD, Assmann SF, Sanborn TA, et al: Comparison of percutaneous coronary intervention and coronary artery bypass grafting after acute myocardial infarction complicated by cardiogenic shock: Results from the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial. *Circulation* 112:1992–2001, 2005.
50. Wald DS, Morris JK, Wald NJ, et al: Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 369:1115–1123, 2012.
51. SHOCK Investigators: Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *JAMA* 295:2511–2515, 2006.
52. Singh M, White J, Hasdai D, et al: Long-term outcome and its predictors among patients with ST-elevation myocardial infarction complicated by shock: insights from the GUSTO-I trial. *J Am Coll Cardiol* 50:1752–1758, 2007.
53. SHOCK Investigators: Functional status and quality of life after emergency revascularization for cardiogenic shock complicating acute myocardial infarction. *J Am Coll Cardiol* 46:266–273, 2005.
54. Ammann P, Straumann E, Naegeli B, et al: Long-term results after acute percutaneous transluminal coronary angioplasty in acute myocardial infarction and cardiogenic shock. *Int J Cardiol* 82: 127–131, 2002.
55. Smith C, Bellomo R, Raman JS, et al: An extracorporeal membrane oxygenation-based approach to cardiogenic shock in an older population. *Ann Thorac Surg* 71:1421–1427, 2001.

Bifurcations and Branch Vessel Stenting

22

ANTONIO COLOMBO | GORAN STANKOVIC

KEY POINTS

- Always consider an ostial lesion as a possible bifurcation lesion except for those in an aortoostial location.
- A 6-Fr guiding catheter is appropriate most of the time; if in doubt, use a 7- or 8-Fr catheter.
- Do not risk losing the side branch; when in doubt, always protect it with a guidewire.
- If wiring the side branch proves to be difficult, consider dilating the main branch first.
- Provisional stenting does not mean accepting a poor final result for an important side branch.
- Treatment of a bifurcation lesion with two stents, in the main and side branches, as intention to treat is an acceptable approach.
- When implanting two stents,do not forget the final "kissing" balloon inflation (FKBI), preceded by high-pressure inflation of the side branch.
- When a dedicated drug-eluting stent (DES) for bifurcation lesions becomes available, many concepts may change, including the emergence of a more liberal usage of a two-stent strategy.
- Optimal antiplatelet therapy is always a key factor for short- and long-term success: stay updated in regard to new developments.

BIFURCATION LESIONS

A *coronary bifurcation lesion* is a lesion that occurs at or adjacent to a significant division of a major epicardial coronary artery. Coronary bifurcation lesions have been the subject of several classifications with the underlying assumption that each type could be associated with a specific treatment. However, attempts to classify bifurcation lesions[1-5] suffer all the limitations of coronary angiography (different plaque distribution and extent of disease when evaluated by intravascular ultrasound [IVUS]).[6] Currently, six different classifications of bifurcation lesions have been defined (Fig. 22-1). The most important distinction to make is to divide bifurcation lesions into *true bifurcations*, in which the main branch (MB) and the side branch (SB) are both significantly narrowed (>50% diameter stenosis), and *nontrue bifurcations*, which include all the other lesions that involve a bifurcation. In routine practice, the Medina classification is still the most simple and widely used approach to classify distribution of atherosclerotic plaque at a bifurcation site.[5] In each of the three bifurcation segments, starting with the proximal MB and proceeding to the distal MB and then the proximal SB, class 1 indicates more than a 50% diameter stenosis, and class 0 indicates the absence of stenosis. The *1,1,1* designation is used when a critical stenosis exists in all three segments; *1,1,0* is used when only the proximal and distal MB are affected, and many other combinations are possible. A limitation of the Medina classification is that the length of the stenosis involving the SB is not specified, and we believe this distinction is a key element to proper planning of the treatment. Despite an array of devices available, stenting that utilizes a DES remains the default approach to treat bifurcation lesions, and the implantation of a single stent on the MB is the most widely used approach.

Contemporary Studies

Several major randomized trials that compared one or two stents in the treatment of coronary bifurcations demonstrated that the implantation of a stent only in the MB remains the preferred strategy. Randomized Study to Evaluate Sirolimus-Eluting Stents (SES) Implanted at Coronary Bifurcation Lesions[7] was the first attempt to provide specific information on this subset of lesions. Eighty-five patients were randomly assigned to either stenting both branches or stenting the MB only with provisional stenting of the SB. Data were analyzed by actual treatment received, not by intention to treat. The crossover rate was very high: 51.2% in the provisional group and 4.7% in the two-stent group. Restenosis at 6 months did not differ significantly between the two-stent and the stent–percutaneous transluminal coronary angiography (PTCA) groups (28.0% vs. 18.7%, respectively; $P = .53$). During the 6-month follow-up, one death occurred in the two-stent group and none occurred in the stent-PTCA group. No significant difference was found between the two groups in Q-wave myocardial infarction (MI; 1.6% vs. 4.5%), non Q-wave MI (9.5% vs. 4.5%), target-vessel revascularization (TVR; 11.1% vs. 9.0%), or target-vessel failure (19.0% vs. 13.6%). Three cases of stent thrombosis occurred, all in the two-stent group. Therefore this study demonstrated that compared with historic studies that utilized bare-metal stents,[1,8,9] a clear improvement has been achieved in the treatment of bifurcation lesions when one or two DESs were implanted.

In a second study, Pan and coworkers[10] compared two strategies for the SES treatment of bifurcation lesions in 91 patients with true coronary bifurcation lesions. Major adverse cardiac events (MACEs) occurred in three patients in the provisional group, two non–Q-wave MIs and one target-lesion revascularization (TLR), and in three patients in the two-stent group, one subacute stent thrombosis with subsequent death and two TLRs. Six-month angiographic reevaluation was obtained in 80 patients (88%), and the restenosis rate of the MB and of the SB was also similar in the two study groups.

A third randomized study was the Nordic Bifurcation Study (Nordic),[11] in which 413 patients were randomized to two stents ($n = 206$) using crush, culotte, Y, or other techniques versus provisional stenting ($n = 207$) with SES implantation. The crossover from provisional stenting to stenting two branches was allowed only if thrombosis in myocardial infarction (TIMI) flow following SB dilation was grade 0. Procedural success was achieved in 97% of cases in the provisional group versus 95% in the two-stent group. The crossover rate was also low, and the SB was stented in only 4.3% of the patients in the provisional stenting group. FKBI was performed in 32% and 74% of the patients, respectively ($P < .001$). At 6 months, no difference was found between the two groups in terms of cardiac death, MI, index lesion MI, TVR, TLR, and stent thrombosis. At 5-year follow-up, the combined safety and efficacy end point of cardiac death, non–procedure-related MI, and TVR remained similar at 15.8% in the provisional stenting group compared with 21.8% in the two-stent group ($P = .15$).[12]

In a fourth trial, the Bifurcations Bad Krozingen (BBK) study, Ferenc and colleagues[13] compared 202 patients randomly allocated to either provisional T stenting or routine T stenting using an SES. FKBI was performed in both groups irrespective of whether they were assigned to routine or provisional T-stenting, and in the provisional T-stent arm, crossover to SB stenting was mandated in case of a flow-limiting dissection or residual stenosis of greater than 75%. The

primary end point was percent diameter stenosis of the SB at 9-month angiographic follow-up, and it was similar between the two groups ($P = .15$). The overall 1-year incidence of TLR was 10.9% after provisional stenting and 8.9% after routine T-stenting ($P = .64$), and the primary clinical outcome—death, MI, or TLR—was equivalent in both groups (12.9% provisional vs. 11.9% routine T-stenting; $P = .83$).

The fifth trial of interest was the Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents (CACTUS) trial.[14] In this study, 350 patients were randomly allocated to either provisional T or crush SES implantation, with mandatory FKBI in both groups. Stent implantation in the SB was allowed by the T-stenting technique only when at least one of the following conditions was met: residual stenosis of 50% or greater; dissection of type B or worse, or TIMI flow grade of 2 or less. A high proportion of patients (92%) had true bifurcations, and the crossover rate in the provisional T group was 31%. The primary angiographic end point was the in-segment restenosis rate, and the primary clinical end point was 6-month rate of MACEs (cardiac death, MI, or TVR). At 6 months, angiographic restenosis rates were not that different between the crush group (4.6% and 13.2% in the MB and SB, respectively) and the provisional stenting group (6.7% and 14.7% in the MB and SB, respectively; P = nonsignificant [NS]). The primary clinical outcome of death, MI, or revascularization was also similar in both groups (15.0% provisional vs. 15.8% crush, P = NS).

In the British Bifurcation Coronary Study: Old, New, and Evolving Strategies (BBC ONE),[15] 500 patients were randomly allocated to either a simple strategy (minimalist provisional T) or a complex strategy (either crush or culotte) using paclitaxel-eluting stents (PESs). In the simple strategy, the MB was stented, followed by optional FKBI/T-stent using criteria that included TIMI flow grade less than 3 in the SB, severe ostial pinching of the SB (>90%), threatened SB closure, or SB dissection greater than type A. Only 30% of the SB underwent further treatment after MB stenting (27% FKBI and 3% stenting). In the complex strategy, both branches were systematically stented (culotte or crush techniques) with mandatory FKBI. At 9-months clinical follow-up, a significant difference was seen between the two groups in terms of death, MI, or revascularization (simple 8.0% vs. complex 15.5%). This difference was largely driven by the higher incidence of MI in the complex group (11.2% vs. 3.6%, $P = .001$). It is surprising to note such a high complication rate in patients randomized to the complex strategy.

Finally, the Double-Kissing Crush Versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions (DKCRUSH-II)[16] trial investigated the difference in MACE rates (cardiac death, MI, or TVR) at 12 months in 370 patients with coronary bifurcation lesions after double-kissing (DK) crush or provisional stenting (PS) techniques. MACE and definite stent thrombosis rates were similar between the DK (10.3% and 2.2%) and PS groups (17.3%, and 0.5%, $P = .070$ and $P = .372$, respectively). However, angiographic restenosis rates in the main vessel (MV) and in the SB were lower in the DK group (3.8% and 4.9%) than in the PS group (9.7% and 22.2%, $P = .036$ and $P < .001$, respectively) as was TVR (6.5% vs. 14.6%, $P = .017$).

The clinical implication of those trials is that in most cases, provisional, rather than elective, stenting of the SB should be performed.[17]

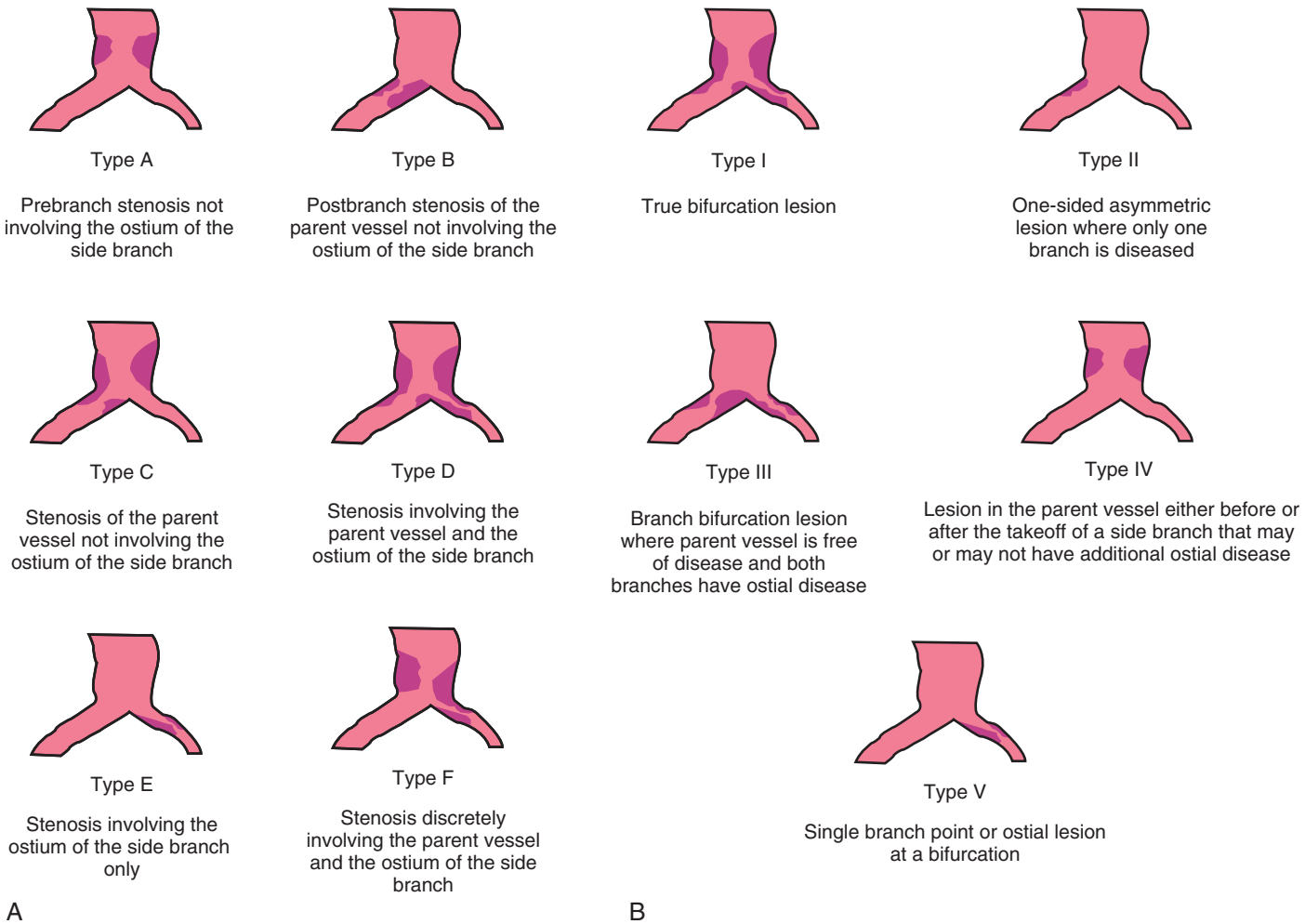
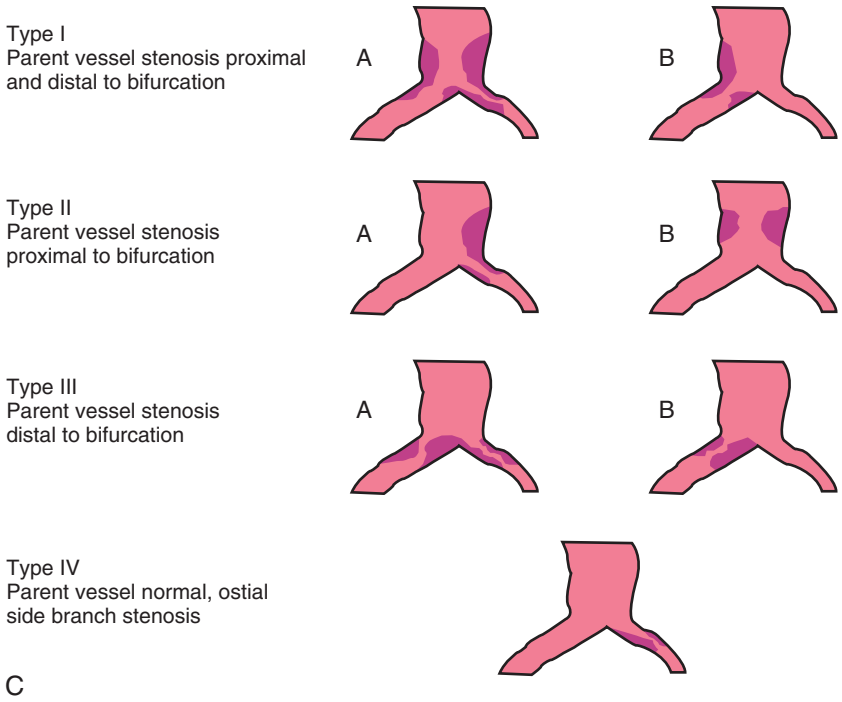


FIGURE 22-1 Various classifications of bifurcations according to plaque distribution. **A,** Duke. **B,** Sanborn.



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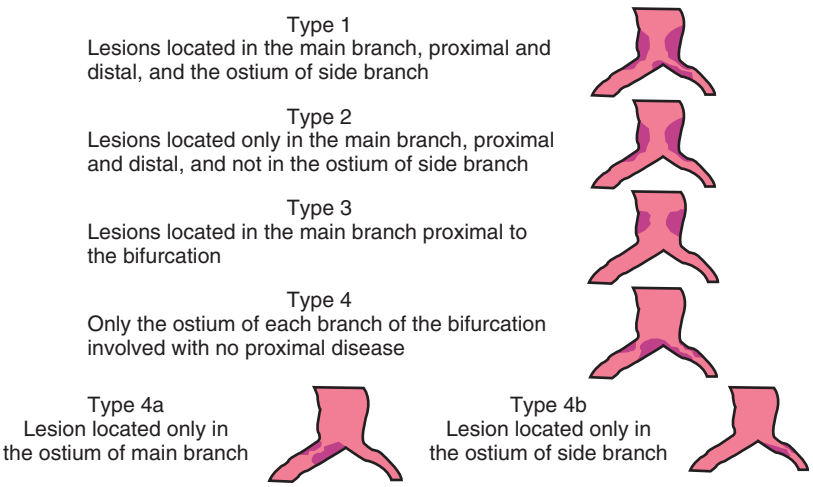

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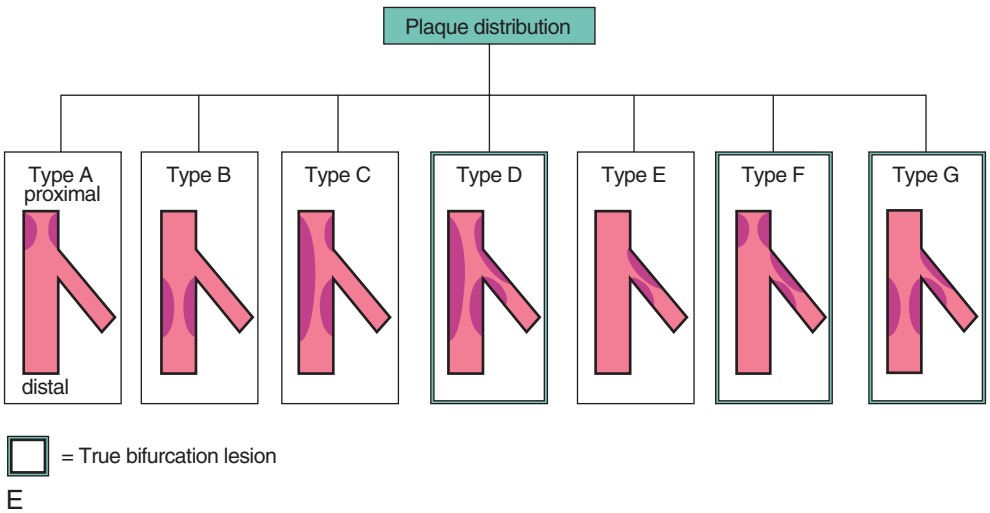

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FIGURE 22-1, cont'd **C,** Safian. **D,** Lefevre. **E,** SYNTAX study.

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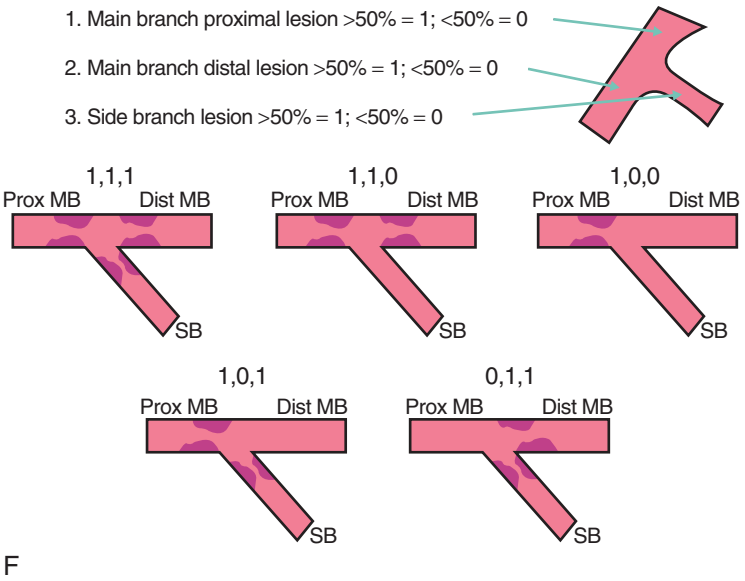

FIGURE 22-1, cont'd **F,** Medina. *Dist,* Distal; *MB,* main branch; *Prox,* proximal; *SB,* side branch. (*A* is from Popma J, Leon M, Topol EJ: *Atlas of interventional cardiology*. Philadelphia, PA, 1994, Saunders. *B* is from Spokojny AM, Sanborn TM: The bifurcation lesion. In Ellis SG, Holmes DR, editors: Strategic approaches in coronary intervention. Baltimore, 1996, Williams and Wilkins. *C* is from Safian RD: Bifurcation lesions. In Safian RD, Freed M, editors: *Manual of interventional cardiology,* Royal Oak, CA, 2001, Physicians' Press. *D* is from Lefevre T, Louvard Y, Morice MC, et al: Stenting of bifurcation lesions: classification, treatments, and results. *Catheter Cardiovasc Interv* 49:274-283, 2000. *E* is from Sianos G, Morel MA, Kappetein AP, et al: The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 1:219-227, 2005. *F* is from Medina A, Suarez de Lezo J, Pan M: A new classification of coronary bifurcation lesions. *Rev Esp Cardiol* 59:183, 2006.)

Provisional stenting appears less expensive and simpler and can be performed with less contrast and in a shorter procedural time. At the same time, the evidence of equivalent results in the two arms does not contradict the choice of crush/culotte stenting in selected cases with complex anatomy or with diffuse disease within the SB.[18] One shortcoming of the aforementioned trials was that the treatment groups, including those that used two stents, were heterogeneous, and the techniques used may have resulted in different clinical outcomes. Clinical outcomes in randomized trials to compare one-stent and two-stent strategies using drug-eluting stents are presented in Figure 22-2.

To evaluate the impact of various two-stent techniques, the Nordic complex bifurcation stenting study[19] was performed, in which 424 patients were randomized to either crush or culotte stenting using SESs (77% of which were true coronary bifurcation lesions). At the 6-month clinical follow-up, no difference was found between the two groups in the primary end point: death, postprocedure MI, or revascularization (crush 4.3% vs. culotte 3.7%, $P = .87$). However, a trend was seen for a higher incidence of periprocedural MI (crush 15.5% vs. culotte 8.8%, $P = .08$) and a significantly higher occurrence of in-stent restenosis in the crush group (crush 10.5% vs. culotte 4.5%, $P = .046$). Clinical outcomes remained similar at 3-year follow-up in the crush and culotte groups, with MACE rates of 20.6% versus 16.7% ($P = .32$), index lesion restenosis of 11.5% versus 6.5% ($P = .09$), and definite stent thrombosis rates of 1.4% versus 4.7% ($P = .09$).[20]

Comparison of Double Kissing Crush Versus Culotte Stenting for Unprotected Distal Left Main Bifurcation Lesions (DKCRUSH-III) study[21] investigated the difference in MACE rates at 1 year after DK crush and culotte stenting in 419 patients with unprotected left main coronary artery (LMCA) distal bifurcation lesions. Patients in the culotte group had higher 1-year MACE rates compared with the DK group (16.3% vs. 6.2%, $P = .001$), which was mainly driven by an increased TVR rate (11.0% vs. 4.3%, $P = .016$). The definite stent thrombosis rate was 1.0% in the culotte group and 0% in the DK group ($P = .248$). In all prespecified subsets—patients with a bifurcation angle of 70 degrees or more, those with a New Risk Stratification Score (NERS) of 20 or higher, and those with a Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score of 23 or higher—the MACE rates at 1 year were consistently lower in the DK group (3.8%, 9.2%, and 7.1%, respectively) compared with the culotte group (16.5%, 20.4%, and 18.9%, respectively; $P < .05$ for all).

To evaluate the impact of a specific DES type on clinical outcome in patients with bifurcation lesions, Pan and coworkers[22] enrolled 205 patients in a prospective randomized trial: 103 were assigned to SES and 102 were assigned to PES; all patients were treated by provisional T-stenting. Angiographic data and immediate procedural results were similar in both groups, and no difference was reported in rates of death or MI in the hospital and during follow-up. The primary end point, angiographic restenosis, was significantly lower in the SES group (9% vs. 29%, $P = .011$), as was TLR at 24 months after stenting (4% vs. 13%, $P = .021$). Similar results were obtained in the Coronary Bifurcation Stenting (COBIS) registry,[23] which compared MACE rates—defined as cardiac death, MI, or TLR—between SESs and PESs. At a mean follow-up of 22 months, treatment with SESs resulted in a lower incidence of MACEs (HR, 0.53; 95% CI, 0.32 to 0.89; $P < .01$) and TLR (HR, 0.55; 95% CI, 0.31 to 0.97; $P = .02$) but not of cardiac death or MI.

The clinical outcome of newer-generation DESs in bifurcation lesions was evaluated in several randomized trials. Burzotta and associates[24] randomized 150 consecutive patients with bifurcated lesions undergoing systematic provisional stenting to SESs or everolimus-eluting stents (EESs) in the Sirolimus Versus Everolimus-Eluting Stent Randomized Assessment in Bifurcated Lesions and Clinical Significance of Residual Side-Branch Stenosis (SEA-SIDE) study. The primary procedural end point was the occurrence of any trouble in the side-branch management, defined as (1) SB TIMI flow grade <3 after MV stenting, (2) need of guidewire(s) different from the workhorse wire to rewire SB after MV stenting, (3) failure to rewire the SB after MV stenting, or (4) failure to dilate the SB after MV stenting and SB rewiring. Primary endpoint was similar between SES and EES (16% vs. 11%, $P = 0.34$). The primary angiographic end point—post-PCI three-dimensional, quantitative coronary angiography (QCA)-estimated

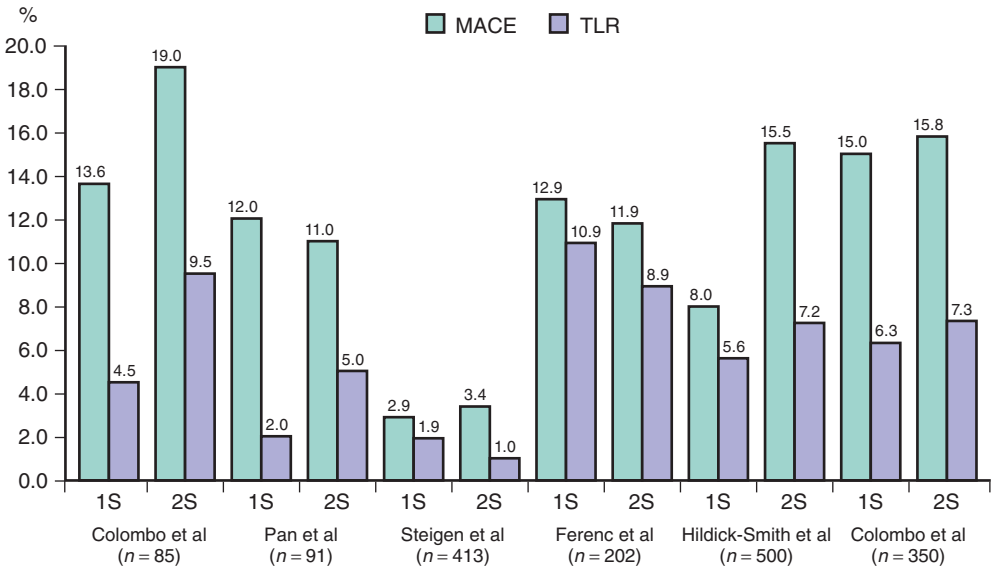

FIGURE 22-2 Clinical outcomes in randomized trials comparing a one- versus two-stent strategy utilizing drug-eluting stents. *1S,* Single stent; *2S,* two stents; *MACE,* major adverse coronary event; *TLR,* target-lesion revascularization. (Data from Colombo A, Moses JW, Morice MC, et al: Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation* 109:1244-1249, 2004; Pan M, de Lezo JS, Medina A, et al: Rapamycin-eluting stents for the treatment of bifurcated coronary lesions: a randomized comparison of a simple versus complex strategy. *Am Heart J* 148:857-864, 2004; Steigen TK, Maeng M, Wiseth R, et al: Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. *Circulation* 114:1955-1961, 2006; Ferenc M, Gick M, Kienzle RP, et al: Randomized trial on routine vs. provisional T-stenting in the treatment of de novo coronary bifurcation lesions. *Eur Heart J* 29:2859-2867, 2008; Hildick-Smith D, de Belder AJ, Cooter N, et al: Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. *Circulation* 121:1235-1243, 2010; and Colombo A, Bramucci E, Sacca S, et al: Randomized study of the crush technique versus provisional side-branch stenting in true coronary bifurcations: the CACTUS [Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents] Study. *Circulation* 119:71-78, 2009.)

minimal lumen diameter—showed similar post-PCI results in the MV and better results in the SB with EESs compared with SESs (minimal lumen diameter at SB ostium: 1.94 ± 0.72 mm vs. 1.64 ± 0.62 mm; $P = .013$). Clinical outcome at 18 months showed no difference in rates of target bifurcation failure (9.0% in SES vs. 10.7% in EES patients, $P = .57$). SESs and EESs were also compared in the randomized Cordoba and Las Palmas (CORPAL) study,[25] in which 293 patients with bifurcation lesions were treated with a provisional SB stenting technique. In-hospital outcome was similar in the two groups, with two non–Q-wave MIs and one death occurring in each group. At 12-month follow-up, the incidence of MACEs was also similar between SES- and EES-treated patients (6.2% vs. 6.1%, respectively; $P = .84$). A pooled analysis of those two randomized trials, SEA-SIDE and CORPAL, showed similar MACE-free survival at 3 years (93.2% in the EES group vs. 91.3% in the SES group, $P = .16$). However, exploratory landmark analysis for late events (occurring after 1 year) showed significantly fewer MACEs in the EES group (1.4% vs. 5.4%, $P = .02$).

In a prospective extension of the SEA-SIDE study, the performance of a zotarolimus-eluting stent (ZES) was compared with that obtained using SES and EES in the Sirolimus Versus Everolimus Versus Zoatrolimus-eluting Stent Assessment In Bifurcated Lesions and Clinical Significance of Residual Side-Branch Stenosis (Z-SEA-SIDE) study.[26] The ZES demonstrated improved performance compared with the SES (SB "trouble" rate was 4% vs. 16%, respectively; $P = .014$) and better SB angiographic results (minimal lumen diameter at SB ostium, 1.94 vs. 1.64 mm, $P = .008$), whereas performance of the ZES was similar to that of the EES.

Approach to Treatment of Bifurcation Lesions

Bifurcations vary not only in anatomy (plaque burden, location of plaque, angle between branches, diameter of branches, bifurcation site) but also in the dynamic changes in anatomy during treatment (plaque/carina shift, dissection). Previous pathologic studies demonstrated that atherosclerosis occurs predominantly in low shear-stress regions of bifurcation, but carina (flow divider) involvement by atherosclerosis is extremely unusual. Nakazawa and colleagues[27] recently demonstrated that in nonstented coronary bifurcations, the lateral wall showed significantly greater intima and necrotic core thickness than the flow divider. After stenting, plaque formation and neointimal growth was also significantly less at the flow divider than at the lateral wall. Those observations were also confirmed in vivo by IVUS preintervention evaluation of distal LMCA bifurcations. Oviedo and associates[28] showed that bifurcation disease is usually diffuse and, contrary to angiographic classifications, that the carina was spared in all lesions, whereas the plaque was present predominantly on the opposite side of the flow divider. However, data presented by van der Giessen and colleagues[29] shed new light on the subject through CT angiography, suggesting that the carina does have some atheroma present in 30% of bifurcations, although the volume of that plaque remains small and was present only if a significant volume of plaque was located at the lateral walls opposite the flow divider (low wall shear-stress areas), indicating that atherosclerotic plaque grows circumferentially.

Koo and coworkers[30] evaluated the mechanisms of changes in the geometry of the ostium of the SB with IVUS and fractional flow reserve (FFR) after MB stenting to test the hypothesis that MB stenting may create worsening of an SB ostial lesion as a result of a combination of MB plaque and carinal shift. The investigators concluded that the decrease in plaque volume in the proximal MB, with no associated increase in plaque volume in the distal MB, was indirect evidence of plaque shift from the MB to the SB ostium after stent implantation. Additionally, the increased luminal volume in the distal MB, with no significant decrease in the plaque volume, was believed to be due to vessel enlargement, and this research provided support to the theory

that carinal shift is likely to contribute to the degree of luminal narrowing of the SB.

As a result of these investigations, we can conclude that no two bifurcations are identical, and no single strategy exists that can be applied to every bifurcation. Thus the more important issue in bifurcation PCI is selecting the most appropriate strategy for an individual bifurcation and optimizing the performance of this technique.

Guiding Catheter Selection

Most bifurcation lesions can be approached with a 6-Fr guiding catheter because a provisional strategy will be utilized most of the time. The exception is when the operator decides from the very beginning, because of lesion characteristics, to implant two stents using a 7- or 8-Fr guiding catheter. When there are doubts regarding the optimal treatment, and the operator will need to make a decision following predilation, we suggest usage of a 7- or 8-Fr guiding catheter.

With currently available very low-profile balloons, it is possible to insert two balloons inside a large lumen (6-Fr) guiding catheter. If two stents are needed, and a 6-Fr guiding catheter is used, some limitations should be considered. Two stents can only be inserted and deployed sequentially. The standard crush technique and the V or kissing stent technique cannot be performed unless a 7- or 8-Fr guiding catheter is used.

A General Outline When Treating a Bifurcation Lesion

Figure 22-3 summarizes a proposed approach to bifurcation lesions. SB stenting should be performed as intention to treat only in cases where disease of the SB extends beyond the ostium and the SB has a significant area of distribution. The most frequently used approach is provisional SB stenting, which is outlined as follows:

1. Placement of two wires (MB and SB)
2. Predilation when needed
3. Stenting of the MB
4. Recrossing with a wire into the SB
5. Crossing with a balloon into the SB
6. Performance of kissing balloon inflation with moderate pressure (8 atm) in the SB, until the balloon is fully expanded
7. Placement of a second stent in the SB only if the result is inadequate

An important aspect when stenting bifurcations is the protection of the SB by insertion of a wire to be left until the stenting procedure on the MB has been completed, which includes high-pressure stent deployment or postdilation. These temporary "jailed" wires can be retrieved provided attention is paid to avoid any trauma to the ostium of the proximal coronary with the guiding catheter, which tends to be pulled in as the guidewire is withdrawn. In the provisional technique, wire crossing through the distal strut (the "carina strut") following MB stenting is strongly suggested because it creates better SB scaffolding than proximal crossing.[31]

To optimize SB access through the carina strut, the proximal optimization technique (POT) is proposed.[31] Optimization of the stent deployment proximal to the carina using a short, bigger balloon may help to access the most distal strut during wire exchange. If the result remains unsatisfactory after MB stenting (>75% residual stenosis, dissection, TIMI flow grade <3 in an SB ≥2.5 mm, or FFR <0.75), SB stenting should be performed. SB stenting can be performed with T stenting or with T-and-protrusion (TAP) stenting, reverse/internal crush and culotte, followed by FKBI.[31]

Difficult Access to the Side Branch

After having attempted using different types of wires with various curves, the operator may be left with the impossible task of advancing a wire into the SB. At this point, the only available options are to (1) abort the procedure because the risk of losing the SB is too high, considering the size and distribution of the branch (typically an angulated circumflex artery); (2) use a microcatheter to navigate a reshaped guidewire through unfavorable MV anatomies, such as with the SuperCross catheter (Vascular Solutions, Minneapolis, MN) with different preshaped tip curves; (3) perform rotational atherectomy on the MV with the intent to remove the plaque, which prevents entry to the SB; (4) dilate the MV with a balloon with the rationale that a favorable plaque shift may facilitate access into the SB; (5) use a *reverse wire technique* based on preparation of the guidewire tip by creation of two sharp curves, a longer proximal one to create a loop in the distal MV and an opposite shorter, distal one to engage the SB ostium during the wire pullback[17]; and (6) to use the Venture wire control catheter (St. Jude Medical, Maple Grove, MN), a low-profile catheter with a tip that can be deflected up to 90 degrees to facilitate wire orientation and provide excellent back-up support (Fig. 22-4).[32] Each of these six options has its rationale; however, the specific anatomic condition, the operator's experience, and the clinical scenario will direct the selection of the best strategy. The fourth option is the one more frequently used and is usually effective.

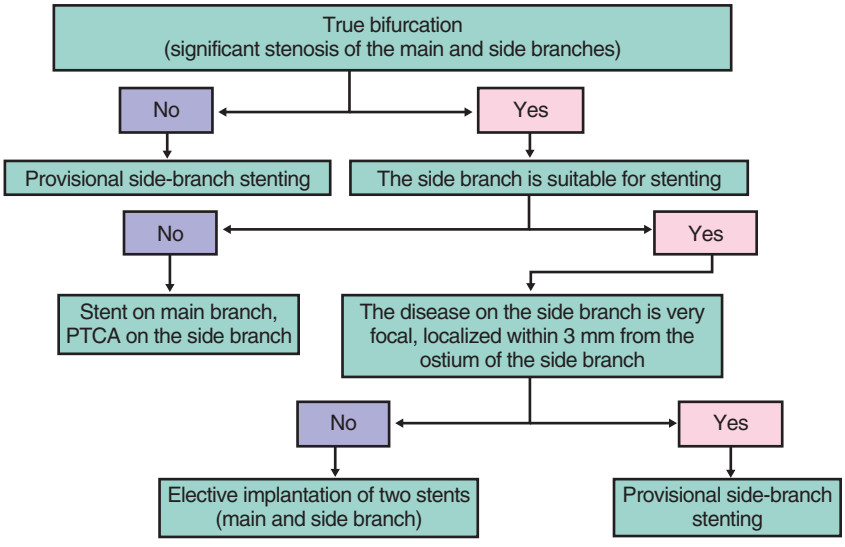

FIGURE 22-3 Our proposed algorithm for stenting bifurcation lesions. *PTCA,* Percutaneous transluminal coronary angioplasty.

The Role of Final Kissing Balloon Inflation

Final kissing balloon inflation (FKBI) is proposed if the SB is dilated through the MB stent struts to correct MB stent distortion and proximal expansion and to provide better scaffolding of the SB ostium and facilitate future access to the SB. The long-term clinical benefit of FKBI, in cases of MV stenting alone, is still unproven. The Nordic-Baltic Bifurcation Study (Nordic III) and the Cordoba & Las Palmas (CORPAL-KISS) trial demonstrated that no systematic clinical advantage exists with a routine kissing strategy when a single stent treatment is used, and retrospective analysis of the COBIS registry showed that FKBI may even increase long-term TLR rate in the MV.[33-35] However, angiographic follow-up at 8 months in the NORDIC III study[33] showed a lower SB restenosis rate in patients with true bifurcation lesions when FKBI was performed (7.6% vs. 20.0%, $P = .024$), and a study by Koo and colleagues[36] showed that FKBI restores normal FFR in the SB in the majority of patients. Several criteria have been proposed to define lesions in which FKBI is required: these include greater than 75% residual stenosis at the SB, TIMI flow grade less than 3, or FFR below 0.75. Therefore two appropriate strategies are to use either a pressure wire to interrogate the significance of the SB lesion and treat or not accordingly or to simply do FKBI on all angiographically significant ostial SB lesions, which reduces the proportion of these lesions that are physiologically significant; in light of the information from Nordic III, there appears to be no penalty for doing so.[33] A two-step sequential strategy has also been proposed as a simpler and more efficient alternative to an FKBI technique; this accomplishes SB dilation with a balloon at least the diameter of the SB, and final optimization of the MV stent is with a balloon sized per the proximal MV with the distal marker at the carina site.[37] As a general approach, we favor performance of FKBI.

A Second Stent in the Side Branch Following Provisional Approach

When we are not satisfied with the result obtained with balloon dilation of the SB and we need to implant a second stent, various strategies

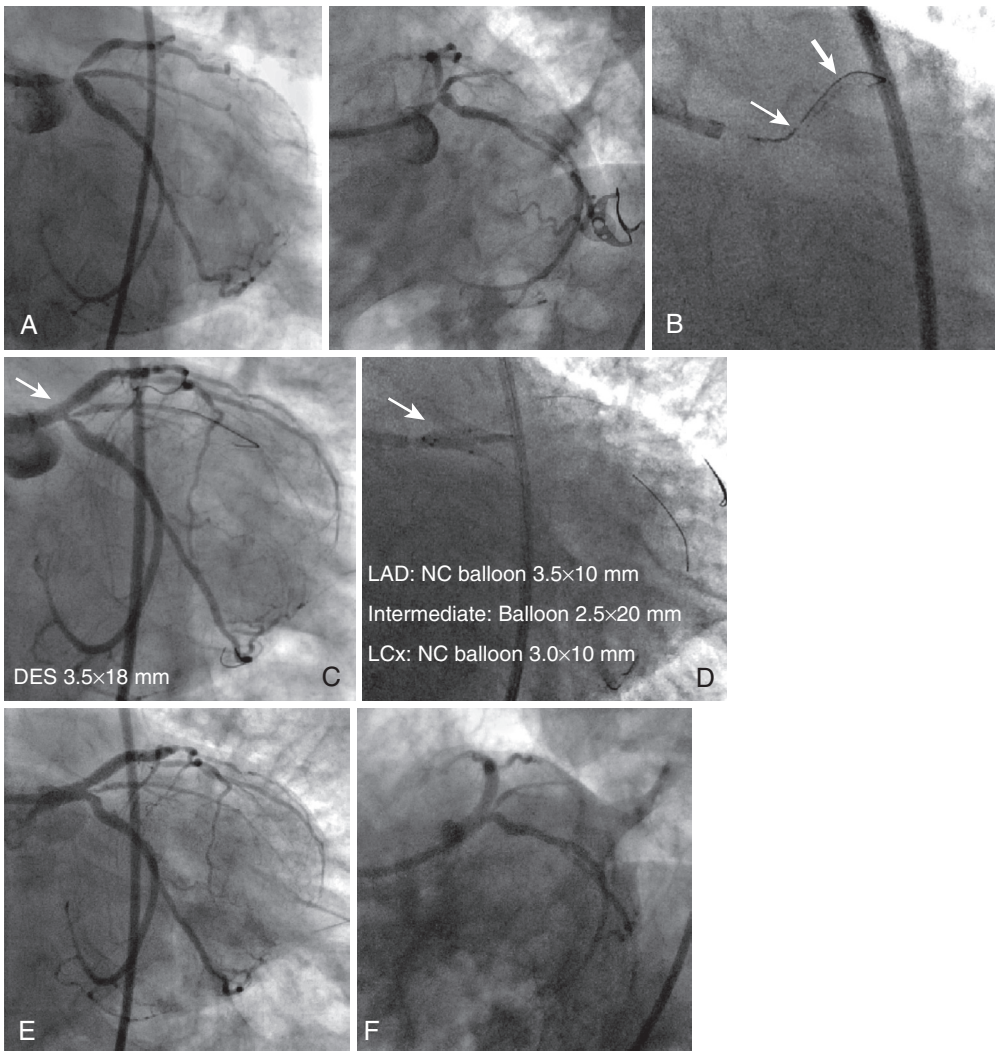

FIGURE 22-4 **A,** Baseline angiogram presents a large, eccentric atherosclerotic plaque that involves the distal part of the left main coronary artery (LMCA) and extends into the ostial segment of the left anterior descending (LAD). **B,** Because of a tight LMCA lesion and unfavorable access to the ostial LAD, a Venture wire control catheter (*arrow*) was used to insert a coronary guidewire (*thick arrow*). **C,** After that, two guidewires were inserted in the intermediate branch and left circumflex artery (LCx). Following predilation of the LMCA/ostial LAD lesion, a drug-eluting stent (DES) was implanted from the ostium of the LMCA toward the LAD. **D,** Final kissing balloon inflation was performed with three balloons, positioned from the LMCA to the LAD, intermediate branch, and LCx. **E** and **F,** Final angiographic result. *NC,* Noncompliant balloon.

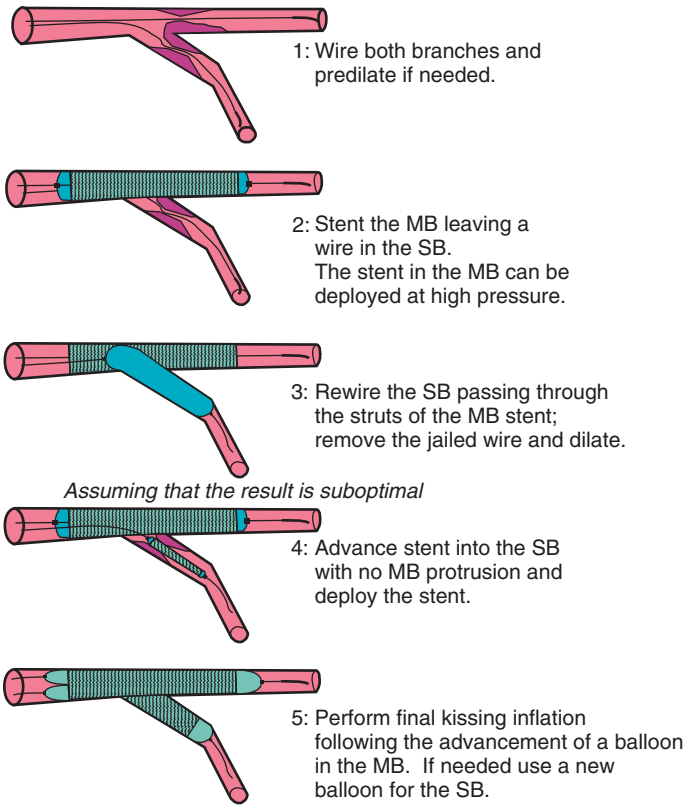

FIGURE 22-5 A schematic representation of the T technique. MB, main branch; SB, side branch.

can be used that include a T technique or a TAP, culotte, or reverse/internal crush configuration. FFR or new imaging techniques, such as optical coherence tomography (OCT), could be of value in the evaluation of the result in the SB after balloon dilation.

The T Technique

The T technique (Fig. 22-5) is probably one of the one most frequently utilized strategies to shift from provisional stenting to stenting the SB.[38,39] This technique consists of advancing a second stent into the SB following adequate dilation of the MB stent struts. The stent is positioned at the ostium of the SB in an effort to minimize any possible gap, and a second kissing balloon inflation is performed. In our view, the T technique is associated with the risk of leaving a small gap between the stent implanted in the MB and the stent implanted in the SB; this gap can be a factor that contributes to an uneven distribution of the drug, leading to ostial restenosis of the SB.

T Stenting and Small Protrusion

The TAP technique is a modification of the T-stenting technique and is based on an intentional minimal protrusion of the SB stent within the MB (Fig. 22-6).[40,41] This technique can be accomplished in four steps: (1) a second stent is advanced into the SB in such a way as to minimally protrude (1 or 2 mm) into the MB; (2) a balloon is advanced into the MB; (3) the SB stent is deployed as usual (≥12 atm), and the MB balloon is simultaneously inflated at the same or higher pressure; and (4) both balloons are deflated and removed. This technique is quite similar to the V-stenting technique, the only difference being that one of the components of the system is a balloon, which is inflated inside a stent previously deployed in the MB.

Despite some concerns about stent protrusion into the MB, we have been able to perform IVUS in the MB and SB, and when needed, to advance additional stents distally into the MB and the SB. Three-year clinical follow-up of 95 patients treated with TAP stenting showed a MACE rate of 12.9%, and no cases of definite or probable stent thrombosis have been reported.[42]

Reverse/Internal Crush: Crush Performed After Main Branch Stenting

The main purpose of performing the reverse crush (Fig. 22-7)[43,44] is to allow an opportunity for provisional SB stenting. This technique was developed with the intent to minimize the possible gap between the MB and SB stents. The reverse crush can be performed using a 6-Fr guiding catheter according to the following steps:

1. A second stent is advanced into the SB and is left in position without being deployed.
2. A balloon sized according to the diameter of the MB and shorter than the stent already deployed is advanced into the MB and positioned at the level of the bifurcation, taking care to stay inside the stent previously deployed in the MB.
3. The stent in the SB is retracted about 3 mm or less into the MB and deployed. The deploying balloon is removed, and an angiogram is obtained to verify the absence of any distal dissection and the need for an additional stent. If such is the case, the wire from the SB is removed, and the balloon in the MB is inflated at high pressure (≥12 atm).
4. The SB struts are recrossed with a wire and a balloon (a 1.5 mm balloon is sometimes needed). The balloon is sized to the SB reference diameter and inflated at high pressure (12 to 20 atm).
5. An FKBI is performed.

In our practice, this technique has been completely replaced by the TAP.

The Provisional Culotte Technique

The culotte technique can be proposed as a provisional SB stenting strategy in Y-shaped angulated bifurcation lesions, as in the original description,[45] although the first stent can be deployed across the most angulated branch, usually the SB (inverted culotte).[46] This technique can be accomplished in three steps: (1) after MB stenting, a second stent is advanced into the SB—protruding into the MB to overlap the proximal part of the MB stent—and is expanded following removal of the MB wire; (2) the MB is rewired through the stent struts and dilated; (3) and an FKBI is performed.

With all the above two-stent techniques, before advancing a stent through the side struts of an implanted stent, it is important to dilate the struts so the advancing stent is not "caught" by the first stent, resulting in stent embolization.

The European Bifurcation Club Approach to Bifurcation Stenting

The European Bifurcation Club (EBC) was founded in 2004 to devise a common terminology for the description and treatment of bifurcation lesions and to exchange ideas on the clinical, technical, and fundamental aspects of the specific treatment strategies implemented in this setting. A synopsis of these discussions is presented below.[17,18,31]

1. The Medina classification should be used for bifurcation lesions (1,0), and the Main, Across, Distal, Side (MADS) classification should be used for bifurcation stenting techniques, which is based on the manner in which the first stent has been implanted.
2. Provisional T-stenting remains the gold standard technique for most bifurcations.
3. Large SBs with ostial disease that extends more than 5 mm from the carina are likely to require a two-stent strategy.
4. In the provisional technique, after wiring both branches, the MB should be predilated when required, whereas SBs without severe calcification or long (>5 mm) significant lesions do not require routine predilation.
5. The SB guidewire should be jailed behind the MB stent in true bifurcation lesions.
6. The MB stent is selected according to distal MB diameter, and postdilation or kissing balloon inflations are required to optimize the proximal MB stent diameter.
7. Wire crossing through the distal strut following MB stenting is recommended.

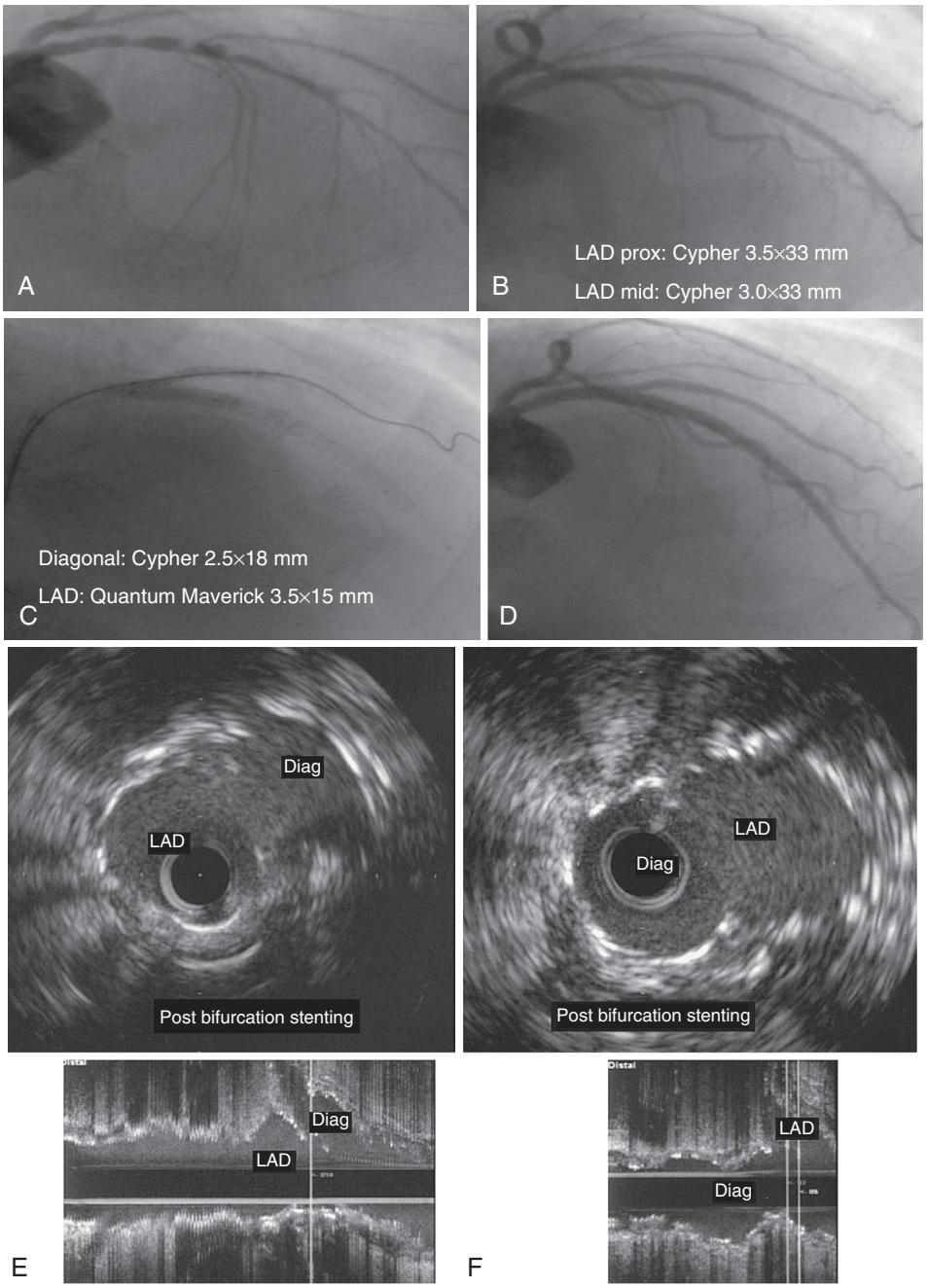

FIGURE 22-6 Example of T stenting and small protrusion (TAP) technique. **A,** Baseline angiogram presents diffuse disease of the left anterior descending artery (LAD) and ostial/proximal segment of the diagonal (Diag) branch. **B,** Following stent implantation in proximal and mid segments of the LAD and balloon angioplasty at the diagonal branch, the result appears unsatisfactory. A second stent is advanced in the diagonal branch to minimally protrude (1 or 2 mm) into the LAD, and the balloon is positioned in the LAD. **C,** The stent in the diagonal branch is deployed, and the balloon in the LAD is simultaneously inflated. **D,** Angiographic view of the final result. Transverse and longitudinal views of final intravascular ultrasound in the LAD (**E**) and the diagonal branch (**F**) confirm optimal stent position in the diagonal branch with minimal protrusion into the LAD.

8. The proximal optimization technique—that is, optimization of the stent deployment proximal to the carina by using a short, half-size bigger balloon—should be used in any case in which recrossing into an SB with either a guidewire or a balloon would be difficult.
9. Kissing balloon inflation for carina reconstruction is mandatory with a two-stent technique.
10. Kissing balloon inflations or pressure-wire interrogation should be used in provisional stenting when an angiographically significant (>75%) SB lesion remains after MB stenting.
11. High-pressure proximal stent inflation using a short, noncompliant balloon should be considered for correction of possible proximal stent distortion after FKBI.

USING TWO STENTS WITH INTENTION TO TREAT

In the event that an operator believes a particular bifurcation will require implantation of two stents, one in the MB and the other in the SB, several techniques described here are those we consider suitable in

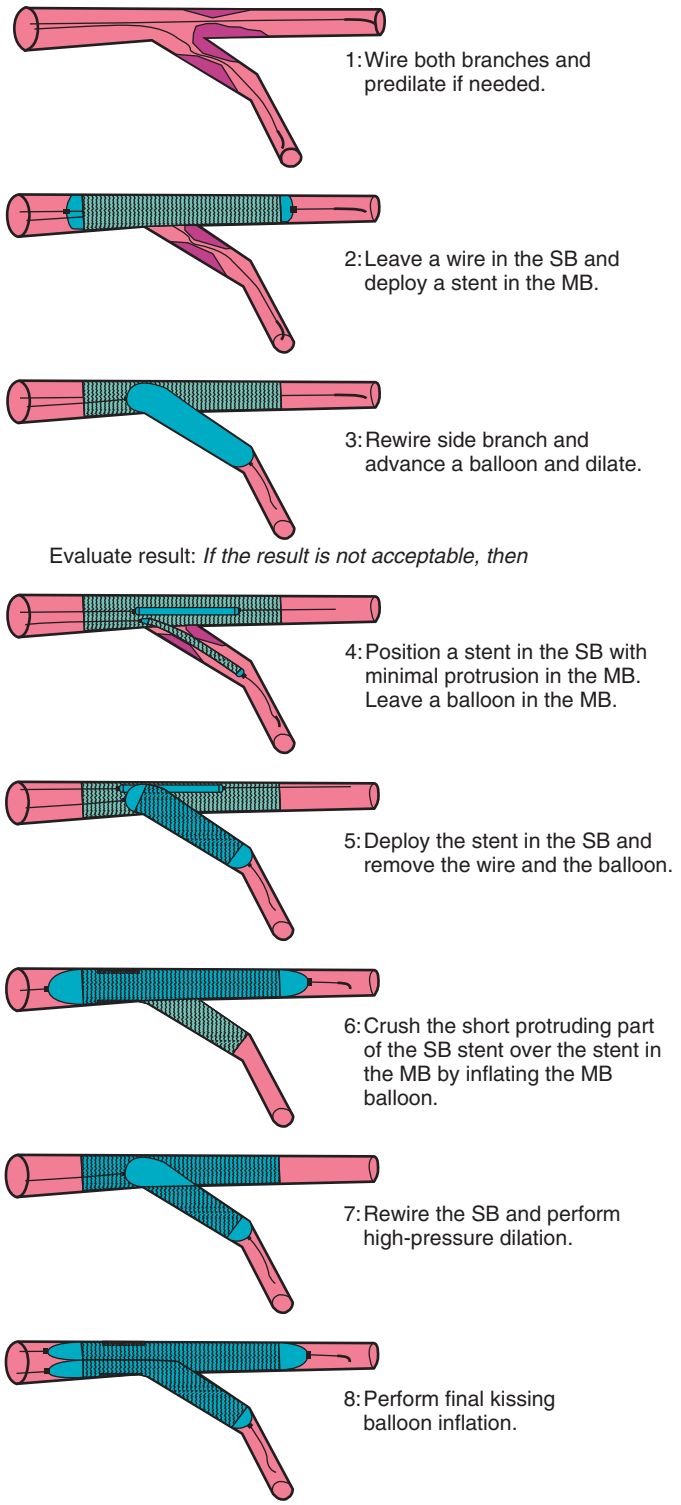

FIGURE 22-7 A schematic representation of the reverse/internal crush technique.

the era of DES. The two-stent approach will be reserved only for selected true bifurcations following evaluation of additional parameters, which will be discussed.

Size and Territory of Distribution of the Side Branch

The term *side branch* is a somewhat misleading connotation, and the term may convey the idea of a vessel of lesser importance compared with the MB. Although this may be true in most cases, various anatomic conditions exist in which the SB is as important as the MB because of both the size and territory of distribution: an LMCA that bifurcates into the left anterior descending (LAD) and left circumflex (LCx) coronary arteries, an RCA that bifurcates in a posterior descending artery and a number of posterolateral branches, and a dominant LCx that bifurcates into a distal circumflex and a large obtuse marginal branch are all examples in which SBs are important vessels that can generate a significant amount of ischemia if left with a critical narrowing. As outlined in Figure 22-3, the size of the territory supplied by the SB becomes a valuable element to guide the decision to accept a mediocre result at the SB ostium (following balloon angioplasty) versus the need to have almost 0% residual stenosis following additional SB stenting.

The Length of the Lesions Present at the Ostium of the Side Branch

Whereas most of the studies have demonstrated that a focal lesion present at the ostium of the SB does not prevent a provisional approach, the situation may be different when the stenosis extends for several millimeters into the SB.

The Angle Between the Main Branch and the Side Branch and the Narrowing at the Ostium of the Side Branch

The angle of origin of the SB from the MB can be acute, close to 90 degrees, or obtuse. The narrower the angle between the two branches, the higher the risk of plaque prolapse and compromise of the ostium of the SB will be.[47] Another element to consider when looking at the angle between the two branches is the difficulty to recross into the SB following stenting of the MB. The severity of the narrowing at the ostium of the SB is another factor that influences placement of two stents. An additional variable to be considered is the result obtained following balloon dilation of the SB. All these elements mean that the decision to implant a second stent may also be made at an intermediate time, following predilation of the MB and SB. These considerations should not overshadow the point that the decision for one, two, or sometimes even three stents (in case of a trifurcation) should be made as early as possible. A timely action will affect the result, and it will help save time and cost in addition to lowering the risk of complications.

TWO-STENT TECHNIQUES

The Culotte Technique

The culotte technique (Fig. 22-8) uses two stents and leads to full coverage of the bifurcation at the expense of an excess of metal covering the proximal end.[45,46] The culotte technique likely provides the best coverage of the carina. Important caveats about this approach are that with some closed-cell design stents, the opening of the struts toward the branches may only reach a maximum diameter of 3 mm. For this reason, the culotte technique should be used only with stents that have a design that allows full opening of the struts toward both branches (open-cell stents). The Nordic complex bifurcation stenting study compared crush or culotte stenting with SESs and demonstrated at 6-month follow-up no difference between the two groups in terms of death, MI, or repeat revascularization, and clinical outcomes remained similar at a 3-year follow-up.[19,20]

Technique Description

The culotte technique is performed in five steps: (1) both branches are predilated; (2) a stent is deployed across the most angulated branch, usually the SB; (3) the nonstented branch is rewired through the stent struts and dilated; (4) a second stent is advanced and expanded into the nonstented branch, usually the MB; and (5) FKBI is performed.

This technique is suitable for all angles of bifurcations and provides near-perfect coverage of the SB ostium. One disadvantage is that, like

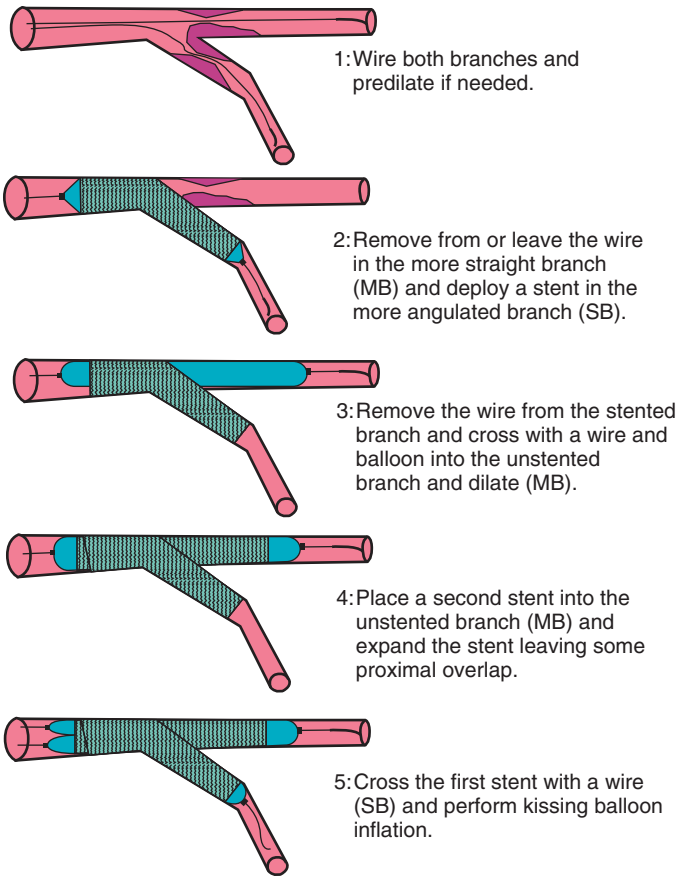

FIGURE 22-8 A schematic representation of the culotte technique.

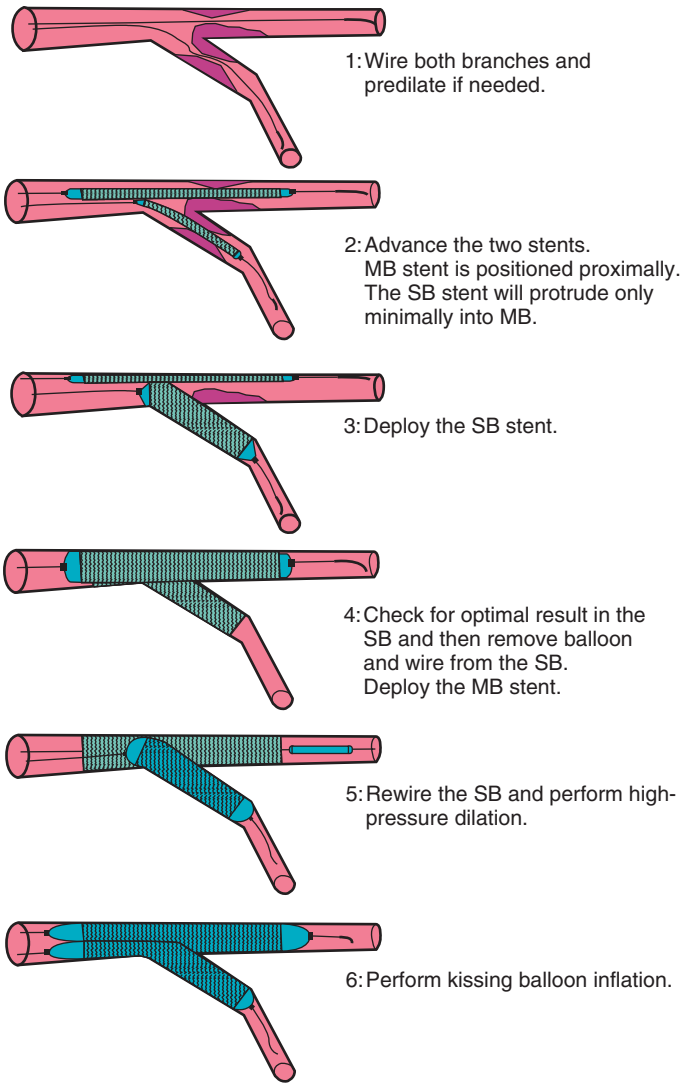

FIGURE 22-9 A schematic representation of the mini-crush technique.

the crush, the culotte technique leads to a high concentration of metal with a double-stent layer at the carina and in the proximal part of the bifurcation. Other disadvantages of the technique are that rewiring both branches through the stent struts can be difficult and time consuming, and the maximum opening achievable is limited when a stent with a closed-cell design is implanted.

The Mini-Crush Technique (Side Branch Stent Crushed by the Main Branch Stent)

The crush technique (Fig. 22-9) was born together with DESs.[48,49] The addition of the word *mini* highlights the need to decrease as much as possible the amount of stent overlap between the SB and MB, as described by Galassi and coworkers,[49] compared with modified T-stenting as described by Kobayashi and others.[50] Ormiston and colleagues[51] reported bench-testing data that stressed the importance of FKBI and concluded that appropriate SB and MB postdilation is needed to fully expand the stent at the SB ostium, to widen gaps between stent struts overlying the SB (facilitating subsequent access), and to prevent stent distortion. Since routine performance of the FKBI was adopted, restenosis at the ostium of the SB seems to be declining.[52]

The main advantage of the crush technique is that immediate patency of both branches is ensured. This objective is notably important when the SB is functionally relevant or if insertion of a guidewire proves difficult. The main disadvantage is that the performance of the FKBI makes the procedure more laborious because of the need to recross multiple struts with a wire and a balloon.

The performance of the crush technique requires a 7- or 8-Fr guiding catheter, and the technique commits the operator to the implantation of two stents. Later we will describe a modification of the crush technique that allows provisional SB stenting and permits performing the same or a similar approach utilizing a 6-Fr guiding catheter. An angiographic example of the crush technique is presented in Figure 22-10. When the angle between the MB and SB is close to 90 degrees, it is possible to minimize the gap even without crushing the SB stent and utilizing the modified T-stenting technique.

Technique Description

This technique is accomplished in six steps. First, both branches are wired and fully dilated. Particular attention is paid to dilate the SB, and a 6-mm long cutting balloon may be used if it appears that the predilating balloon does not fully expand at the ostium of the SB. Second, the stent for the SB is positioned in the SB, and then the MB stent is advanced. In the third step, the SB stent is pulled back into the MB for about 2 to 3 mm. This step is verified in at least two projections.

In step four, the stent in the SB is deployed at least at 12 atm. The balloon is deflated and removed from the guiding catheter. An angiogram is taken to verify that the SB has an appropriate lumen and normal flow and that no distal dissection or residual lesions are present. If an additional stent is needed in the SB, this is the time to perform the implant. Following this check, the wire is removed from the SB, and the stent in the MB is fully deployed at high pressure, usually above 12 atm. An angiogram is taken following removal of the balloon from the MB.

Next, in step five, a wire is advanced into the SB aiming to cross through the central or proximal strut.[53] This maneuver may be time

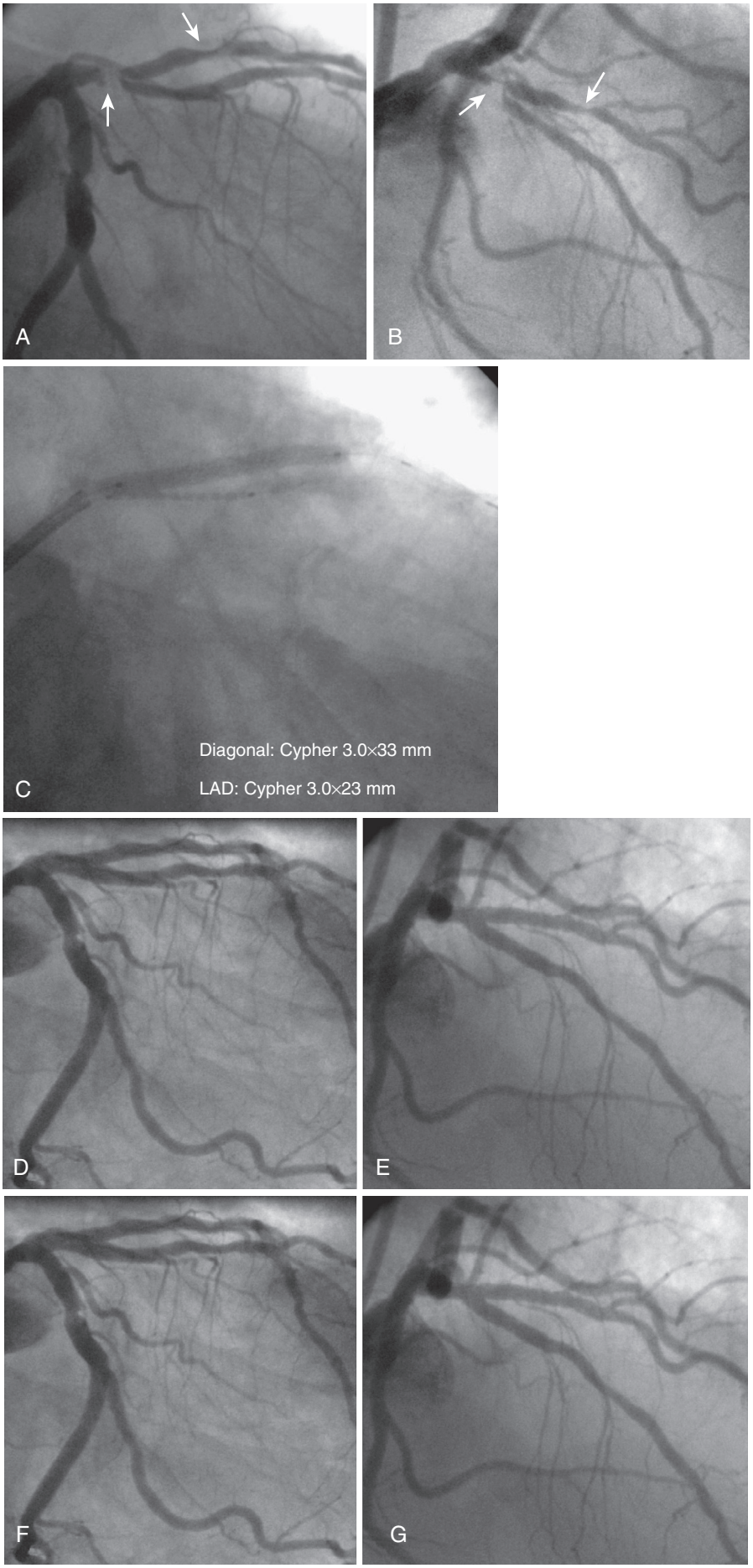

FIGURE 22-10 Example of crush stenting technique. **A** and **B,** Baseline angiogram of bifurcation lesion involving left anterior descending artery (LAD) and a large diagonal branch. **C,** Following lesion predilation, two stents are positioned, and the stent in the LAD is placed more proximally than the stent in the diagonal branch. The side-branch stent is inflated first (*diagonal branch*). Note that the long stent was chosen for the diagonal branch to also cover a lesion distal to the bifurcation site (*arrows* in **A** and **B**). Optimal final result (**D** and **E**) was maintained at 10-month angiographic follow-up (**F** and **G**).

consuming, based on initial experience with this technique. Besides trying with the initial floppy wire (Balance Universal, Abbott Vascular Devices, Redwood City, CA/Guidant, Santa Clara, CA), the next-best choices are the Rinato/Prowater (Asahi Intec, Japan/Abbott Vascular), Crossit 100 (Abbott Vascular/Guidant), and Pilot 50 and Pilot 150 (Abbott Vascular/Guidant). We frequently try first to cross through the stent struts into the SB with a 1.5 to 1.25 mm diameter balloon. If this very small balloon cannot cross, we consider repositioning the wire traversing the stent struts in another spot. If the problem is still present, we then try a fixed-wire balloon, such as an ACE (Boston Scientific-Scimed, Minneapolis, MN). It is important to perform a final dilation of the stent toward the SB with a balloon appropriately sized to the diameter of this branch and inflated at high pressure (≥12 atm). Finally, a second balloon is advanced over the wire that was left in place in the MB, and FKBI is performed at 8 atm or more.

Step Crush and Double-Kissing Crush

When a two-stent technique is required as intention to treat, and a 6-Fr guiding catheter is the only available approach (radial approach), the *step crush* or *the modified balloon crush* techniques can be used.[54] The final result is basically similar to that obtained with the standard crush technique, with the only difference being that each stent is advanced and deployed separately. The need for a 6-Fr guiding catheter is the main reason to utilize this technique.

The DK crush and sleeve techniques are other variants of the crush technique that may optimize stent deployment and apposition.[55,56] Importantly, implementation of the DK crush technique decreased the 12-month rate of TVR compared with a provisional SB stenting strategy in one randomized study.[16]

Technique Description

The first part of this technique is the same as the standard crush technique. Then a stent is advanced into the SB, protruding a few millimeters into the MB, and a balloon is advanced into the MB over the bifurcation. Next, the stent into the SB is deployed, the delivery balloon is removed, and an angiogram is performed; if the result is adequate, the wire is also removed. The MB balloon is then inflated (to crush the protruding SB stent) and removed. Optionally, kissing balloon inflation can be performed at that time (the DK crush technique proposed by Chen and associates).[16,55] After that, a second stent is advanced into the MB and is deployed (usually at ≥12 atm). The steps that follow are similar to those of the crush technique and involve recrossing into the SB, SB stent dilation, and FKBI.

The V-Stent and the Simultaneous Kissing Stent Techniques

The V-stent (Fig. 22-11) and simultaneous kissing stent (SKS) techniques are performed by delivering and implanting two stents together.[57,58] One stent is advanced into the SB, and the other is advanced into the MB. Both stents are pulled back to create a new carina as close as possible to the original one. The main advantage of the V technique is that the operator will never lose access to any of the two branches. In addition, when an FKBI is performed, there is no need to recross any stent. Figure 22-12 shows an example of a V-stenting technique performed on the LMCA. When the two stents protrude into the MB with the creation of a "double barrel" and a very proximal carina, it is referred to as a *simultaneous kissing stent*.[58] We prefer the V-stenting technique for selected bifurcation lesions where the lesions are distal to the bifurcation (Medina 0,1,1); in the presence of a proximal stenosis in the MB, we prefer a different approach rather that creating an overlap with the SKS.

Technique Description

In this technique, both branches are wired and fully predilated. It is important to perform an adequate predilation to allow full stent expansion. In step two, the two stents are positioned into the branches with a slight protrusion of both stents into the proximal MB. Different

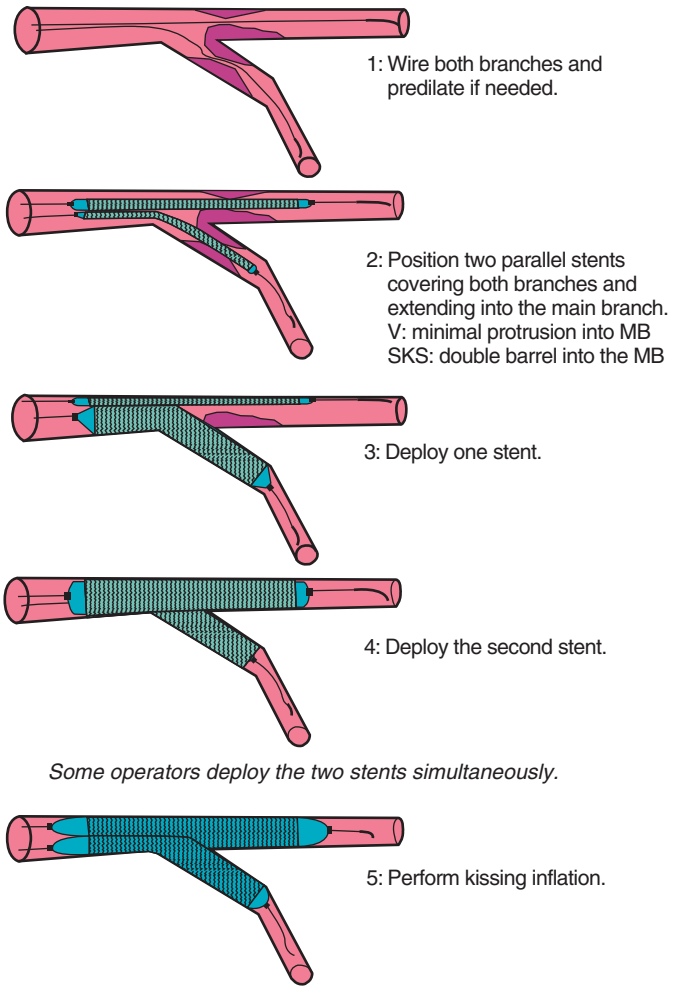

FIGURE 22-11 A schematic representation of the V technique.

operators allow a variable amount of protrusion creating sometimes a rather long (≥5 mm) double barrel in the proximal MB (SKS). Although we recognize that it is impossible to be so accurate as to position the stent exactly at the ostium of each branch, we generally try to limit the length of the new carina to less than 5 mm. Sometimes it is necessary to advance the first stent more distally into the vessel to facilitate the advancement of the second stent; this maneuver is essential when the kissing stent technique is used to stent a trifurcation using three kissing stents (a 9-Fr guiding catheter is needed). Following accurate stent positioning, it is important to verify their correct placement in two projections before deploying the stents. In our experience, each balloon is first inflated individually at high pressure (≥12 atm), whereas other operators inflate the balloons simultaneously.

The third step is to inflate both balloons simultaneously. The size of the balloon and of the stents is chosen according to the diameter of the vessels to be stented. In the event that the reference vessel size proximal to the bifurcation is relatively small, and the operator fears the risk that the two balloons inflated simultaneously may be oversized, the kissing inflation is performed at low pressure (4 atm).

Using the V technique, a metallic neocarina is created within the vessel proximal to the bifurcation. Theoretic concerns about the risk of thrombosis related to this new carina have not been confirmed. The types of lesions we consider most suitable for this technique are very proximal lesions, such as a bifurcation of a short LMCA free of disease. Ideally, the angle between the two branches should be less than 90 degrees. The V technique is also suitable for other bifurcations, provided that the portion of the vessel proximal to the bifurcation is

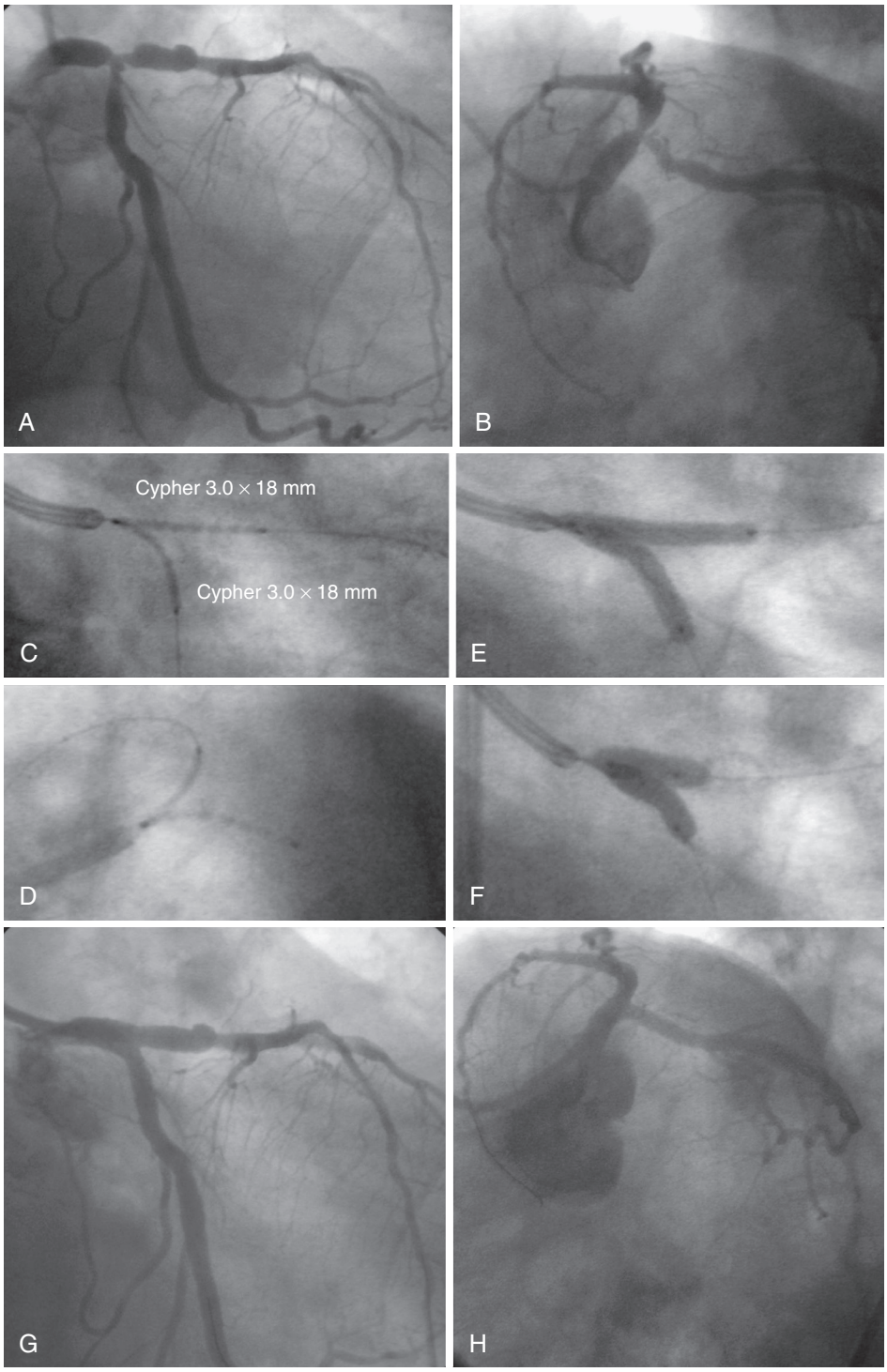

FIGURE 22-12 Example of V-stenting technique. **A** and **B,** Baseline angiogram of a left main coronary artery (LMCA) bifurcation lesion, with two large branches and the left anterior descending and left circumflex coronary arteries. The V-stenting technique was used because the disease was mainly at the level of the very distal LMCA, and the angle of the two branches was favorable for a V-stenting technique. **C** and **D,** Stent positioning in two projections. **E** and **F,** Stent deployment and postdilation with 4 mm balloons. **G** and **H,** The final result.

free of disease and there is no need to deploy a stent more proximally. It is quite intuitive how problematic positioning a stent proximal to the double barrel would be, with an inevitable bias toward one of the two branches and a high likelihood of leaving a gap.

The Y and Skirt Techniques

The Y-stent technique has a particular historic value because it was the first bifurcation stenting technique demonstrated in a live-case course.[59] This technique involves an initial predilation, followed by stent deployment in each branch. If the results are not adequate, a third stent may also be deployed in the MB.[60] To approximate the stent proximal to the already-deployed stents, it is necessary to modify the stent-delivery system by placing one stent over two balloons ("skirt" stenting).[61] This technique is the last resort for treating very demanding bifurcations in which uninterrupted wire access to both branches must be maintained.

Flower-Petal Stenting

The technique of flower-petal stenting involves implanting a stent in the SB with a single strut protruding into the MB; the protruding strut closest to the carina is wired and dilated to create a larger strut or "flower petal"; this protruding petal is then flattened and plastered down over the carina with a series of MB inflations, including an MB stent and kissing balloon inflations, thus ensuring complete ostial coverage and scaffolding.[62] The most challenging part of this technique is wiring a single strut close to the carina, and in its original description, it required IVUS guidance and was not always successful. The technique was modified to allow ex vivo wiring of the proximal strut and subsequent balloon insertion into this strut. This approach requires partial inflation of the proximal segment of the stent, performed before stent insertion in the guiding catheter. Although this creates a bulkier dual-wire and balloon system, the technique is suitable for a 6-Fr guide catheter and is mainly applied in bifurcation lesions located in the distal LMCA.

The key elements of the most frequently used two-stent techniques are summarized in Table 22-1. Whereas no definitive statement can be made regarding the best strategy to be used when there is a need to implant two stents in a bifurcation, in Figure 22-13, we present a schematic approach according to the anatomy of the lesion.

Controversies in the Technical Approach to Isolated Ostial Left Anterior Descending or Circumflex Lesions

Approach to Ostial Left Anterior Descending Coronary Artery Lesions

A left main 0,1,0 lesion (ostial LAD) is traditionally considered to be unfavorable for percutaneous intervention because of the technical difficulty and potential risk of serious complications. Two interventional strategies are traditionally used in this lesion subset: precise stent implantation at the LAD ostium level or stenting the LMCA toward the LAD. IVUS guidance has been proposed to assess plaque distribution before deciding which technique should be applied in a specific lesion. Precise stenting of the LAD ostium is feasible in cases with a large bifurcation angle and IVUS documentation of absence of disease in the distal LMCA. Precise LAD ostial stenting consists of scaffolding the counter-carina with a mild protrusion of the stent covering the ostium of the circumflex artery. In this technique, the proximal stent marker should be positioned just proximal to the angiographic carina (the transducer of the IVUS catheter could be filmed when it is positioned at the level of the carina to provide a reference for subsequent stent placement). The two disadvantages of precise ostial LAD stenting are that if the device is positioned too proximally, it protrudes into the LMCA and may compromise the LCx, making subsequent intervention difficult; or if the ostial LAD lesion is not totally covered by the stent, acute recoil and late restenosis can be expected.[31] Therefore optimal positioning of the stents is critical for the treatment of this lesion. Furthermore, with branch ostial disease, involvement of the distal LMCA is common, which thus leads to the impending danger of incomplete lesion coverage if stenting is not extended to the involved LMCA. From this perspective, a left MB ostial lesion is necessarily a bifurcation disease, and it should be treated in a similar manner. Therefore ostial disease of LAD and LCx would ideally be treated percutaneously by stenting from the LMCA into the diseased MB with provisional SB stenting.[31]

Approach to Isolated Side Branch Ostial (0,0,1) Bifurcation Lesions: Lesions at the Ostium of a Diagonal/Obtuse Marginal/Posterolateral Branch

Although infrequent, isolated SB ostial lesions (0,0,1) are very challenging, especially in Y-shaped angulations, and they can become the origin of a new lesion in the MB. Each operator should always remember the "sad story of the ostial diagonal lesion" and be aware that overly aggressive treatment of these lesions may not always be the best approach; they can lead to trauma of the LAD and can cause a new stenosis of this vessel. Unfortunately, we cannot propose an easy solution to this conundrum other than to alert the operator to this possible risk. Occasionally, a simple cutting balloon dilation at the ostium of a diagonal branch can be a minimalistic approach.

Brunel and colleagues[63] have developed an "inverted" technique for the treatment of Medina 0,0,1 lesions, derived from the usual provisional T-stenting. Stent is implanted from the proximal main branch through the SB, with reopening of the strut through the distal MB and systematic FKBI. Alternative approaches include the use of a single short stent (precise ostial positioning is very difficult, and complete ostial coverage is difficult to impossible except for a 90-degree bifurcation); also, a shunt technique or dedicated stents can be used.[31] One strategy to be considered is to evaluate the functional significance, with FFR, of the lesion located at the SB; finally, we should not dismiss the fact that optimal medical therapy is a reasonable approach.

TABLE 22-1 Main Characteristics of Two-Stent Techniques

	T/TAP	Mini Crush	Culotte	SKS
Guide catheter (Fr)	6	7*	6	7
Provisional SB stenting	Yes	No	Possible	No
Preserved GW access to MB	Yes	Yes	No	Yes
Preserved GW access to SB	No	No	No	Yes
Bifurcation Angle				
<70°	Not ideal	Ideal	Suitable	Suitable
>70°	Ideal	Not ideal	Not ideal	Not ideal
MB and SB Diameters				
Similar diameters	Suitable	Suitable	Ideal	Ideal
Discrepancy in diameters	Suitable	Ideal	Not ideal	Not ideal

*A 6-Fr guide catheter could be used for balloon "step crush" and "double-kissing crush."
GW, Guidewire; *MB,* main branch; *SB,* side branch; *SKS,* simultaneous kissing stent; *T/TAP,* T stenting or T stenting and protrusion.

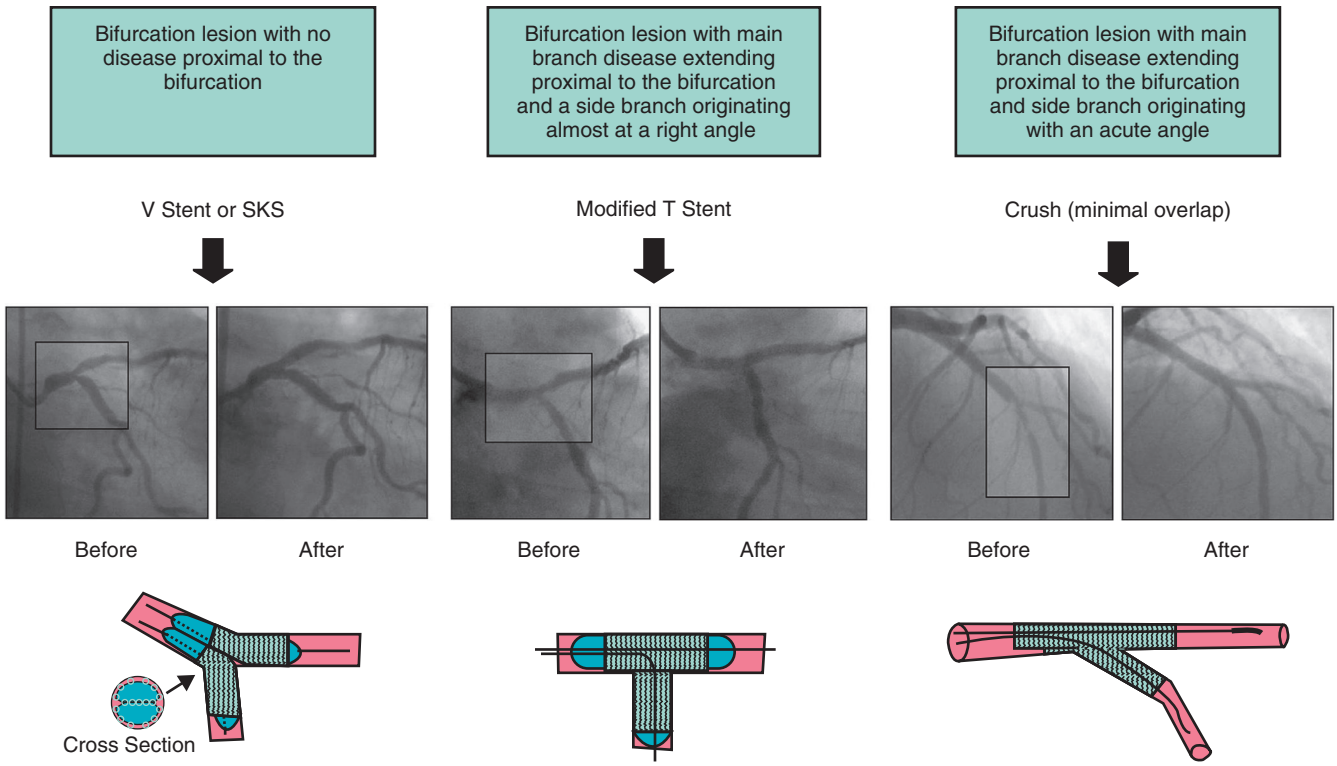

FIGURE 22-13 Proposed approach when implanting two stents on a bifurcation as intention to treat. *SKS,* Simultaneous kissing stents.

Dedicated Bifurcation Stents

The conventional approach to bifurcation PCI still has a number of limitations such as (1) maintaining access to the SB throughout the procedure; (2) MB stent struts jailing the SB ostium, resulting in difficulty in rewiring the SB or passing the balloon/stent into the SB through the stent struts; (3) distortion of the MB stent by SB dilation; (4) inability to fully cover and scaffold the ostium of the SB; (5) inability of the stent structure to withstand SB balloon dilation and deformation; and finally, (6) operator skills and technical experience are a consideration.[64] Thus far, the main advantage of most dedicated bifurcation stents is to allow the operator to perform the procedure on a bifurcation lesion without the need to rewire the SB. Dedicated bifurcation stents can be broadly divided into two main categories, the first of which includes stents for provisional SB stenting that facilitate or maintain access to the SB after MB stenting and do not require recrossing of MB stent struts (examples include the Petal, formerly AST, stent, [Boston Scientific, Natick, MA]; Multilink Frontier/Pathfinder/SBA [Abbott Vascular]; Invatec Twin-Rail [Medtronic/Invatec, Brescia, Italy]; Nile Croco/Pax [Minvasys, Genevilliers, France]; Antares [TriReme Medical, Pleasanton, CA]; Y-Med SideKick [Y-Med, San Diego, CA]; and the Stentys [Stentys SAS, Clichy, France]). These stents allow placement of a second stent on the SB if needed. The second category includes stents that usually require another stent implanted in the bifurcation (examples include the Axxess Plus [Devax, Irvine, CA]; Sideguard [Cappella, Auburndale, MA]; and the Tryton [Tryton Medical, Newton, MA]). The Tryton and Sideguard are designed to treat the SB first and require recrossing into the SB after MB stenting for final kissing inflation. The Axxess Plus is the exception because it is implanted in the proximal MB at the level of the carina and does not require recrossing into the SB but may require the additional implantation of two further stents in the distal MB and SB to completely treat some types of bifurcation lesions.

The TAXUS Petal Bifurcation Paclitaxel-Eluting Stent System (Boston Scientific, Natick, MA) is made of a platinum-enhanced alloy and is designed to provide a uniform layer of metal in the MB that extends 2 mm into the SB. It is the short segment stent or "nipple" extending into the SB from which this device derives the name "Petal." This stent is crimped over two balloons, with the SB balloon positioned underneath the petal elements. Upon inflation, the MB balloon deploys the stent into the main artery, while the side balloon deploys the petal into the ostium of the SB. The first generation of this stent, called the *AST Petal*, developed by Advanced Stent Technologies, was a 316 L stainless steel slotted-tube design.

Formerly the Frontier System, the Pathfinder everolimus-eluting side branch access (SBA), the Abbott Bifurcation Stent (ABS), is a chromium-cobalt stent that uses the Xience V DES platform. The ABS stent is crimped onto two balloons: the MB balloon, which is mounted on a rapid-exchange lumen, extends the length of the stent; the SB balloon, which is mounted on an over-the-wire (OTW) lumen, exits the stent at the midpoint. The Twin-Rail (Medtronic/Invatec, Brescia, Italy) is similar to the Multilink Frontier/Pathfinder/SBA (Abbott Vascular) double-balloon system except that in the latter, the SB balloon is a short, tapered balloon, whereas the Twin-Rail uses a full dilation balloon.

The Nile Pax (BMS version of the Nile Croco), a polymer-free dedicated bifurcation PES, is a 6-Fr–compatible chromium-cobalt stent mounted on two independent rapid exchange (Rx) PTCA catheters with a specific SB balloon shape. This stent-delivery system is similar to that of the Multi-link Frontier and Twin-Rail, but unlike these systems, which comprise a single catheter with a single inflation port, the Nile Croco/Pax has two independent yet joined catheters that require independent manipulation and pressure monitoring.

The Antares stent (TriReme Medical, Pleasanton, CA), with automatic SB support deployment, consists of a single-balloon, expandable, 316 L stainless steel stent. It has an SB support structure in the center of the stent provided with two radiopaque tantalum markers for positioning and orienting at the bifurcation site. Stent deployment is achieved using a single rapid-exchange balloon catheter and an SB-stabilizing wire encased in a peel-away lumen to minimize wire crossing. As the stent approaches the targeted bifurcation, the catheter is torqued to align the stent's central opening with the SB ostium. Upon

expansion of the main stent body, the ostial crown is automatically deployed with elements protruding approximately 2 mm into the SB to scaffold the ostium. The Antares is similar to the Petal stent but has the advantage of tracking over a single wire; and unlike the Petal, which uses a balloon to expand the SB elements, the SB elements expand automatically with this stent.

The SideKick stent integrates an MB fixed-wire platform with a rapid-exchange steerable SB guidewire designed to preserve SB access during bifurcation stenting. Three models are available, each with different exit ports (proximal, mid, and distal) that are selected depending on the location of the disease in the bifurcation. When the device is close to the carina, a guidewire is passed through the SB exit port and MB stent struts into the SB, thus avoiding recrossing into the SB.

Stentys is a self-expanding nitinol stent made of a Z-shaped mesh linked by small interconnections. The stent is coated on the abluminal side with paclitaxel on a durable polymer matrix (poly[ethylene succinate] [PESU]), a polysulfone that permits controlled drug elution. The unique feature of this stent is the ability to disconnect the stent struts with an angioplasty balloon. Thus an opening for the SB can be created anywhere in the stent after it is implanted in the vessel, while at the same time, the disconnected struts scaffold the SB ostium.

The Axxess Plus stent, Devax, (Biosensors, Singapore) is a self-expanding, nickel-titanium conical stent placed at the level of the carina by means of a skirt technique, and it was the first of these dedicated bifurcation stents designed to elute an antirestenotic drug (biolimus A9). The Axxess Plus has a rapid-exchange delivery system with a hydrophilic coating to allow controlled deployment upon withdrawal of a cover sheath using the actuator. However, the Axxess stent may be limited by the fact that it needs to be precisely nested at the carina to be effective and in most cases will need another stent to treat the bifurcation fully.

The Sideguard Ostium Protection Device (Cappella/ArraVasc; Galway, Ireland) is a self-expanding trumpet-shaped nitinol stent deployed using a special balloon-release sheath system. It is currently a BMS, but the next generation will be drug eluting with a biodegradable polymer. Radiopaque markers located at the distal and proximal ends of the Sideguard delivery system facilitate positioning of the stent at the SB ostium. The stent is deployed using a nominal pressure balloon, which helps tear a protective sheath that keeps the Sideguard in place until deployment. Once released, the Sideguard self-expands into place. The delivery system and the guidewire are then removed from the SB. A conventional stent is then placed in the MB, the SB is reaccessed with a guidewire, and the procedure is completed with a standard FKBI.

The Tryton Side Branch stent (Tryton Medical, Newton, MA) is a slotted-tube, cobalt-chromium balloon expandable stent designed for implantation in the SB of a bifurcation. The stent consists of three zones: (1) a *distal SB zone*, which treats the disease in the SB; (2) a *transition zone*, which is positioned at the SB ostium; and (3) an *MB zone*. Treatment of a bifurcation with the Tryton stent generally commits the operator to implanting two stents in the bifurcation, and the technique is identical in approach to that used when performing the culotte technique. The Tryton stent is deployed across the SB ostium first. A standard MB stent is then tracked through the proximal MB zone of the Tryton into the distal MB and is deployed. The MB stent struts then have to be recrossed to perform an FKBI. The Randomized Controlled Study to Evaluate the Safety & Effectiveness of the Tryton Side Branch Stent Used With DES in Treatment of de Novo Bifurcation Lesions in the Main Branch & Side Branch in Native Coronaries, did not meet the primary end point of statistical noninferiority in patients who underwent stenting of the MV and the SB versus those who underwent stenting of the MV alone with a provisional strategy to stent the SB if necessary (the composite end point of target-vessel failure for the provisional arm was 12.8% and for the Tryton arm it was 17.4%, $P = .108$).[65]

Dedicated bifurcation stents may potentially overcome limitations of conventional stents in bifurcations (multiple layers, distortion, crossing through the side of the stent, gaps in scaffolding). However, although efforts to produce dedicated bifurcation stent-delivery systems are strongly encouraged and research is fostered, none of the currently available systems can challenge the results offered by the provisional T-stent strategy in the majority of bifurcation lesions.

Bioresorbable Scaffolds

All randomized trials and registries to evaluate bioresorbable scaffolds (BRSs) excluded bifurcation lesions even if the SB was totally free from disease. This fact does not mean that current BRSs cannot be implanted in bifurcations. When performing BRS implantation in a bifurcation lesion, the following points should be clear:

1. The provisional approach should be the default technique.
2. After having implanted the BRS in the MB, if SB dilation is necessary, balloons larger than 2.5 mm should not be used to avoid fracture of a connecting bridge between two radial rings.
3. If SB dilation has been performed, it is important to inflate a balloon in the MB to correct scaffold malapposition caused by SB dilatation.
4. Kissing balloon dilation should be avoided and replaced by sequential balloon inflation. The MB balloon should be deflated last.
5. When MB and SB stenting is performed with the intention to treat, there is the option to utilize a BRS or a metal stent for the SB. A BRS can be considered for the SB when the size of this vessel is 2.5 mm or larger and the angle with the MB is favorable for the T technique. When two BRSs are implanted, one in the MB and another in the SB, the T technique should be used. The culotte and the crush techniques should be avoided to prevent scaffold fractures and excessive overlap in consideration of the thickness of the struts. When a metal stent is implanted in the SB with the intention to treat, we suggest use of the mini-crush technique.
6. When SB stenting is needed as a crossover from provisional stenting, metal stent implantation on the SB should be considered using the T or the TAP techniques.

For a more in-depth understanding of BRS stenting in bifurcation lesions, we suggest that the reader refer to dedicated reviews.[66,67]

ROLE OF ADJUNCTIVE PROCEDURES

Rotational Atherectomy

As discussed for ostial lesions, the role of rotablation is important to allow optimal stent expansion in lesions with severe superficial calcifications. Even if no data are available regarding the role of this technology with DESs, we think it is intuitive to aim for optimal stent expansion and symmetry. In a setting of a very calcific lesion, this goal can only be obtained with adequate lesion preparation.

The main area of discussion is how frequently a calcific lesion should be pretreated with rotational atherectomy and when, conversely, a high-pressure balloon is sufficient. Except for information obtained with IVUS, or when no balloon would cross the lesion, we cannot provide additional objective guidelines to make a scientific decision. The operator's judgment remains the most frequent tool dictating the choice of rotational atherectomy. Burr size is typically small (1.25 or 1.5 mm) with the intent to modify the plaque, minimizing the risk of embolization. In our experience, SB stent underdeployment due to inadequate preparation remains the most important cause of restenosis at the ostium of the SB.[68]

Cutting Balloon

Bifurcation lesions with a fibrotic plaque at the SB ostium are an ideal setting for this device. The Restenosis Reduction by Cutting Balloon Evaluation (REDUCE III)[69] randomized trial evaluated the role of cutting balloon dilation before stenting versus standard balloon dilation in a variety of lesions. This trial reported a lower restenosis rate (11.8% vs. 18.8%, $P = .04$) when lesions were predilated with the cutting balloon. The fact that the final postprocedure lumen diameter

was larger in the cutting balloon arm and that the late loss was 0.74 mm for both strategies leads us to believe the main advantage was better stent expansion. As discussed in the context of rotational atherectomy, it is difficult to demonstrate that a niche device has an advantage in every lesion. For this reason we suggest using the cutting balloon in selected moderately calcific and fibrotic lesions, especially when the origin of the SB is involved.

Associated Pharmacologic Treatment

When performing bifurcation stenting with one or two stents, we do not usually change our protocol of periprocedural heparin administration (100 U/kg without elective glycoprotein [GP] IIb/IIIa inhibitors and 70U/kg with elective GP IIb/IIIa inhibitors). Usage of GP IIb/IIIa inhibitors is reserved for thrombus-containing lesions and patients with acute coronary syndromes. GP IIb/IIIa inhibitors are sometimes administered when the final result at the SB appears suboptimal and the operator does not want to implant another stent. An alternative to GP IIb/IIIa inhibitors and heparin is bivalirudin. We routinely administer a 600-mg loading dose of clopidogrel in the catheterization laboratory.[70] In our current practice, the duration of combined thienopyridine and aspirin treatment following stent implantation is usually for a minimum or 6 months and is usually extended to 1 year.

CONCLUSIONS

The introduction of DESs has made a remarkable improvement in the treatment of bifurcation lesions. However, randomized DES trial data from several trials has shown that routine two-vessel stenting does not improve either angiographic or clinical outcomes for most patients with coronary bifurcation lesions. Therefore provisional SB stenting remains the gold standard technique for most bifurcations. Nevertheless, many bifurcation lesions require the implantation of two stents for the intention to treat, and operators should be confident in such settings. Finally, the introduction of the DES dedicated for different types of bifurcations may further facilitate the conquest of one of the most challenging areas in interventional cardiology.

REFERENCES

1. Lefevre T, Louvard Y, Morice MC, et al: Stenting of bifurcation lesions: classification, treatments, and results. *Catheter Cardiovasc Interv* 49:274–283, 2000.
2. Safian RD: Bifurcation lesions. In Safian RD, Freed M, editors: *Manual of interventional cardiology*, Royal Oak, 2001, Physicians Press, pp 221–236.
3. Aliabadi D, Tilli FV, Bowers TR, et al: Incidence and angiographic predictors of side branch occlusion following high-pressure intracoronary stenting. *Am J Cardiol* 80:994–997, 1997.
4. Louvard Y, Lefevre T, Morice MC: Percutaneous coronary intervention for bifurcation coronary disease. *Heart* 90:713–722, 2004.
5. Medina A, Suárez de Lezo J, Pan M: [A new classification of coronary bifurcation lesions]. *Rev Esp Cardiol* 59:183, 2006. [Article in Spanish].
6. Fujii K, Kobayashi Y, Mintz GS, et al: Dominant contribution of negative remodeling to development of significant coronary bifurcation narrowing. *Am J Cardiol* 92:59–61, 2003.
7. Colombo A, Moses JW, Morice MC, et al: Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation* 109:1244–1249, 2004.
8. Al Suwaidi J, Berger PB, Rihal CS, et al: Immediate and long-term outcome of intracoronary stent implantation for true bifurcation lesions. *J Am Coll Cardiol* 35:929–936, 2000.
9. Yamashita T, Nishida T, Adamian MG, et al: Bifurcation lesions: two stents versus one stent–immediate and follow-up results. *J Am Coll Cardiol* 35:1145–1151, 2000.
10. Pan M, de Lezo JS, Medina A, et al: Rapamycin-eluting stents for the treatment of bifurcated coronary lesions: a randomized comparison of a simple versus complex strategy. *Am Heart J* 148:857–864, 2004.
11. Steigen TK, Maeng M, Wiseth R, et al: Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. *Circulation* 114:1955–1961, 2006.
12. Maeng M, Holm NR, Erglis A, et al: Long-term results after simple versus complex stenting of coronary artery bifurcation lesions: Nordic Bifurcation Study 5-year follow-up results. *J Am Coll Cardiol* 62:30–34, 2013.
13. Ferenc M, Gick M, Kienzle RP, et al: Randomized trial on routine vs. provisional T-stenting in the treatment of de novo coronary bifurcation lesions. *Eur Heart J* 29:2859–2867, 2008.
14. Colombo A, Bramucci E, Sacca S, et al: Randomized study of the crush technique versus provisional side-branch stenting in true coronary bifurcations: the CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) Study. *Circulation* 119:71–78, 2009.
15. Hildick-Smith D, de Belder AJ, Cooter N, et al: Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: the British Bifurcation Coronary Study: old, new, and evolving strategies. *Circulation* 121:1235–1243, 2010.
16. Chen SL, Santoso T, Zhang JJ, et al: A randomized clinical study comparing double kissing crush with provisional stenting for treatment of coronary bifurcation lesions: results from the DKCRUSH-II (Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions) trial. *J Am Coll Cardiol* 57:914–920, 2011.
17. Stankovic G, Lefevre T, Chieffo A, et al: Consensus from the 7th European Bifurcation Club meeting. *EuroIntervention* 9:36–45, 2013.
18. Hildick-Smith D, Lassen JF, Albiero R, et al: Consensus from the 5th European Bifurcation Club meeting. *EuroIntervention* 6:34–38, 2010.
19. Erglis A, Kumsars I, Niemela M, et al: Randomized comparison of coronary bifurcation stenting with the crush versus the culotte technique using sirolimus eluting stents: the Nordic stent technique study. *Circ Cardiovasc Interv* 2:27–34, 2009.
20. Kervinen K, Niemela M, Romppanen H, et al: Clinical outcome after crush versus culotte stenting of coronary artery bifurcation lesions: the Nordic Stent Technique Study 36-month follow-up results. *JACC Cardiovasc Interv* 6:1160–1165, 2013.
21. Chen SL, Xu B, Han YL, et al: Comparison of double kissing crush versus culotte stenting for unprotected distal left main bifurcation lesions: results from a multicenter, randomized, prospective DKCRUSH-III study. *J Am Coll Cardiol* 61:1482–1488, 2013.
22. Pan M, Suárez de Lezo J, Medina A, et al: Drug-eluting stents for the treatment of bifurcation lesions: a randomized comparison between paclitaxel and sirolimus stents. *Am Heart J* 153(15):e1–e7, 2007.
23. Song YB, Hahn JY, Choi SH, et al: Sirolimus-versus paclitaxel-eluting stents for the treatment of coronary bifurcations results: from the COBIS (Coronary Bifurcation Stenting) Registry. *J Am Coll Cardiol* 55:1743–1750, 2010.
24. Burzotta F, Trani C, Todaro D, et al: Prospective randomized comparison of sirolimus- or everolimus-eluting stent to treat bifurcated lesions by provisional approach. *JACC Cardiovasc Interv* 4:327–335, 2011.
25. Pan M, Medina A, Suárez de Lezo J, et al: Randomized study comparing everolimus- and sirolimus-eluting stents in patients with bifurcation lesions treated by provisional side-branch stenting. *Catheter Cardiovasc Interv* 80:1165–1170, 2012.
26. Burzotta F, Trani C, Talarico GP, et al: Resolute zotarolimus-eluting stent to treat bifurcated lesions according to the provisional technique: a procedural performance comparison with sirolimus- and everolimus-eluting stents. *Cardiovasc Revasc Med* 14:122–127, 2013.
27. Nakazawa G, Yazdani SK, Finn AV, et al: Pathological findings at bifurcation lesions: the impact of flow distribution on atherosclerosis and arterial healing after stent implantation. *J Am Coll Cardiol* 55:1679–1687, 2010.
28. Oviedo C, Maehara A, Mintz GS, et al: Intravascular ultrasound classification of plaque distribution in left main coronary artery bifurcations: where is the plaque really located? *Circ Cardiovasc Interv* 3:105–112, 2010.
29. van der Giessen AG, Wentzel JJ, Meijboom WB, et al: Plaque and shear stress distribution in human coronary bifurcations: a multislice computed tomography study. *EuroIntervention* 4:654–661, 2009.
30. Koo BK, Waseda K, Kang HJ, et al: Anatomic and functional evaluation of bifurcation lesions undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv* 3:113–119, 2010.
31. Stankovic G, Darremont O, Ferenc M, et al: Percutaneous coronary intervention for bifurcation lesions: 2008 consensus document from the fourth meeting of the European Bifurcation Club. *EuroIntervention* 5:39–49, 2009.
32. Aranzulla TC, Sangiorgi GM, Bartorelli A, et al: Use of the Venture wire control catheter to access complex coronary lesions: how to turn procedural failure into success. *EuroIntervention* 4:277–284, 2008.
33. Niemela M, Kervinen K, Erglis A, et al: Randomized comparison of final kissing balloon dilatation versus no final kissing balloon dilatation in patients with coronary bifurcation lesions treated with main vessel stenting: the Nordic-Baltic Bifurcation Study III. *Circulation* 123:79–86, 2011.
34. Pan M, Medina A, Suárez de Lezo J, et al: Coronary bifurcation lesions treated with simple approach (from the Cordoba & Las Palmas [CORPAL] Kiss Trial). *Am J Cardiol* 107:1460–1465, 2011.
35. Gwon HC, Hahn JY, Koo BK, et al: Final kissing ballooning and long-term clinical outcomes in coronary bifurcation lesions treated with 1-stent technique: results from the COBIS registry. *Heart* 98:225–231, 2012.
36. Koo BK, Park KW, Kang HJ, et al: Physiological evaluation of the provisional side-branch intervention strategy for bifurcation lesions using fractional flow reserve. *Eur Heart J* 29:726–732, 2008.
37. Foin N, Torii R, Mortier P, et al: Kissing balloon or sequential dilation of the side branch and main vessel for provisional stenting of bifurcations: lessons from micro-computed tomography and computational simulations. *JACC Cardiovasc Interv* 5:47–56, 2012.
38. Carrie D, Karouny E, Chouairi S, Puel J: "T"-shaped stent placement: a technique for the treatment of dissected bifurcation lesions. *Cathet Cardiovasc Diagn* 37:311–313, 1996.
39. Nakamura S, Hall P, Maiello L, Colombo A: Techniques for Palmaz-Schatz stent deployment in lesions with a large side branch. *Cathet Cardiovasc Diagn* 34:353–361, 1995.
40. Burzotta F, Gwon HC, Hahn JY, et al: Modified T-stenting with intentional protrusion of the side-branch stent within the main vessel stent to ensure ostial coverage and facilitate final kissing balloon: the T-stenting and small protrusion technique (TAP-stenting). Report of bench testing and first clinical Italian-Korean two-centre experience. *Catheter Cardiovasc Interv* 70:75–82, 2007.
41. Burzotta F, Sgueglia GA, Trani C, et al: Provisional TAP-stenting strategy to treat bifurcated lesions with drug-eluting stents: one-year clinical results of a prospective registry. *J Invasive Cardiol* 21:532–537, 2009.
42. Naganuma T, Latib A, Basavarajaiah S, et al: The long-term clinical outcome of T-stenting and small protrusion technique for coronary bifurcation lesions. *JACC Cardiovasc Interv* 6:554–561, 2013.
43. Hussain F: Provisional reverse "mini-crush" technique for bifurcation angioplasty. *J Invasive Cardiol* 20:E154–E157, 2008.
44. Ormiston JA, Currie E, Webster MW, et al: Drug-eluting stents for coronary bifurcations: insights into the crush technique. *Catheter Cardiovasc Interv* 63:332–336, 2004.
45. Chevalier B, Glatt B, Royer T, Guyon P: Placement of coronary stents in bifurcation lesions by the "culotte" technique. *Am J Cardiol* 82:943–949, 1998.
46. Kaplan S, Barlis P, Dimopoulos K, et al: Culotte versus T-stenting in bifurcation lesions: immediate clinical and angiographic results and midterm clinical follow-up. *Am Heart J* 154:336–343, 2007.
47. Brunel P, Lefevre T, Darremont O, Louvard Y: Provisional T-stenting and kissing balloon in the treatment of coronary bifurcation lesions: results of the French multicenter "TULIPE" study. *Catheter Cardiovasc Interv* 68:67–73, 2006.
48. Colombo A, Stankovic G, Orlic D, et al: Modified T-stenting technique with crushing for bifurcation lesions: immediate results and 30-day outcome. *Catheter Cardiovasc Interv* 60:145–151, 2003.
49. Galassi AR, Colombo A, Buchbinder M, et al: Long-term outcomes of bifurcation lesions after implantation of drug-eluting stents with the "mini-crush technique. *Catheter Cardiovasc Interv* 69:976–983, 2007.
50. Kobayashi Y, Colombo A, Akiyama T, et al: Modified "T" stenting: a technique for kissing stents in bifurcational coronary lesion. *Cathet Cardiovasc Diagn* 43:323–326, 1998.
51. Ormiston JA, Webster MW, Webber B, et al: The "crush" technique for coronary artery bifurcation stenting: insights from micro-computed tomographic imaging of bench deployments. *JACC Cardiovasc Interv* 1(4):351–357, 2008.
52. Ge L, Airoldi F, Iakovou I, et al: Clinical and angiographic outcome after implantation of drug-eluting stents in bifurcation lesions with the crush stent technique: importance of final kissing balloon post-dilation. *J Am Coll Cardiol* 46:613–620, 2005.

53. Murasato Y, Hikichi Y, Horiuchi M: Examination of stent deformation and gap formation after complex stenting of left main coronary artery bifurcations using microfocus computed tomography. *J Interv Cardiol* 22:135–144, 2009.
54. Collins N, Dzavik V: A modified balloon crush approach improves side branch access and side branch stent apposition during crush stenting of coronary bifurcation lesions. *Catheter Cardiovasc Interv* 68:365–371, 2006.
55. Chen S, Zhang J, Ye F, et al: DK crush (double-kissing and double-crush) technique for treatment of true coronary bifurcation lesions: illustration and comparison with classic crush. *J Invasive Cardiol* 19:189–193, 2007.
56. Jim MH, Ho HH, Chan AO, Chow WH: Stenting of coronary bifurcation lesions by using modified crush technique with double kissing balloon inflation (sleeve technique): immediate procedure result and short-term clinical outcomes. *Catheter Cardiovasc Interv* 69:969–975, 2007.
57. Schampaert E, Fort S, Adelman AG, Schwartz L: The V-stent: a novel technique for coronary bifurcation stenting. *Cathet Cardiovasc Diagn* 39:320–326, 1996.
58. Sharma SK: Simultaneous kissing drug-eluting stent technique for percutaneous treatment of bifurcation lesions in large-size vessels. *Catheter Cardiovasc Interv* 65:10–16, 2005.
59. Baim DS: Is birfurcation stenting the answer? *Cathet Cardiovasc Diagn* 37:314–316, 1996.
60. Helqvist S, Jorgensen E, Kelbaek H, et al: Percutaneous treatment of coronary bifurcation lesions: a novel "extended Y" technique with complete lesion stent coverage. *Heart* 92:981–982, 2006.
61. Kobayashi Y, Colombo A, Adamian M, et al: The skirt technique: a stenting technique to treat a lesion immediately proximal to the bifurcation (pseudobifurcation). *Catheter Cardiovasc Interv* 51:347–351, 2000.
62. Kinoshita Y, Katoh O, Matsubara T, et al: First clinical experience of "flower petal stenting": a novel technique for the treatment of coronary bifurcation lesions. *JACC Cardiovasc Interv* 3:58–65, 2010.
63. Brunel P, Martin G, Bressollette E, et al: "Inverted" provisional T stenting, a new technique for Medina 0,0,1 coronary bifurcation lesions: feasibility and follow-up. *EuroIntervention* 5:814–820, 2010.
64. Latib A, Colombo A, Sangiorgi GM: Bifurcation stenting: current strategies and new devices. *Heart* 95:495–504, 2009.
65. Généreux P, Kumsars I, Lesiak M, et al: A randomized trial of a dedicated bifurcation stent versus provisional stenting in the treatment of coronary bifurcation lesions. *J Am Coll Cardiol* 65(6):533–543, 2015.
66. Ormiston JA, Webber B, Ubod B, et al: Absorb everolimus-eluting bioresorbable scaffolds in coronary bifurcations: a bench study of deployment, side branch dilatation and post-dilatation strategies. *EuroIntervention* 10(10):1169–1177, 2015.
67. Dzavik V, Colombo A: The absorb bioresorbable vascular scaffold in coronary bifurcations: insights from bench testing. *JACC Cardiovasc Interv* 7:81–88, 2014.
68. Costa RA, Mintz GS, Carlier SG, et al: Bifurcation coronary lesions treated with the "crush" technique: an intravascular ultrasound analysis. *J Am Coll Cardiol* 46:599–605, 2005.
69. Ozaki Y, Suzuki T, Yamaguchi T, et al: Can intravascular ultrasound guided cutting balloon angioplasty before stenting be a substitute for drug eluting stent? Final Results of the Prospective Randomized Multicenter Trial Comparing Cutting Balloon With Balloon Angioplasty Before Stenting (Reduce III) [abstract]. *J Am Coll Cardiol* 43(Suppl A):1138–1166, 2004.
70. Patti G, Colonna G, Pasceri V, et al: Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. *Circulation* 111:2099–2106, 2005.

23 Percutaneous Coronary Intervention for Unprotected Left Main Coronary Artery Stenosis

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KEY POINTS

- Significant left main coronary artery (LMCA) disease should be defined by functional assessment in addition to angiographic stenosis.
- The integrated use of fractional flow reserve (FFR) and intravascular ultrasound (IVUS) improves outcomes following LMCA stenting.
- The use of drug-eluting stents significantly reduces repeat revascularization following LMCA stenting.
- Long-term prognosis following ostial LMCA stenting is excellent.
- For the distal LMCA bifurcation, single crossover stenting is better than a two-stent technique. The decision between a single- versus a two-stent technique should be made by following evaluation by IVUS.
- When using either the simple crossover or two-stent technique, achieving sufficient minimal stent cross-sectional area after LMCA bifurcation stenting is important to prevent in-stent restenosis and adverse clinical outcomes.
- Outcomes following treatment of LMCA disease with drug-eluting stents were similar to coronary artery bypass surgery in patients with low and intermediate lesion complexity.

Several etiologies contribute to left main coronary artery stenosis (Table 23-1). LMCA disease was first described by James Herrick in 1912 in patients dying of cardiogenic shock after acute myocardial infarction (MI).[1] Clinically significant LMCA disease has been found in 3% to 5% of all patients who undergo coronary angiography and in 10% to 30% of patients who undergo bypass surgery.[2] Although LMCA stenosis might be considered an attractive target for balloon angioplasty because of its large caliber, short lesion length, and lack of tortuosity, the initial results of balloon angioplasty were not favorable but rather had a high rate of procedural complications and early mortality.[3,4]

Histologically, the LMCA has the most elastic tissue of all the coronary vessels, which accounts for the poor response of the LMCA to simple balloon angioplasty.[5] Use of coronary stents has been shown to reduce the immediate need for coronary artery bypass grafting (CABG) to treat abrupt vessel closure, as well as the likelihood of restenosis, after balloon angioplasty.[6] The widespread availability of drug-eluting stents (DESs), together with improved stenting techniques, has lowered the threshold for performing percutaneous coronary intervention (PCI) instead of CABG for LMCA disease. As a result, during the last decade, the prevalence of LMCA stenting increased significantly worldwide. In addition, several large registries and randomized controlled trials have demonstrated that LMCA stenting yields mortality and morbidity rates comparable with CABG.[7-9] Thus stenting of unprotected LMCA (ULMCA) stenosis has been considered as a potential alternative to CABG.[10,11]

ANATOMY AND PATHOLOGY

The LMCA arises from the left aortic sinus just below the sinotubular junction of the aortic root. In approximately two thirds of patients, the LMCA bifurcates into the left anterior descending (LAD) and left circumflex (LCX) arteries; in one third of patients, the LMCA trifurcates into the LAD, LCX, and ramus intermedius. The LMCA is responsible for supplying, on average, 75% of the left ventricle. Examination of 100 autopsy cases found that the LMCA had an average length of 10.8 mm (±5.2 mm, range 2 to 23 mm), an average diameter of 4.9 (±0.8) mm, and an average angle of division of the terminal branches of 86.7 degrees (±28.8, range 40 to 165 degrees); in addition, a positive correlation was found between LMCA length and the angles of its terminal branches.[12] The anatomic portion of the LMCA stenosis is divided into three anatomic regions: the ostium, midshaft, and distal bifurcation. Histologically, the ostial portion resembles the aorta, being rich in aortic smooth muscle cells and elastic fibers. The distal bifurcation is the part of the LMCA most susceptible to the development of an atherosclerotic lesion because of low shear flow disturbance. Especially in the bifurcation, the lateral wall—that is, the wall opposite the flow divider—is the most frequent site of atherosclerotic plaque accumulation, whereas the flow divider (the bifurcation carina) is usually spared because of high shear stress.[13]

The pathologic plaque composition of LMCA disease varies from the pathologic intimal thickening to thin-cap fibroatheroma with or without plaque rupture.[14] In cases that include minimal LMCA disease, the most frequent underlying plaque type was pathologic intimal thickening (64%) followed by fibroatheroma with early or late core (17%). However, most lesions with significant LMCA stenosis, defined as more than a 50% narrowing, showed more complex plaques, such as fibroatheromas with late core, thin-cap fibroatheroma, surface ruptures, fissures, and intraplaque hemorrhage. Recent IVUS analysis demonstrated the diffuse nature of atherosclerosis involving both the parent (LMCA) segment and both flow dividers (LAD and LCX). Atherosclerotic plaques extend from the LMCA to the LAD in 90% of patients and to the LCX in 62% of patients.[15]

Definition of Significant Left Main Coronary Artery Stenosis

Traditionally, angiographic stenosis diameter of 50% has been considered a cutoff for significant LMCA stenosis. Angiography, however, has limitations in assessing lesion morphology and the true luminal size of the LMCA. In addition, noninvasive testing, such as with myocardial perfusion imaging (MPI), is often not helpful in the patient with an LMCA stenosis. Therefore the intermediate LMCA stenosis should be evaluated by the direct measurement of fractional flow reserve (FFR), and the stenosis with an FFR below 0.80 is considered the significant LMCA stenosis. However, FFR of an intermediate LMCA stenosis should be interpreted with caution. Isolated LMCA stenoses are very rare, and most stenoses are associated with disease in the LAD and/or LCX, both of which tend to increase FFR measured across the LMCA stenosis. Therefore reassessment of the functional significance of intermediate LMCA stenosis is recommended after the correction of distal coronary artery stenoses.[16]

In addition, IVUS is a useful tool to determine the functional significance of intermediate LMCA stenosis. Jasti and colleagues[17] reported that a minimal luminal area (MLA) of 5.9 mm^2 had the highest sensitivity and specificity (93% and 95%, respectively) for

TABLE 23-1 Causes of Left Main Coronary Artery Stenosis

Atherosclerosis
Nonatherosclerotic causes
Idiopathic causes
- Irradiation
- Takayasu arteritis
- Syphilitic aortitis
- Rheumatoid arthritis
- Aortic valve disease
- Kawasaki disease
- Cardiac surgery or transcatheter aortic valve implantation
- Injury after left main coronary intervention

determining a significant LMCA stenosis, compared with FFR as the gold standard. However, this cutoff may overestimate the actual functional significance of a stenosis, resulting in unnecessary LMCA stenting. Park and colleagues[18] recently addressed 112 patients with isolated intermediate LMCA stenosis who underwent preinterventional IVUS and FFR measurements to determine the IVUS MLA criteria that correspond to an FFR below 0.80. They found the IVUS MLA value within the LMCA that best predicted FFR below 0.80 was less than 4.5 mm^2 (77% sensitivity, 82% specificity, 84% positive predictive value [PPV], 75% negative predictive value [NPV], area under the curve [AUC] 0.83; 95% confidence interval [CI], 0.76 to 0.96; $P < .001$). The PPV of IVUS-measured MLA less than 4.5 mm^2 is acceptably high; thus if an FFR measurement is not feasible, IVUS MLA criteria can be used.

STENTING TECHNIQUES

Ostial and Shaft Lesion

Stenting can be performed safely if meticulous guiding technique and careful hemodynamic monitoring are performed. Coaxial alignment of the guiding catheter is important to minimize ostial injury and to ensure proper positioning of the stent. As long as coaxial alignment is maintained, it is usually easy to advance and position the balloon at the target lesion. Once the balloon is properly positioned, the guiding catheter can be gently retracted 1 to 2 cm into the aorta with gentle forward pressure on the balloon catheter. The ostial LMCA lesion is dilated and stented with the guide tip positioned in the aortic sinus. The proximal end of the stent is positioned to protrude very slightly outside the ostium and is expanded against the aortic wall, as in any standard stenting of an aortoostial lesion. After the deployment of the stent, the stented segment is further dilated with high-pressure balloon inflations to achieve optimal stent cross-sectional area. Stent size is selected based on the reference artery size and lesion length. The balloon inflation is brief (<30 seconds) and multiple (more than three times) to avoid prolonged global ischemia and ischemia-related complications. Aortoostial coverage is not mandatory for treatment of disease limited to the shaft of the LMCA.

Bifurcation Lesion

Because of technical challenges, stenting of LMCA bifurcation disease should be restricted to highly skilled interventionalists who understand the risk/benefit ratio of the percutaneous approach. For LMCA bifurcation disease, the single-stent technique provides more favorable long-term clinical outcomes compared with the two-stent technique. Therefore in practice, the single-stent crossover technique is used more frequently and is found in approximately 60% of all LMCA bifurcation treatments.[19] Selection of a single- or two-stent technique should be based on disease involvement of the LCX ostium (Table 23-2), because side-branch compromise after stent crossover is frequent in the setting of significant ostial disease of the side branch. Thus when making the choice between a single- or two-stent strategy, IVUS provides accurate

TABLE 23-2 Favorable or Unfavorable Anatomic Features for Single-Stent Crossover Stenting in the Treatment of Unprotected Left Main Coronary Artery Stenosis

	Anatomic Features
Favorable	• Insignificant stenosis at the ostial LCX with Medina classification 1,1,0 or 1,0,0 • Diminutive LCX with <2.5 mm in diameter right-dominant coronary system • Wide angle with LAD • No concomitant disease in LCX • Focal disease in LCX
Unfavorable	• Insignificant stenosis at the ostial LCX with Medina classification 1,1,1; 1,0,1; or 0,1,1 • Large size of LCX with ≥2.5 mm in diameter left-dominant coronary system • Narrow angle with LAD • Concomitant disease in LCX • Diffuse disease in LCX

From Moussa ID, Colombo A, eds: *Tips and tricks in interventional therapy of coronary bifurcation lesions,* New York, 2010, Informa Healthcare, p. 135.
LAD, Left anterior descending coronary artery; *LCX,* left circumflex coronary artery.

information about both main and side-branch disease status and vascular remodeling in LMCA bifurcation lesions. Direct imaging of the LCX, if possible, is necessary for accurate assessment of the side branch, including its ostium, because IVUS evaluation of a side-branch ostium from the main vessel is only moderately reliable.[20] If the operators choose to use a single-stent approach, there is always the possibility of placing a second stent on the LCX, if the result is not optimal. This condition is defined as *provisional stenting.* Usually, a wire in the LCX before stenting is needed in cases with (1) narrowing at the LCX ostium; (2) severe stenosis of the main branch, with a large plaque burden at risk for plaque shifting; (3) a narrow angle of the LCX origination; and (4) deterioration of the LCX ostium after predilation of the main branch. Such dilation is usually recommended to ensure optimal balloon expansion and easy stent delivery; however, predilation of a side branch is performed only if it is diseased or if it significantly deteriorates after dilation of the main branch. Final kissing balloon inflation (FKBI) after single-stent crossover in LMCA bifurcation is not mandatory if the LCX flow is not compromised. As a bailout procedure for a suboptimal result or for significant dissection at the ostial LCX, provisional T-stenting and a reverse crush technique are popularly used, in which case sequential high pressure in both branches with noncompliant balloons followed by an FKBI is also mandatory for good long-term outcomes. If the LCX is large (left-dominant system) and at high risk of flow compromise after crossover stenting (narrow angle and significant ostial stenosis), an initial two-stent technique is preferred. These techniques fall mainly into four broad categories: T-stenting, crush stenting, culotte stenting, and simultaneous kissing stenting (SKS). Owing to a paucity of data, no consensus has been reached as to which two-stent approach might be better than others. In both the single-stent or two-stent technique, optimal stent expansion is very important to prevent restenosis and other adverse clinical outcomes.

Kang and colleagues[21] studied the optimal IVUS-derived minimal stent cross-sectional area (MSA) criteria for prevention of in-stent restenosis (ISR) in 403 patients undergoing sirolimus-eluting stent implantation for LMCA stenosis. They classified the LMCA into four segments: (1) the LCX ostium, (2) the LAD ostium, (3) the polygon of confluence (POC), and (4) the LMCA above the POC. The best IVUS-MSA criteria that predicted angiographic ISR on a segmental basis were 5.0 mm^2 for the LCX ostium, 6.3 mm^2 for the LAD ostium, 7.2 mm^2 for the POC, and 8.2 mm^2 for the proximal LMCA above the POC (Fig. 23-1). Therefore the operator should perform IVUS evaluation after stent implantation and should make an effort to achieve above the MSA using adjunctive balloon dilation.

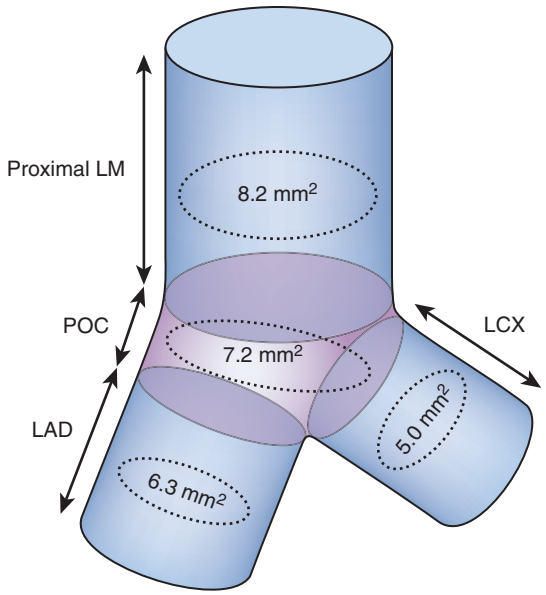

FIGURE 23-1 Cut-off values of minimal stent area for the prediction of angiographic in-stent restenosis on a segmental basis. *LAD,* Left anterior descending artery; *LCX,* left circumflex artery; *LM,* left main; *POC,* polygon of confluence.

ADJUVANT DEVICES AND METHODS

Intravascular Ultrasound

Intravascular ultrasound (IVUS) provides important quantitative and qualitative information about coronary artery lesions. It is often difficult to evaluate the actual size of the LMCA using angiography alone. Often the left main trunk is short and lacks a normal segment for comparison. In addition, contrast in the aortic cusp sometimes obscures the ostium, and "streaming" of contrast may result in a false impression of luminal narrowing. Furthermore, angiography underestimates stenosis severity; therefore IVUS before stenting provides useful information about the selection of adequately sized balloons and stents.

In 201 matched pairs from the Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Interventional Angioplasty Versus Surgical Revascularization (MAIN-COMPARE) registry, Park and colleagues[22] demonstrated a tendency of lower risk of 3-year mortality with IVUS guidance compared with angiography guidance (6.0% vs. 13.6%, respectively; log-rank $P = .063$; hazard ratio [HR] 0.54). In particular, for 145 matched pairs of patients who received a DES, the 3-year mortality was significantly lower for IVUS guidance compared with angiography guidance (4.7% vs. 16.0%, respectively; log-rank $P = .048$; HR 0.39). It is interesting to note that the mortality rate started to diverge beyond 1 year after the procedure. In contrast, the use of IVUS did not reduce the risk of mortality in 47 matched pairs of patients receiving a bare-metal stent (8.6% vs. 10.8%, respectively; log-rank $P = .35$; HR 0.59). Therefore IVUS guidance may play a role in reducing very late stent thrombosis and subsequent long-term mortality.[22] The Spanish IVUS study also demonstrated the importance of IVUS surveillance during LMCA stenting.[23] The IVUS-guided group was associated with a lower incidence of all causes of death and stent thrombosis.

IVUS guidance provides information on negative remodeling, reference vessel size and morphologic complexity, stent underexpansion, incomplete lesion coverage, small stent area, large residual plaque, and incomplete stent apposition in postinterventional evaluation. For LMCA lesions in particular, the use of IVUS is helpful in determining a treatment strategy and in optimizing the stent procedure. Therefore we strongly recommend mandatory use of IVUS in PCI for unprotected LMCA stenosis.

Fractional Flow Reserve

A fractional flow reserve (FFR) value greater than 0.75 to 0.80 has been suggested to be a strong predictor of favorable survival and low event rates in patients with intermediate LMCA disease, making it useful for the identification of patients in whom deferral of revascularization would be associated with favorable clinical outcomes. In an evaluation of patients with intermediate LMCA stenosis, patients with an FFR of 0.80 or more treated medically have survival rates comparable to patients with an FFR below 0.80 who underwent CABG. Therefore FFR-guided decision making for the treatment of intermediate LMCA stenosis is associated with favorable prognosis, and intermediate LMCA disease with an FFR greater than 0.75 to 0.80 can be safely deferred. In an evaluation of 213 patients with intermediate LMCA stenosis, 138 patients with an FFR of 0.80 or more were treated medically, whereas 75 patients with an FFR below 0.80 underwent CABG. Their 5-year survival rates were 89.8% and 85.4%, respectively ($P = .48$).[24] Table 23-3 summarizes key studies that demonstrate FFR-guided decision making in intermediate LMCA stenosis.[17,24-27]

Hemodynamic Support

Patients with normal left ventricular (LV) function are tolerant of global ischemia during balloon and stent occlusion. Although an intraaortic balloon pump (IABP) is not routinely recommended during the procedure, it should be used to prevent hemodynamic collapse in patients with severely depressed LV function. More advanced support using LV assist devices (e.g., Impella; Abiomed, Danvers, MA) may be indicated for high-risk patients, such as those with low left ventricular ejection fraction (LVEF), very calcified stenosis, or thrombus-containing LMCA stenosis.

Medication Versus Revascularization

Most natural studies of medically treated LMCA disease were conducted three decades ago in small numbers of patients (Table 23-4). Early observational studies demonstrated that the long-term prognosis for patients with medically treated LMCA stenosis was poor, with 3-year survival rates of 50%.[28-30]

Controlled trials to compare CABG with medical therapy alone found that CABG provided a survival benefit in patients with more than 50% LMCA stenosis. In the Veterans Administration (VA) Cooperative Study,[31] 113 patients with LMCA disease were randomly allocated to medical therapy ($n = 53$) or bypass surgery ($n = 60$); during follow-up (average, 30 months), the long-term mortality rate was significantly greater in the medical group than in the surgery group (36% vs. 20%). Similar results were observed in the European Coronary Surgery Study (ECSS)[32] and the Coronary Artery Surgery Study (CASS).[33] In the CASS study, which included 1492 patients with LMCA disease, the 3-year survival rate was 91% for the surgical group and 69% for the medically-treated group. The subsequent meta-analysis[34] of seven randomized trials demonstrated that the 5-year relative risk reduction for mortality provided by CABG over medical therapy was greater for LMCA disease than for three-vessel or one- or two-vessel disease (odds ratios [ORs] 0.32, 0.58, and 0.77, respectively), and the absolute survival benefit time from CABG among patients with LMCA disease was 19.3 months.

Bittl and colleagues[35] performed a bayesian cross-design and network meta-analysis of 12 studies (four randomized clinical trials and eight observational studies) that compared CABG with PCI ($n = 4574$ patients) and of seven studies (two randomized clinical trials and five observational studies) that compared CABG with medical therapy ($n = 3224$ patients). They found that medical therapy is associated with higher 1-year mortality than the use of PCI for patients with ULMCA stenosis (OR 3.22; 95% bayesian credible interval, 1.96 to 5.30).

TABLE 23-3 Clinical Outcomes of Left Main Coronary Artery Stenosis Managed by Fractional Flow Reserve–Guided Decision Making

	Hamilos et al[24]		Bech et al[25]		Courtis et al[26]		Lindstaedt et al[27]		Jasti et al[17]	
Age (yr)	64 ± 9	68 ± 11	63 ± 9	60 ± 9	61 ± 10	63 ± 10	61 ± 10	64 ± 9	62 ± 11	
Mean follow-up (mo)	35 ± 25		29 ± 15		13 ± 10	14 ± 12	29 ± 18	29 ± 14	38	
Patients (*N*)	75	138	30	24	60	82	27	24	14	37
FFR cutoff value	<0.80	≥0.80	<0.75	≥0.75	<0.75*	>0.80	<0.75*	>0.80	<0.75	≥0.75
Treatment	CABG	Medication†	CABG	Medication†	Revasc. (CABG 54, PCI 6)	Medication	CABG	Medication†	Revasc. (CABG 7, PCI 7)	Medication†
Clinical Outcomes										
Death, *n* (%)	7 (9.6)	9 (6.5)	1	0	3 (5)	3 (4)	4 (14.8)	0	0	3 (NC)
MI, *n* (%)	0	1	1	0	1 (2)	4 (5)	1 (3.7)	0	0	0
Revascularization, *n* (%)	4 (5.5)	17 (12.3)	2	5	0	9 (11)	1 (3.7)	6 (25)†	0	4

CABG, Coronary artery bypass grafting; *FFR,* fractional flow reserve; *LMCA,* left main coronary artery; *MI,* myocardial infarction; *NC,* noncardiac death; *PCI,* percutaneous coronary intervention; *Revasc.,* revascularization; *Rx,* medication.
*Individualized decision was recommended based on additional clinical data if FFR was between 0.75 and 0.80.
†Medical treatment or PCI elsewhere in the coronary tree.

TABLE 23-4 Long-Term Prognosis of Patients With Left Main Coronary Artery Disease Treated Medically or Surgically

Authors	Year	Follow-Up Duration	TREATMENT	
			Medication	CABG
VA[31]	1976	2.5 yr	64% (n = 53)	80% (n = 60)
ECSS[32]	1980	5 yr	68% (n = 31)	86% (n = 28)
CASS[33]	1981	4 yr	63% (n = 309)	88% (n = 1183)

CABG, Coronary artery bypass grafting; *CASS,* Coronary Artery Surgery Study; *ECSS,* European Coronary Surgery Study; *VA,* Veterans Administration Coronary Artery Bypass Surgery Cooperative Study.

Unprotected Left Main Coronary Artery Stenting

Bare-Metal Stenting

In the past, LMCA intervention has shown acceptable short- and midterm outcomes using bare-metal stents (BMSs). The Unprotected Left Main Trunk Investigation Multicenter Assessment (ULTIMA) registry[36] enrolled 279 patients with ULMCA stenosis who were treated with BMSs; of these, 46% were inoperable or at high surgical risk. Among these high-risk patients, the in-hospital mortality was 13.7%, and the 1-year incidence of all-cause mortality was 24.2%; among the 32% patients at low-risk (age <65 years, LVEF >30%), no periprocedural deaths were reported, and the 1-year mortality rate was only 3.4%. In a series of elective, low-risk patients who were also not at increased risk for CABG, PCI with BMS for ULMCA disease showed favorable short- and midterm outcomes (in-hospital mortality, 0% to 4.3%; mortality at 6 to 12 months, 2.5% to 10.8%).[37-41] However, considerable risk of restenosis (18% to 31%) and repeat revascularization (7.3% to 33.6%) limit the durability of LMCA stenting with BMS use.

Park and colleagues[37] reported data on LMCA stenting in selected patients who were good surgical candidates with normal LV function. The procedural success rate was 99.1%, and the 6-month restenosis rate was 19%. At 2-year follow-up, cardiac death–free survival was 99.1% and cardiac event–free survival was 87%. For LMCA bifurcation disease, Park and colleagues[42] also found that elective stenting for LMCA bifurcation (n = 63) in highly selected patients with normal LVEF and a large reference vessel might be safe and effective with good initial and long-term outcomes. Procedure success was high with no major adverse events, and the overall angiographic restenosis rate was 28%. Moreover, no significant differences were noted in the rates of 2-year freedom from target-lesion revascularization (TLR) among LMCA ostial, shaft, and bifurcation stenting (82%, 86%, and 85%, respectively). These data suggest that judicious patient selection may be essential to achieve favorable results in LMCA stenting. Unfortunately, patients with poor surgical risks are also poor candidates for PCI. Therefore BMS LMCA stenting should be reserved for selected patients who have normal LV function, are not candidates for CABG, or refuse CABG.

Drug-Eluting Stent Implantation

The DES remarkably decreases in-stent restenosis, and many experienced interventional cardiologists currently perform PCI with DESs for patients with ULMCA disease. Although limited by their nonrandomized nature, small numbers of patients, and short follow-up periods, several observational studies have shown promising outcomes for PCI using DESs compared with BMSs.[43-45] In addition, a meta-analysis that compared outcomes for DES and BMS use after LMCA stenting was reported. A total of 44 studies and 10,342 patients who received a DES or BMS were analyzed. The respective (DES vs. BMS) cumulative event rates at 3 years were 8.8% and 12.7% for death, 4.0% and 3.4% for MI, 8.0% and 16.4% for target-vessel revascularization (TVR)/TLR, and 21.4% and 31.6% for major adverse cardiovascular events (MACEs). Adjusted outcomes at 3 years favored DES use, including the reduction of mortality.[46]

Subsequently, several small observational studies have compared outcomes of the two types of first-generation DESs in patients with LMCA disease.[47,48] In a single center, nonrandomized study that compared sirolimus-eluting stents (SESs) with paclitaxel-eluting stents (PESs) in 110 patients with LMCA disease, angiographic results and long-term clinical outcomes were comparable.[47] The Intracoronary Stenting and Antithrombotic Regimen: Drug-Eluting Stents for Unprotected Left Main Stem Disease (ISAR–LEFT MAIN)[49] randomized trial compared SESs and PESs and found them equally effective and safe in patients undergoing unprotected LMCA stenting. The study enrolled 607 patients (305 SES and 302 PES) with relatively high-risk clinical characteristics (mean age, 69 years; 30% with diabetes, 40% with acute coronary syndrome, 50% with prior PCI) and angiographic characteristics (63% with distal bifurcation stenosis and 70% with multivessel disease). At 12-month follow-up, the incidence of death (6.6% vs. 5.0%), MI (4.6% vs. 5.0%), stroke (1.0% vs. 1.7%), and major cardiac events (death, MI, or revascularization; 15.8% vs. 13.6%) were similar in the SES and PES groups, as were angiographic restenosis rates at 6 to 9 months (19.4% vs. 16.0%) and 2-year revascularization rates (7.8% vs. 6.5%). The incidence of definite (0.3% vs. 0.7%) and probable (0% vs. 0.3%) stent thrombosis at 2 years was also similar in the two study arms.

Recently, second- and third-generation DESs have replaced the first-generation devices. ISAR–LEFT MAIN 2[50] compared the safety and efficacy of the zotarolimus-eluting stent (ZES) and the everolimus-eluting stent (EES) for treatment of unprotected LMCA disease. At 1 year, the cumulative incidence of the primary end point was 17.5% in the ZES group and 14.3% in the EES group (relative risk [RR] 1.26; 95% CI, 0.85 to 1.85; P = .25). All-cause mortality at 1 year was equal in the two groups (5.6%; RR 1.00; 95% CI, 0.52 to 1.93; P = .98). Angiographic restenosis occurred in 21.5% of patients in the ZES group and in 16.8% in the EES group (RR 1.28; 95% CI, 0.86 to 1.92; P = .24). Therefore treatment of LMCA lesions with a ZES or an EES provided comparable clinical and angiographic outcomes at 1-year follow-up.

STENT THROMBOSIS AND ANTIPLATELET THERAPY AFTER DRUG-ELUTING STENT IMPLANTATION

Since the introduction of the DES, concerns have been raised regarding the long-term safety of DES use with particular regard to late stent thrombosis and late mortality. Increasing concern over stent thrombosis, which may have catastrophic consequences in patients who received ULMCA stenting, and a lack of long-term clinical data have hampered the widespread use of PCI with DES as an alternative to CABG. However, recent data alleviate some of the concerns about the safety of PCI with DES for the treatment of ULMCA disease. Currently, reported rates of stent thrombosis in patients who received DES implantation for ULMCA disease among several large observational and randomized studies have been reported to range between 1% and 2% within 1 to 3 years (Table 23-5). In addition, recent reports from the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial[51] found LMCA PCI with DES was associated with a lower risk of stent thrombosis. These data suggest LMCA PCI with DES results in lower or, at worst, similar rates of stent thrombosis compared with patients with other coronary lesions in routine clinical practice. Therefore prolonged dual-antiplatelet therapy or a more potent regimen may not be necessary for the prevention of stent thrombosis after ULMCA stenting.

In-Stent Restenosis After Left Main Coronary Artery Drug-Eluting Stenting

In spite of the good initial and long-term outcomes of PCI for LMCA stenosis, in-stent restenosis (ISR) remains a challenging problem. The rates of angiographic restenosis after LMCA stenting with a DES has been found to vary widely, from 8% to 42%.[52] Restenotic lesions, complex stenting with two or more stents in a bifurcation lesion, the total number of stents, and bifurcation lesions were identified as independent predictors of ISR.[52] The LCX ostium was the most common

TABLE 23-5 The Incidence of Stent Thrombosis After Drug-Eluting Stent Implantation for Left Main Coronary Artery Stenosis

Study Name	N	Stent	STENT THROMBOSIS (%)		Follow-Up Duration (yr)
			Definite	Definite or Probable	
MAIN-COMPARE[7]	784	DES	1.5	—	5
DELTA[61]	1874	Cypher (938) Taxus (893) Endeavor (4) Xience V (43)	1.1	1.7	3.5
ASAN MAIN[62]	176	Cypher	—	1.8	5
PRECOMBAT[8]	300	Cypher	0.3	—	2
PRECOMBAT 2[53]	334	Xience V	0	0	1.5
ISAR-LEFT-MAIN[49]	302 305	Taxus Cypher	0.3 0.7	0.3 1.0	2 2
ISAR-LEFT-MAIN 2[50]	324 326	Endeavor Xience V	0.6 0.6	0.9 0.6	1 1
SYNTAX[58]	357	Taxus	5.1		5
Chieffo et al[63]	731	DES	0.5	1.0	2.5
EXCELLENT[64]	160 115	Xience V Cypher	— —	0.6 1.7	1 1

location of the restenosis.[53] Both underexpansion of stents and neointimal hyperplasia were the most important mechanisms of ISR.[54] Real-world registry studies reported that most patients with left main ISR were treated by PCI (drug-eluting stenting or balloon angioplasty), and approximately 10% of patients received CABG as an initial treatment strategy.[55] Long-term outcome was favorable regardless of revascularization strategies. The Asan Medical Center registry found that in patients with ISR treated by repeated revascularization or medical treatment, the rate of MACE at 3 years was 87%, no patients died, 1 patient experienced acute MI, and 6 patients received repeated revascularization. In addition, the angiographic surveillance did not affect the patient's long-term outcomes; therefore a routine angiographic follow-up was not recommended.[52]

Comparison of Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting in Unprotected Left Main Coronary Artery Stenosis

Registry Data

The MAIN-COMPARE registry arose from a large, multicenter, long-term follow-up study to compare PCI with BMS or DES and CABG for ULMCA disease. This registry included 2240 patients with unprotected LMCA disease who underwent stenting (BMS 318, DES 784) or CABG (1138) at 12 major cardiac centers in Korea.[7] At 3 years after propensity matching, the risks of death and the composite of death, Q-wave MI, or stroke were similar in the PCI and CABG groups, and these results were consistent when either BMS or DES was compared with concurrent CABG. However, the rate of TVR was significantly lower in the CABG group than in the PCI group, with hazard ratios varying by the type of stent. DES recipients were almost sixfold more likely, and BMS recipients were almost tenfold more likely, to require revascularization compared with those who underwent surgery. In the 5-year results of the MAIN-COMPARE registry,[56] after adjustment for differences in baseline risk factors with the inverse probability of treatment weighting, the 5-year risk of death (HR 1.13; 95% CI, 0.88 to 1.44, $P = .35$) and the combined risk of death, Q-wave MI, or stroke (HR 1.07; 95% CI, 0.84 to 1.37, $P = .59$) were not significantly different for patients undergoing stenting versus those undergoing CABG (Fig. 23-2). The risk of TVR was significantly higher in the stenting group than in the CABG group (HR 5.11; 95% CI, 3.52 to 7.42; $P = .001$).

Randomized Trials

The Left Main Coronary Artery Stenting (LE MANS)[57] trial was the first randomized comparison of PCI with stenting (52 patients) and CABG (53 patients) for treatment of ULMCA stenosis with or without

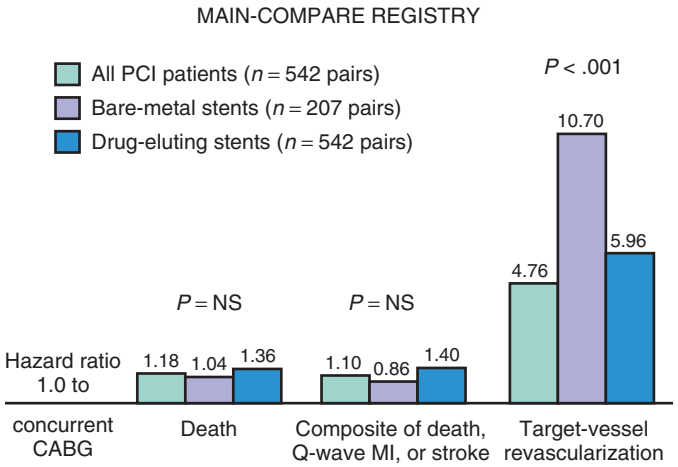

FIGURE 23-2 Hazard ratios for clinical outcomes of stenting with reference to bypass surgery among propensity-matched cohorts in the MAIN-COMPARE registry.[7] The risk of death or the composite of death, Q-wave myocardial infarction (MI), or stroke were similar, but the risk of revascularization was significantly higher in the percutaneous coronary intervention (PCI) patients. *CABG,* Coronary artery bypass grafting; *NS,* not significant.

multivessel coronary artery disease (CAD). DESs were placed in 35% of PCI patients, and left internal mammary artery (LIMA) grafts were used in 72% of CABG patients. At 1 year, the primary end point of absolute change in LVEF was significantly greater in the PCI group than in the CABG group (3.3% ± 6.7% vs. 0.5% ± 0.8%; $P = .047$), whereas the secondary end points—survival and major adverse cardiac or cerebrovascular events (MACCEs)—were comparable in the two groups. However, this study was limited by the small number of patients and the nonspecific and inconclusive primary end point chosen to evaluate treatment effects.

In a subgroup LMCA analysis from the SYNTAX trial,[9] PCI demonstrated 12-month rates of MACCE, death, MI, or stroke equivalent to those seen after CABG, but a higher rate of TVR was observed in the DES arm, which was offset by an increase in the rate of stroke in the surgical arm. A post hoc analysis of the patients with LMCA disease found that those who also had two- or three-vessel disease had a significantly higher rate of MACCEs compared with those with

LMCA disease alone or in combination with one-vessel disease (1VD; 19.8% and 19.3% vs. 7.1% and 7.5%, respectively). The 5-year outcomes of SYNTAX were reported[58] with no significant differences in the rates of death (12.8% vs. 14.6%; $P = .94$), MI (8.2% vs. 4.8%; $P = .2$), and MACCEs (36.9% vs. 31.0%; $P = .14$) between PCI and CABG patients. However, the stroke rate was lower (1.5% vs. 4.3%; $P = .03$), and the revascularization rate was higher (26.7% vs. 15.5%; $P = .003$) after PCI (Table 23-6). Patients with high SYNTAX scores—that is, those with increased lesion numbers and complexity—had higher death and revascularization rates in the PCI arm. It should be noted that the analysis for ULMCA disease was not the primary objective analysis but rather the post hoc analysis, which was hypothesis generating.

The Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease (PRECOMBAT) trial[8] randomized 600 patients with ULMCA to either CABG or PCI with SES in a noninferiority study in Korea. PCI was noninferior to CABG for the 1-year MACCE rate, which was the primary end point, (absolute difference, 2%; upper margin of 95% CI, 5.6%; HR 1.56; P for noninferiority = .011). At 2 years, the MACCE rate (12.2% vs. 8.1%; HR 1.5; 95% CI, 0.9 to 2.52; $P = .12$) and the composite rate of death, MI, or stroke (4.4% vs. 4.7%; HR 0.92; 95% CI, 0.43 to 1.96; $P = .83$) remained comparable between the PCI and CABG groups. However, the 2-year rate of ischemia-driven TVR was significantly higher in the PCI group than in the CABG group (9% vs. 4.2%; HR 2.18; 95% CI, 1.1 to 4.32; $P = .022$). Recently, the 5-year outcome of PRECOMBAT study was published. At 5 years, MACCE occurred in 52 patients in the PCI group and 42 patients in the CABG group (cumulative event rates of 17.5% and 14.3%; HR, 1.27; 95% CI, 0.84 to 1.90; $P = .26$). The two groups did not differ significantly in terms of death from any cause, myocardial infarction, or stroke as well as their composite (8.4% and 9.6%; HR, 0.89; 95% CI, 0.52 to 1.52; $P = .66$). Ischemia-driven target vessel revascularization occurred more frequently in the PCI group than in the CABG group (11.4% and 5.5%; HR, 2.11; 95% CI, 1.16 to 3.84; $P = .012$).[59]

Another small randomized trial by Boudriot and colleagues[60] compared sirolimus-eluting stenting ($n = 100$) with CABG ($n = 101$) in patients with ULMCA disease. The primary end point was noninferiority in freedom from MACE (cardiac death, MI, and TVR) at 12 months. At 1 year, the incidence of the primary end point was 13.9% in the CABG group and 19.0% in the PCI group ($P = .19$ for noninferiority). The combined rates for death and MI were similar (7.9% in CABG vs. 5.0% in PCI), but repeat revascularization was significantly higher in the PCI group (14.0% vs. 5.9% of CABG).

CURRENT STATUS OF LEFT MAIN CORONARY ARTERY STENTING

The current PCI guideline for the treatment of LMCA stenosis was recently updated to a class IIb indication with a B level of evidence from the American College of Cardiology/American Heart Association and European Society of Cardiology (Table 23-7).[10] In addition, the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery reported the indications for LMCA stenting relative to CABG[11]: (1) isolated or single-vessel disease, ostium/shaft,

TABLE 23-6 Summary of 5-Year Outcomes of PRECOMBAT Trial and LM Subset From SYNTAX Trial

	PRECOMBAT TRIAL[7]				SYNTAX TRIAL[61]			
Clinical Outcomes	Surgery ($N = 300$)	Stents ($N = 300$)	HR (95% CI)	*P* value	Surgery ($N = 348$)	Stents ($N = 357$)	HR (95% CI)	*P* value
MACCE	14%	18%	1.27 (0.84-1.90)	.26	31%	37%	1.23 (0.95-1.59)	.12
All death/stroke/MI	10%	8%	0.89 (0.52-1.52)	.66	21%	19%	0.91 (0.65-1.27)	.57
All death	8%	6%	0.73 (0.39-1.37)	.32	15%	13%	0.88 (0.58-1.32)	.53
Cardiac death	7%	4%	0.54 (0.26-1.13)	.10	7%	9%	1.23 (0.71-2.11)	.46
Stroke	1%	1%	0.99 (0.14-7.02)	.99	4%	2%	0.33 (0.12-0.92)	.03
MI	2%	2%	1.20 (0.37-3.93)	.76	5%	8%	1.67 (0.91-3.10)	.10
Revascularization	14%	13%	1.86 (1.09-3.17)	.020	16%	27%	1.82 (1.28-2.57)	<.001

CABG, Coronary artery bypass grafting; *CI,* confidence interval; *HR,* hazard ratio; *LMCA,* left main coronary artery; *MACCE,* major adverse cardiac and cerebrovascular events, including death, stroke, myocardial infarction, and repeat revascularization; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention.

TABLE 23-7 The American College of Cardiology/American Heart Association/European Society of Cardiology Guidelines for Elective Percutaneous Coronary Intervention for Unprotected Left Main Coronary Artery Disease

Guidelines	Class of Recommendation	LOE
ACC/AHA 2011[10]	IIa—For SIHD when both of the following are present: • Anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (e.g., a low SYNTAX score [≤22], ostial or trunk left main stenosis) • Clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (e.g., STS-predicted risk of operative mortality ≥ 5%)	B
	IIb—For SIHD when both of the following are present: • Anatomic conditions associated with a low to intermediate risk of PCI procedural complications and an intermediate to high likelihood of good long-term outcome (e.g., low-intermediate SYNTAX score <33, bifurcation left main stenosis) • Clinical characteristics that predict an increased risk of adverse surgical outcomes (e.g., moderate-severe COPD, disability from prior stroke, or prior cardiac surgery; STS-predicted risk of operative mortality >2%)	B
	III—For SIHD in patients (vs. performing CABG) with unfavorable anatomy for PCI and who are good candidates for CABG	B
ESC 2014[11]	IIa—Left main (isolated or 1VD, ostium/shaft)	B
	IIb—Left main (isolated or 1VD, bifurcation)/left main + 2VD or 3VD, SYNTAX score ≤32	B
	IIIb—Left main + 2VD or 3VD, SYNTAX score ≥33	B

ACC, American College of Cardiology; *AHA,* American Heart Association; *CABG,* coronary artery bypass graft; *COPD,* chronic obstructive pulmonary disease; *ESC,* European Society of Cardiology; *LOE,* level of evidence; *PCI,* percutaneous coronary intervention; *SIHD,* stable ischemic heart disease; *STS,* Society of Thoracic Surgeons; *SYNTAX,* Synergy Between PCI With Taxus and Cardiac Surgery; *VD,* vessel disease.

class IIa B; (2) isolated or single-vessel disease, distal bifurcation, class IIb B; (3) left main plus two- or three-vessel disease, SYNTAX score 32 or less, class IIb B; and (4) left main plus two- or three-vessel disease, SYNTAX score 33 or greater, class III B. Therefore DES implantation is currently considered an alternative option for selected patients with ULMCA disease.

CONCLUSIONS

Current evidence from clinical trials and extensive off-label experience indicates that stenting yields mortality and morbidity rates that compare favorably with CABG, especially in patients with low and intermediate lesion complexity; this may prompt many interventional cardiologists to choose PCI with a DES as a good treatment option for patients with LMCA disease. Large randomized clinical trials with long-term follow-up, such as the Evaluation of Xience Prime Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) will provide more data. An integrated approach that combines more advanced devices with specialized techniques, adjunctive physiologic and imaging support, and adjunctive pharmacologic agents has greatly improved PCI success rates and long-term clinical outcomes for these complex lesions.

REFERENCES

1. Herrick J: Clinical features of sudden obstruction of the coronary arteries. *JAMA* 59:2015–2020, 1912.
2. El-Menyar AA, Al Suwaidi J, Holmes DR, Jr: Left main coronary artery stenosis: state-of-the-art. *Curr Probl Cardiol* 32:103–193, 2007.
3. O'Keefe JH, Jr, Hartzler GO, Rutherford BD, et al: Left main coronary angioplasty: early and late results of 127 acute and elective procedures. *Am J Cardiol* 64:144–147, 1989.
4. Eldar M, Schulhoff N, Herz I, et al: Results of percutaneous transluminal angioplasty of the left main coronary artery. *Am J Cardiol* 68:255–256, 1991.
5. Bergelson BA, Tommaso CL: Left main coronary artery disease: assessment, diagnosis, and therapy. *Am Heart J* 129:350–359, 1995.
6. Macaya C, Alfonso F, Iniguez A, et al: Stenting for elastic recoil during coronary angioplasty of the left main coronary artery. *Am J Cardiol* 70:105–107, 1992.
7. Seung KB, Park DW, Kim YH, et al: Stents versus coronary-artery bypass grafting for left main coronary artery disease. *N Engl J Med* 358:1781–1792, 2008.
8. Park SJ, Kim YH, Park DW, et al: Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med* 364:1718–1727, 2011.
9. Morice MC, Serruys PW, Kappetein AP, et al: Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation* 121:2645–2653, 2010.
10. American College of Cardiology Foundation/American Heart Association Task Force: 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 126:e354–e471, 2012.
11. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI), et al: Guidelines on myocardial revascularization. *Eur Heart J* 31:2501–2555, 2010.
12. Reig J, Petit M: Main trunk of the left coronary artery: anatomic study of the parameters of clinical interest. *Clin Anat* 17:6–13, 2004.
13. Prosi M, Perktold K, Ding Z, Friedman MH: Influence of curvature dynamics on pulsatile coronary artery flow in a realistic bifurcation model. *J Biomech* 37:1767–1775, 2004.
14. Virmani R, Kolodgie FD, Burke AP, et al: Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 20:1262–1275, 2000.
15. Oviedo C, Maehara A, Mintz GS, et al: Intravascular ultrasound classification of plaque distribution in left main coronary artery bifurcations: where is the plaque really located? *Circ Cardiovasc Interv* 3:105–112, 2010.
16. Park SJ, Ahn JM, Kang SJ: Unprotected left main percutaneous coronary intervention: integrated use of fractional flow reserve and intravascular ultrasound. *J Am Heart Assoc* 1:e004556, 2012.
17. Jasti V, Ivan E, Yalamanchili V, et al: Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. *Circulation* 110:2831–2836, 2004.
18. Park SJ, Ahn JM, Kang SJ, et al: Intravascular ultrasound-derived minimal lumen area criteria for functionally significant left main coronary artery stenosis. *JACC Cardiovasc Interv* 7:868–874, 2014.
19. Kim WJ, Kim YH, Park DW, et al: Comparison of single- versus two-stent techniques in treatment of unprotected left main coronary bifurcation disease. *Catheter Cardiovasc Interv* 77:775–782, 2011.
20. Kang SJ, Mintz GS, Oh JH, et al: Intravascular ultrasound assessment of distal left main bifurcation disease: the importance of the polygon of confluence of the left main, left anterior descending, and left circumflex arteries. *Catheter Cardiovasc Interv* 82:737–745, 2011.
21. Kang SJ, Ahn JM, Song H, et al: Comprehensive intravascular ultrasound assessment of stent area and its impact on restenosis and adverse cardiac events in 403 patients with unprotected left main disease. *Circ Cardiovasc Interv* 4:562–569, 2011.
22. Park SJ, Kim YH, Park DW, et al: Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. *Circ Cardiovasc Interv* 2:167–177, 2009.
23. de la Torre Hernandez JM, Baz Alonso JA, Gomez Hospital JA, et al: Clinical impact of intravascular ultrasound guidance in drug-eluting stent implantation for unprotected left main coronary disease: pooled analysis at the patient-level of 4 registries. *JACC Cardiovasc Interv* 7:244–254, 2014.
24. Hamilos M, Muller O, Cuisset T, et al: Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation* 120:1505–1512, 2009.
25. Bech GJ, Droste H, Pijls NH, et al: Value of fractional flow reserve in making decisions about bypass surgery for equivocal left main coronary artery disease. *Heart* 86:547–552, 2001.
26. Courtis J, Rodes-Cabau J, Larose E, et al: Usefulness of coronary fractional flow reserve measurements in guiding clinical decisions in intermediate or equivocal left main coronary stenosis. *Am J Cardiol* 103:943–949, 2009.
27. Lindstaedt M, Yazar A, Germing A, et al: Clinical outcome in patients with intermediate or equivocal left main coronary artery disease after deferral of surgical revascularization on the basis of fractional flow reserve measurements. *Am Heart J* 152(156):e1–e9, 2006.
28. Lim JS, Proudfit WL, Sones FM: Left main coronary arterial obstruction: long-term follow-up of 141 nonsurgical cases. *Am J Cardiol* 36:131–135, 1975.
29. Campeau L, Corbara F, Crochet D, Petitclerc R: Left main coronary artery stenosis: the influence of aortocoronary bypass surgery on survival. *Circulation* 57:1111–1115, 1978.
30. Conley MJ, Ely RL, Kisslo J, et al: The prognostic spectrum of left main stenosis. *Circulation* 57:947–952, 1978.
31. Takaro T, Hultgren HN, Lipton MJ, Detre KM: The VA cooperative randomized study of surgery for coronary arterial occlusive disease II. Subgroup with significant left main lesions. *Circulation* 54:III107–III117, 1976.
32. Long-term results of prospective randomized study of coronary artery bypass surgery in stable angina pectoris. European Coronary Surgery Study Group. *Lancet* 320:1173–1180, 1982.
33. Chaitman BR, Fisher LD, Bourassa MG, et al: Effect of coronary bypass surgery on survival patterns in subsets of patients with left main coronary artery disease. Report of the Collaborative Study in Coronary Artery Surgery (CASS). *Am J Cardiol* 48:765–777, 1981.
34. Yusuf S, Zucker D, Peduzzi P, et al: Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 344:563–570, 1994.
35. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Bayesian methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. *Circulation* 127:2177–2185, 2013.
36. Tan WA, Tamai H, Park SJ, et al: Long-term clinical outcomes after unprotected left main trunk percutaneous revascularization in 279 patients. *Circulation* 104:1609–1614, 2001.
37. Park SJ, Hong MK, Lee CW, et al: Elective stenting of unprotected left main coronary artery stenosis: effect of debulking before stenting and intravascular ultrasound guidance. *J Am Coll Cardiol* 38:1054–1060, 2001.
38. Park SJ, Park SW, Hong MK, et al: Stenting of unprotected left main coronary artery stenoses: immediate and late outcomes. *J Am Coll Cardiol* 31:37–42, 1998.
39. Silvestri M, Barragan P, Sainsous J, et al: Unprotected left main coronary artery stenting: immediate and medium-term outcomes of 140 elective procedures. *J Am Coll Cardiol* 35:1543–1550, 2000.
40. Black A, Cortina R, Bossi I, et al: Unprotected left main coronary artery stenting: correlates of midterm survival and impact of patient selection. *J Am Coll Cardiol* 37:832–838, 2001.
41. Takagi T, Stankovic G, Finci L, et al: Results and long-term predictors of adverse clinical events after elective percutaneous interventions on unprotected left main coronary artery. *Circulation* 106:698–702, 2002.
42. Park SJ, Lee CW, Kim YH, et al: Technical feasibility, safety, and clinical outcome of stenting of unprotected left main coronary artery bifurcation narrowing. *Am J Cardiol* 90:374–378, 2002.
43. Park SJ, Kim YH, Lee BK, et al: Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis: comparison with bare metal stent implantation. *J Am Coll Cardiol* 45:351–356, 2005.
44. Chieffo A, Stankovic G, Bonizzoni E, et al: Early and mid-term results of drug-eluting stent implantation in unprotected left main. *Circulation* 111:791–795, 2005.
45. Valgimigli M, van Mieghem CA, Ong AT, et al: Short- and long-term clinical outcome after drug-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: insights from the Rapamycin-Eluting and Taxus Stent Evaluated At Rotterdam Cardiology Hospital registries (RESEARCH and T-SEARCH). *Circulation* 111:1383–1389, 2005.
46. Pandya SB, Kim YH, Meyers SN, et al: Drug-eluting versus bare-metal stents in unprotected left main coronary artery stenosis a meta-analysis. *JACC Cardiovasc Interv* 3:602–611, 2010.
47. Valgimigli M, Malagutti P, Aoki J, et al: Sirolimus-eluting versus paclitaxel-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: a combined RESEARCH and T-SEARCH long-term analysis. *J Am Coll Cardiol* 47:507–514, 2006.
48. Lee SH, Ko YG, Jang Y, et al: Sirolimus-versus paclitaxel-eluting stent implantation for unprotected left main coronary artery stenosis. *Cardiology* 104:181–185, 2005.
49. Mehilli J, Kastrati A, Byrne RA, et al: Paclitaxel- versus sirolimus-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol* 53:1760–1768, 2009.
50. Mehilli J, Richardt G, Valgimigli M, et al: Zotarolimus- versus everolimus-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol* 62:2075–2082, 2013.
51. Farooq V, Serruys PW, Zhang Y, et al: Short-term and long-term clinical impact of stent thrombosis and graft occlusion in the SYNTAX trial at 5 years: Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial. *J Am Coll Cardiol* 62:2360–2369, 2013.
52. Lee JY, Park DW, Kim YH, et al: Incidence, predictors, treatment, and long-term prognosis of patients with restenosis after drug-eluting stent implantation for unprotected left main coronary artery disease. *J Am Coll Cardiol* 57:1349–1358, 2011.
53. Kim YH, Park DW, Ahn JM, et al: Everolimus-eluting stent implantation for unprotected left main coronary artery stenosis. The PRECOMBAT-2 (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) study. *JACC Cardiovasc Interv* 5:708–717, 2012.
54. Kang SJ, Mintz GS, Park DW, et al: Mechanisms of in-stent restenosis after drug-eluting stent implantation: intravascular ultrasound analysis. *Circ Cardiovasc Interv* 4:9–14, 2011.
55. Sheiban I, Sillano D, Biondi-Zoccai G, et al: Incidence and management of restenosis after treatment of unprotected left main disease with drug-eluting stents 70 restenotic cases from a cohort of 718 patients: FAILS (Failure in Left Main Study). *J Am Coll Cardiol* 54:1131–1136, 2009.
56. Park DW, Seung KB, Kim YH, et al: Long-term safety and efficacy of stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 5-year results from the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry. *J Am Coll Cardiol* 56:117–124, 2010.
57. Buszman PE, Kiesz SR, Bochenek A, et al: Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol* 51:538–545, 2008.
58. Morice MC, Serruys PW, Kappetein AP, et al: Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation* 129:2388–2394, 2014.

59. Ahn JM, Roh JH, Kim YH, et al: Randomized trial of stents versus bypass surgery for left main coronary artery disease: five-year outcomes of the PRECOMBAT Study. *J Am Coll Cardiol* 2015 (in press).
60. Boudriot E, Thiele H, Walther T, et al: Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. *J Am Coll Cardiol* 57:538–545, 2011.
61. Chieffo A, Meliga E, Latib A, et al: Drug-eluting stent for left main coronary artery disease. The DELTA registry: a multicenter registry evaluating percutaneous coronary intervention versus coronary artery bypass grafting for left main treatment. *JACC Cardiovasc Interv* 5:718–727, 2012.
62. Park DW, Kim YH, Yun SC, et al: Complexity of atherosclerotic coronary artery disease and long-term outcomes in patients with unprotected left main disease treated with drug-eluting stents or coronary artery bypass grafting. *J Am Coll Cardiol* 57:2152–2159, 2011.
63. Chieffo A, Park SJ, Meliga E, et al: Late and very late stent thrombosis following drug-eluting stent implantation in unprotected left main coronary artery: a multicentre registry. *Eur Heart J* 29:2108–2115, 2008.
64. Park KW, Lim WH, Ahn HS, et al: Everolimus- versus sirolimus-eluting stents for the treatment of unprotected left main coronary artery stenosis (results from the EXCELLENT registry). *Int J Cardiol* 168:2738–2744, 2013.

Complex and Multivessel Percutaneous Coronary Intervention

24

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KEY POINTS

- In patients with less complex angiographic multivessel disease, percutaneous coronary intervention (PCI) is associated with the same frequency of death and myocardial infarction (MI) as coronary artery bypass grafting (CABG).
- In patients with more complex angiographic multivessel disease, PCI is associated with an increased frequency of death and MI compared with CABG.
- In most diabetic patients with multivessel disease, CABG is the preferred revascularization strategy.
- Patients with multivessel coronary artery disease (CAD) represent an important group of patients and provides a mortality benefit.

Although various definitions of *multivessel disease* have been used in different studies, in clinical terms, this term generally refers to the presence of two- or three-vessel disease as delineated by coronary angiography. Patients with three-vessel coronary disease or two-vessel disease with proximal left anterior descending (LAD) coronary artery involvement represent a subgroup of patients with CAD in whom survival benefit with bypass surgery has been clearly established.[1] Over the years, considerable advances have been made in revascularization techniques by means of both CABG and PCI. With the constant evolution of techniques has come a tremendous interest in comparing the outcomes of these modalities with a view to determining appropriate clinical practice. In broad terms, the clinical studies that have compared CABG with PCI can be viewed in terms of three major groups when evaluated from the standpoint of important developments in the history of PCI. With the advent of percutaneous transluminal coronary angioplasty (PTCA), multiple studies were conducted to compare PTCA with CABG; these represent the first group of studies to compare PCI with CABG. The development of coronary stents had led to a second series of comparisons of PCI with stenting to CABG. Important lessons have been learned from both of these groups of studies, and the findings of the important literature from this period will be presented below. With the arrival of the drug-eluting stents (DESs), more recent studies have continued to focus on comparisons of PCI with drug-eluting stenting to CABG. This last group of studies is the most relevant to contemporary clinical practice; it will be discussed in detail because it continues to evolve with the application of second- and third-generation DES devices, which now include different drugs and different polymer strategies such as biodegradable polymers. In addition, data are now available on completely biodegradable vascular scaffolds. This later group of devices may develop to become a fourth major group in the history of percutaneous revascularization.

PERCUTANEOUS CORONARY BALLOON ANGIOPLASTY VERSUS CORONARY ARTERY BYPASS GRAFTING

Multiple trials have compared the outcomes of patients with multivessel disease revascularized by balloon angioplasty versus CABG. Important landmark studies on this subject are summarized below.

The Bypass Angioplasty Revascularization Investigation (BARI)

In the BARI trial,[2] symptomatic patients with multivessel CAD (N = 1829) were randomly assigned to initial treatment with PTCA or CABG. The 10-year survival was 71% for PTCA and 73.5% for CABG (P = .18). At 10 years, the PTCA group had substantially higher subsequent revascularization rates compared with the CABG group (76.8% vs. 20.3%, P < .001), but the angina rates for the two groups were similar. In the subgroup of patients who had not been treated for diabetes, survival rates were nearly identical by randomization (PTCA 77% vs. CABG 77.3%, P = .59). In the subgroup who had been treated for diabetes, the CABG group had higher survival compared with the PTCA group (57.8% vs. 45.5%, respectively; P = .025; Figs. 24-1 through 24-3).

The Randomized Intervention Treatment of Angina (RITA)

In the RITA trial,[3] 1011 patients with coronary heart disease (45% single-vessel and 55% multivessel disease) were randomly assigned to initial treatment with PTCA or CABG. The median follow-up was 6.5 years. The primary end point of death or nonfatal MI occurred in 17% of the PTCA group and in 16% of the CABG group (P = .64). Subsequent nonrandomized CABG was undertaken in 134 (26%) of the PTCA group, and a second CABG was undertaken in 14 (3%) of the CABG group. In the PTCA group, 138 patients (27%) required an additional nonrandomized PTCA at some point; 45 of these also required a nonrandomized CABG. In the CABG group, 47 (9%) required nonrandomized PTCA subsequently; 7 of these also required a second CABG. The prevalence of angina was consistently higher in the PTCA group, with an absolute average 10% increase compared with the CABG group (P < .001).

The German Angioplasty Versus Bypass Surgery Investigation (GABI)

The GABI trial[4] compared the outcomes in patients 1 year after complete revascularization with CABG or PTCA. A total of 8981 patients with multivessel CAD were randomly assigned to undergo CABG (177 patients) or PTCA (182 patients). During the first year of follow-up, further interventions were necessary in 44% of the patients in the PTCA group (repeated PTCA in 23%, CABG in 18%, and both in 3%) but in only 6% of the patients in the CABG group (repeated CABG in 1% and PTCA in 5%, P < .001). One year after treatment, 74% of the patients in the CABG group and 71% of those in the PTCA group were free of angina.

The Emory Angioplasty Versus Surgery Trial (EAST)

EAST[5] was a single-center, randomized comparison of a strategy of initial coronary angioplasty (n = 198) or CABG (n = 194) for patients with multivessel CAD. The primary end point of death, MI, or a large ischemic defect at 3 years was not different, and repeat revascularization was significantly greater in the angioplasty group. Survival at 8 years was 79.3% in the angioplasty group and 82.7% in the surgical group (P = .40). Patients with proximal LAD stenosis and those with diabetes tended to have better rates of late survival with surgical intervention, although this did not reach statistical significance. After the

first 3 years, repeat interventions remained relatively equal for both treatment groups.

The Coronary Angioplasty Versus Bypass Revascularization Investigation (CABRI)

CABRI[6] was a multinational, multicenter, randomized trial to compare the strategies of revascularization with CABG and PTCA in patients with symptomatic multivessel CAD. Of the 1054 patients recruited, 513 were randomized to CABG and 541 to PTCA. After 1 year of follow-up, 2.7% of those randomized to CABG and 3.9% of those randomized to PTCA had died, a difference that was not statistically significant. However, patients randomized to PTCA required significantly more reinterventions; at 1 year, only 66.4% required a single-vessel revascularization procedure compared with 93.5% of patients randomized to CABG (relative risk [RR], 5.23; 95% confidence interval [CI], 3.90 to 7.03; $P < .001$). The patients in the PTCA group took significantly more medication at 1 year (RR, 1.30; 95% CI, 1.18 to 1.43; $P < .001$). They were also more likely to have clinically significant angina (RR, 1.54; 95% CI, 1.09 to 2.16; $P = .012$); this association was present in both sexes but was significant only in females.

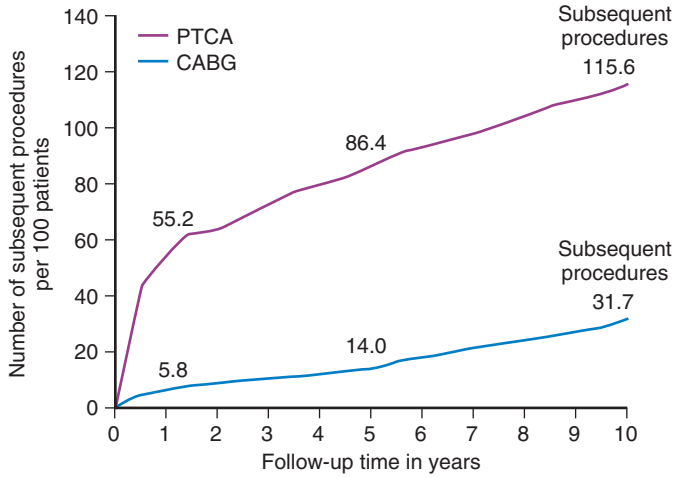


FIGURE 24-1 Revascularization in BARI. *Blue line,* coronary artery bypass grafting (CABG). *Purple line,* percutaneous transluminal coronary angiography (PTCA). (Modified from BARI investigators: The final 10-year follow-up results from the BARI randomized trial. *J Am Coll Cardiol* 49[15]:1600-1606, 2007.)

The Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery (ERACI)

In ERACI,[7] 127 patients who had multivessel CAD and a clinical indication for myocardial revascularization were randomized to undergo coronary angioplasty ($n = 63$) or bypass surgery ($n = 64$). At 3 years, freedom from combined cardiac events—death, Q-wave MI, angina, and repeat revascularization procedures—was significantly greater for the bypass surgery group compared with the coronary angioplasty group (77% vs. 47%, $P < .001$). No differences were reported in overall mortality (4.7% vs. 9.5%, $P = .5$) and cardiac mortality (4.7% vs. 4.7%) or in the frequency of MI (7.8% vs. 7.8%, $P = .8$) between the two groups. However, patients who had bypass surgery were more frequently free of angina (79% vs. 57%, $P < .001$) and required fewer additional reinterventions (6.3% vs. 37%, $P < .001$) compared with patients who had coronary angioplasty.

Summary

Although perhaps no longer directly relevant to current clinical practice, these early trials yielded two important findings:

1. Survival in patients with multivessel disease was found to be similar for PTCA and CABG except in patients with diabetes, for whom CABG was advantageous.
2. The key difference between the procedures was found to lie in the substantially greater need for revascularization procedures in patients treated with PTCA.

With the development of coronary stents, it was clearly established that stenting was associated with a lower risk of repeat revascularization procedures compared with balloon angioplasty alone. This led to a second series of comparisons of CABG with PCI, this time with the use of coronary artery stents. These trials are summarized later.

PERCUTANEOUS CORONARY INTERVENTION WITH BARE-METAL STENTING VERSUS CORONARY ARTERY BYPASS GRAFTING

Arterial Revascularization Therapies Study (ARTS)

In the ARTS trial,[8] a total of 1205 patients were randomly assigned to CABG ($n = 605$) or stent implantation ($n = 600$). At 5 years, no

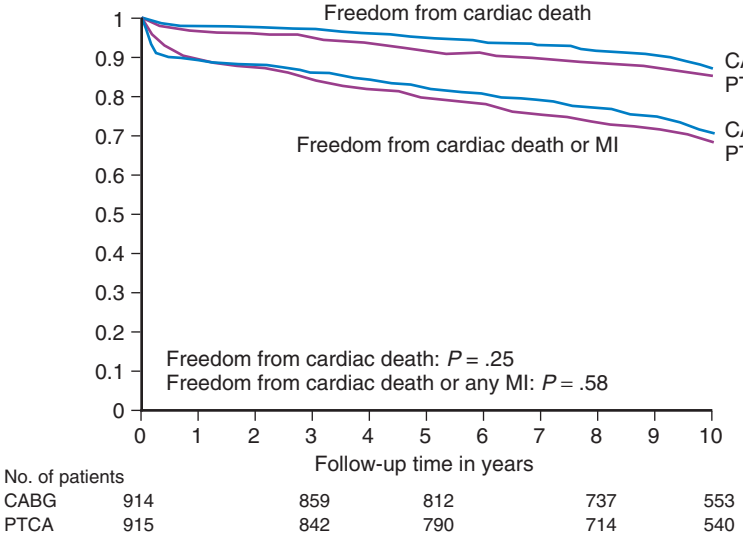


FIGURE 24-2 Cardiac death or myocardial infarction (MI) in BARI. *Blue line,* coronary artery bypass grafting (CABG). *Purple line,* percutaneous transluminal coronary angiography (PTCA). (Modified from BARI investigators: The final 10-year follow-up results from the BARI randomized trial. *J Am Coll Cardiol* 49[15]:1600-1606, 2007.)

significant difference in survival was seen between the stent and CABG groups (8% for stents vs. 7.6% for CABG, $P = .83$). In a subgroup of 208 patients with diabetes, mortality trended higher in the stent group (13.4%) compared with the CABG group (8.3%; $P = .27$). The overall freedom from death, stroke, or MI was not significantly different between the groups (18.2% in the stent group vs. 14.9% in the surgical group, $P = .14$). However, the incidence of repeat revascularization was significantly higher in the stent group (30.3%) than in the CABG group (8.8%, $P < .001$). The composite event-free survival rate was 58.3% in the stent group and 78.2% in the CABG group ($P < .0001$). This difference was largely driven by the differences in revascularization rates.

Angina With Extremely Serious Operative Mortality Evaluation (AWESOME)

In the AWESOME study,[9] patients from 16 Veterans Affairs Medical Centers were screened to identify those with myocardial ischemia refractory to medical management and the presence of one or more risk factors for adverse outcome with CABG. A total of 232 patients were randomized to CABG, and 222 were randomized to PCI. The 30-day survivals for CABG and PCI were 95% and 97%, respectively. At 36 months, no significant difference in survival was reported: it was 79% and 80% for CABG and PCI, respectively. However, a difference was seen in survival free of revascularization: 66% and 44% for CABG and PCI, respectively ($P = .001$).

The Medicine, Angioplasty, or Surgery Study (MASS-II)

MASS-II[10] included 611 patients who were randomly assigned to undergo CABG ($n = 203$), PCI ($n = 205$), or medical therapy ($n = 203$). The inclusion of the medical-therapy arm made this trial different from many of the other studies. The rates of event-free survival—namely, the combined incidence of overall mortality, MI, or refractory angina that required revascularization—were significantly different among patients in the three therapeutic groups at 5-year ($P = .0026$) and 10-year ($P < .0001$) follow-up. Pairwise treatment comparisons of the primary end points at 5-year follow-up demonstrated no significant difference between PCI and medical therapy (hazard ratio [HR], 0.93; 95% CI, 0.67 to 1.30). At 10-year follow-up, this comparison continued to demonstrate a nonsignificant difference between the PCI and medical-therapy groups (HR, 0.79; 95% CI, 0.62 to 1.01). After multivariate Cox analysis at 10-year follow-up, a protective effect of CABG compared with medical therapy (HR, 0.43; 95% CI, 0.32 to 0.58; $P < .001$) and PCI (HR, 0.53; 95% CI, 0.39 to 0.72; $P < .001$) was observed.[11]

The cumulative survival rates at 10 years for patients assigned to each group were 74.9% for PCI, 75.1% for CABG, and 69.0% for medical therapy ($P = .089$). In terms of nonfatal MI, CABG was significantly superior to PCI and medical therapy at the 10-year ($P = .016$) but not the 5-year ($P = .785$) follow-up. The incidence of uncomplicated MI was 8.3% and 10.3% at the 5- and 10-year follow-up, respectively, in the CABG group. In the PCI arm, 11.2% and 13.2% had had an uncomplicated MI at the follow-up at 5 and 10 years, respectively. In the medical therapy group, 15.3% and 20.7% had experienced an uncomplicated or nonfatal MI by the 5- and 10-year follow-up, respectively.

At 5-year follow-up, 3.4% of those in the CABG group required PCI compared with 24.1% for patients in the medical-therapy group and 32.2% in the PCI group, respectively ($P = .021$). At 10-year follow-up, additional interventions were needed in 7.4% of patients in the CABG group compared with 41.5% for patients in the PCI group and 39.4% for those in the medical-therapy group because of uncontrolled angina ($P < .001$). Patients treated with surgery were most likely to be free of angina symptoms after 10 years of follow-up. In the medical-therapy group, 43% were free of angina symptoms after the 10-year follow-up compared with 64% in the CABG group and 59% in the PCI group.

In terms of cardiac death, 20.7%, 10.8%, and 14.1% had died of MI in the medical-therapy, CABG, and PCI groups by 10-year follow-up, respectively ($P = .019$). The incidence of stroke was similar at 6.9% in those who received medical therapy, 8.4% in the CABG group, and 5.4% in the PCI group ($P = .550$) at 10 years.

Stent or Surgery Trial (SoS)

The aim of the SoS trial[12] was to assess the effect of stent-assisted PCI versus CABG in the management of patients with multivessel disease. In 53 centers in Europe and Canada, symptomatic patients with multivessel CAD were randomized to CABG ($n = 500$) or stent-assisted PCI ($n = 488$) and were followed for a median of 2 years. In the PCI group, 21% of patients ($n = 101$) required additional revascularization procedures compared with 6% ($n = 30$) in the CABG group ($P < .0001$). At a median follow-up of 6 years, 53 patients (10.9%) died in the PCI group compared with 34 (6.8%) in the CABG group (HR, 1.66; 95% CI, 1.08 to 2.55; $P = .022$). The incidence of death or Q-wave MI was similar in both groups (PCI 9%, $n = 46$; CABG 10%, $n = 49$; $P = .80$). Fewer deaths were reported in the CABG group than in the PCI group (PCI 5%, $n = 22$; CABG 2%, $n = 8$; $P = .01$). This seemed to result, at least in part, from a higher proportion of noncardiovascular deaths in the PCI arm (from cancer) compared with the CABG arm. Additionally, the mortality rate in the CABG group was lower than the rates

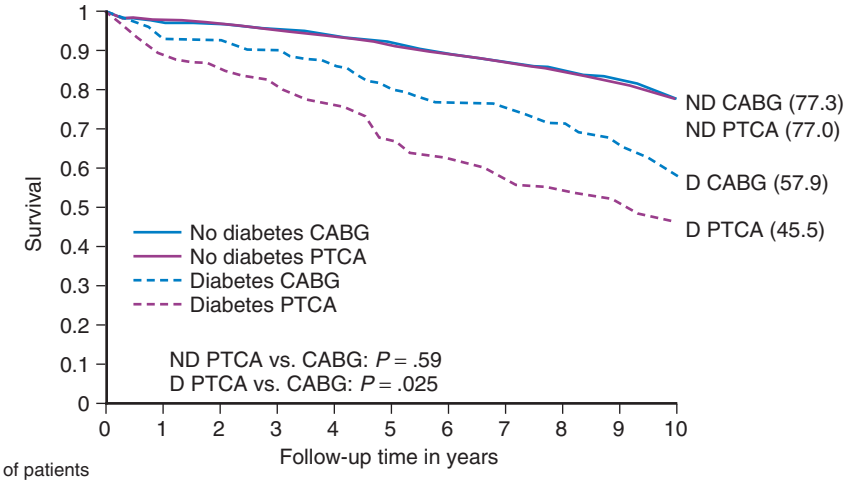


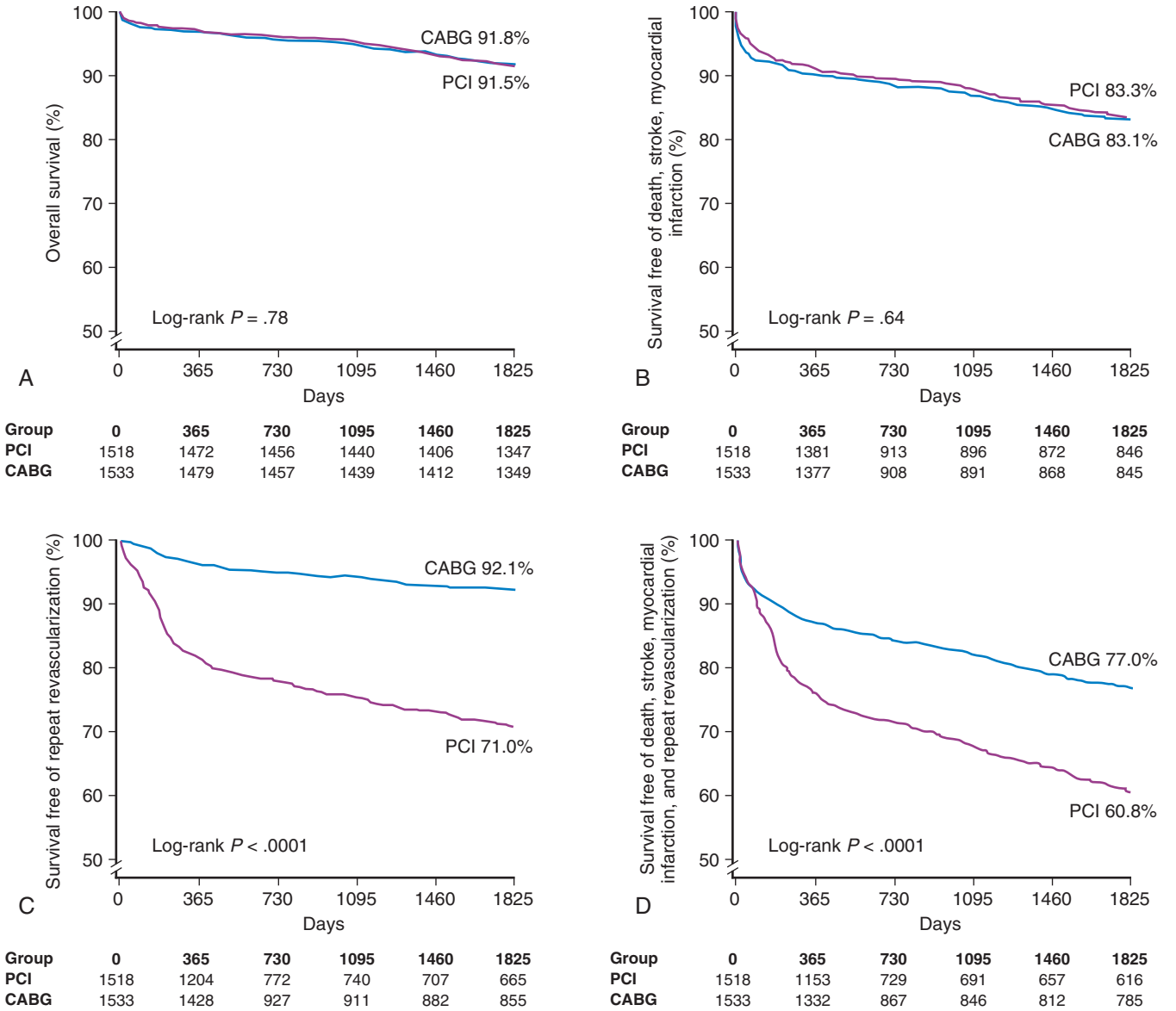
FIGURE 24-3 Overall survival by diabetes status in BARI. *CABG,* Coronary artery bypass grafting; *D,* diabetes; *ND,* no diabetes; *PTCA,* percutaneous transluminal coronary angiography. (Modified from BARI investigators: The final 10-year follow-up results from the BARI randomized trial, *J Am Coll Cardiol* 49[15]:1600-1606, 2007.)

that had been reported in previous studies. Subsequently, it was seen that at a median follow-up of 6 years, 53 patients (10.9%) had died in the PCI group compared with 34 (6.8%) in the CABG group (HR, 1.66; 95% CI, 1.08 to 2.55; $P = .022$).

ERACI II

The ERACI II trial[13] randomized a total of 450 patients with multivessel disease to undergo either PCI ($n = 225$) or CABG ($n = 225$). At the 5-year follow-up, patients initially treated with PCI had similar survival and freedom from nonfatal acute MI than those initially treated with CABG (92.8% vs. 88.4% and 97.3% vs. 94%, respectively, $P = .16$). Freedom from repeat revascularization procedures (PCI or CABG) was significantly lower with PCI compared with CABG (71.5% vs. 92.4%, $P = .0002$). Accordingly, driven by a greater need for revascularization, freedom from major adverse cardiac events (MACEs) was also significantly lower with PCI compared with CABG (65.3% vs. 76.4%, $P = .013$). However, at 5 years, similar numbers of patients randomized to each revascularization procedure were asymptomatic or had class I angina.

A pooled analysis of the four randomized trials described earlier—ARTS, ERACI II, SoS, and MASS II—with a total of 3051 patients from all four trials evaluated the relative safety and efficacy of PCI with stenting and CABG for the treatment of multivessel CAD (Fig. 24-4). At 5 years, the cumulative incidence of death, MI, and stroke was similar in the PCI with stenting group and in the CABG group (16.7% vs. 16.9%, respectively; HR, 1.04; 95% CI, 0.86 to 1.27; $P = .69$). Repeat revascularization, however, occurred significantly more often after PCI compared with CABG (29.0% vs. 7.9%, respectively; HR, 0.23; 95% CI, 0.18 to 0.29; $P < .001$). Major adverse cardiac and cerebrovascular events (MACCEs) were significantly higher in the PCI group than in the CABG group (39.2% vs. 23.0%, respectively; HR, 0.53; 95% CI, 0.45 to 0.61, $P < .001$).[14] In another study,[15] the authors identified 23 randomized controlled trials in which a total of 5019 patients were



Group	0	365	730	1095	1460	1825
PCI	1518	1472	1456	1440	1406	1347
CABG	1533	1479	1457	1439	1412	1349

Group	0	365	730	1095	1460	1825
PCI	1518	1381	913	896	872	846
CABG	1533	1377	908	891	868	845

Group	0	365	730	1095	1460	1825
PCI	1518	1204	772	740	707	665
CABG	1533	1428	927	911	882	855

Group	0	365	730	1095	1460	1825
PCI	1518	1153	729	691	657	616
CABG	1533	1332	867	846	812	785

FIGURE 24-4 Outcomes of percutaneous coronary intervention (PCI) with bare-metal stenting versus coronary artery bypass grafting (CABG) in a meta-analysis of four trials. (Modified from Daemen J, Boersma E, Flather M, et al: Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation* 118[11]:1146-1154, 2008.)

randomly assigned to PCI and 4944 to CABG. Again, this meta-analysis included data from patients treated with PTCA alone and PTCA with stenting. The difference in survival after PCI or CABG was less than 1% at the 10-year follow-up. Survival did not differ between PCI and CABG for patients with diabetes in the six trials that reported on this subgroup. Procedure-related strokes were more common after CABG than after PCI (1.2% vs. 0.6%; risk difference 0.6%, $P = .002$). Angina relief was greater after CABG than after PCI, with risk differences ranging from 5% to 8% at 1 to 5 years ($P < .001$). The absolute rates of angina relief at 5 years were 79% after PCI and 84% after CABG. Repeated revascularization was more common after PCI than after CABG (risk difference, 24% at 1 year and 33% at 5 years; $P < .001$); the absolute rates at 5 years were 46.1% after balloon angioplasty, 40.1% after PCI with stents, and 9.8% after CABG. In comparisons based on observational studies, the CABG-PCI hazard ratio for death favored PCI among patients with the least severe disease and CABG among those with the most severe disease.

Summary

In a manner similar to what was observed with the trials of PTCA versus CABG, the use of stenting continued to be associated with a higher frequency of the need for revascularization procedures. However, there was no significant difference in mortality.

The development of DESs represented an important milestone in the history of interventional cardiology. With the reduced risk of restenosis associated with the use of these stents, interest is ongoing in comparisons of PCI using a DES with CABG. Some of the important studies that have looked at this are reviewed below.

PERCUTANEOUS CORONARY INTERVENTION WITH DRUG-ELUTING STENTS VERSUS CORONARY ARTERY BYPASS GRAFTING

Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX)

In the SYNTAX trial,[15] a total of 1800 patients were randomized to undergo CABG or PCI using paclitaxel-eluting stents (PESs). Patients for whom only one of the two treatment options was beneficial because of anatomic features or clinical conditions were entered into a parallel, nested CABG or PCI registry. A noninferiority comparison of the two groups was performed for the primary end point—MACCE (i.e., death from any cause, stroke, MI, or repeat revascularization) in the 12-month period after randomization. The 12-month MACCE rates were also analyzed on the basis of the SYNTAX score, which reflects a comprehensive anatomic assessment wherein higher scores indicate more complex CAD; a low score was defined as 22 or less, an intermediate score as 23 to 32, and a high score as 33 or greater. A higher proportion of patients had complete revascularization after CABG than after PCI (63.2% vs. 56.7%, $P = .005$). Overall, the rate of complete revascularization was lower in both treatment groups in this study compared with previous studies. This was likely to have resulted from a different definition of completeness of revascularization used in the earlier trials and the more complex anatomic characteristics of the patients in this trial. In the CABG group, off-pump surgery was performed in 15% of patients, one or more arterial grafts were used in 97.3% of patients, and an average of 2.8 conduits and 3.2 distal anastomoses per patient were performed. In the PCI group, 14.1% of patients underwent staged procedures, 63.1% had at least one bifurcation or trifurcation treated, more than four stents on average were implanted per patient, and a third of patients had placement of stents with a total length of more than 100 mm. These characteristics reflect a population of patients with fairly complex anatomy. At 12 months, the incidence of MACCEs was lower in the CABG group (12.4%) than in the PCI group (17.8%, $P = .002$; Fig. 24-5). This was largely driven by the rate of repeat revascularization at 12 months, which was significantly higher among patients in the PCI group than among those in the CABG group (13.5% vs. 5.9%, $P < .001$). Death occurred in 4.4% of the PCI group compared with 3.5% of the CABG group ($P = .37$). The rate of death from cardiac causes was greater with PCI than with CABG (3.7% vs. 2.1%, $P = .05$); the rate of death from noncardiac causes, although not significant, was higher with CABG (1.4% vs. 0.7%, $P = .13$). MI occurred in 3.3% of the CABG group versus 4.8% of the PCI group ($P = .11$). Stroke was significantly more likely to occur with CABG (2.2% vs. 0.6% with PCI; $P = .003$). The 12-month rates of symptomatic graft occlusion (in the CABG group) and stent thrombosis (in the PCI group) were similar ($P = .89$). In the CABG group, the binary 12-month rates of MACCEs were similar among patients with low SYNTAX scores (0 to 22; 14.7%), those with intermediate scores (23 to 32; 12%), and those with high scores (≥33; 10.9%). However, in the PCI group, the rate of MACCEs had increased significantly among patients with high SYNTAX scores (23.4%) compared with those with low scores (13.6%) or intermediate scores (16.7%; $P = .002$ for high vs. low scores; $P = .04$ for high vs. intermediate scores; Fig. 24-6). A significant interaction was reported between the SYNTAX score and the treatment group ($P = .01$); patients with low or intermediate scores in the CABG group and in the PCI group had similar rates of MACCEs, whereas among patients with high scores, the event rate had increased significantly in the PCI group. The 3- and 5-year results of this trial have now been published. The cumulative MACCE rate through 3 years was significantly higher in the PCI arm compared with the CABG arm (CABG 20.2% vs. PCI 28.0%, $P < .001$; see Fig. 24-5). This was driven in part by increased repeat revascularization in the PCI arm (CABG 10.7% vs. PCI 19.7%; $P < .001$). The composite safety end point of death/stroke/MI was not significantly different between treatment groups 3-years after randomization (CABG 12.0% vs. PCI 14.1%; $P = .21$). Death from all causes was not different between the treatment groups at 3 years (CABG 6.7% vs. PCI 8.6%; $P = .13$). The cumulative rate of cardiac death was significantly higher in the PCI arm (CABG 3.6% vs. PCI 6.0%; $P = .02$), but the incidence of stroke was not significantly different between CABG (3.4%) and PCI patients (2.0%, $P = .07$). The MI rate was 3.6% in the CABG and 7.1% in the PCI arm ($P = .002$). No significant interactions were observed between left main (LM) or three-vessel disease (3VD) status and the treatment group 3-year MACCE rate or any of the components. The treatment effect of PCI compared with CABG was not significantly different between patients in either of these groups.[17]

The 5-year SYNTAX data demonstrated MACCE rates of 26.9% in the CABG group versus 37.3% in the PCI group ($P < .0001$). Incidences of MI (3.8% CABG, 9.7% PCI; $P < .0001$) and repeat revascularization (13.7% vs. 25.9%; $P < .0001$) were both found to be higher in the PCI group. All-cause mortality was not significantly different in the two groups (11.4% in the CABG group vs. 13.9% in the PCI group; $P = .10$), as was the stroke rate (3.7% vs. 2.4%; $P = .09$). Patients with 3VD with SYNTAX scores in the lowest tertile (≤22) had similar MACCE rates between treatment arms (28.6% CABG vs. 32.1% PCI, $P = .12$). In those 3VD patients with intermediate (23 to 32), or high (≥33) SYNTAX scores, the rate of MACCE was significantly increased in favor of CABG (intermediate score, 36.0% PCI vs. 25.8% CABG; $P = .008$; high score, 44.0% PCI vs. 26.8% CABG; $P < .0001$). MI was significantly higher in the PCI arm of the 3VD intermediate SYNTAX score tertile (11.2% vs. 3.6%, $P = .0009$). In 3VD patients with a SYNTAX score of 33 or higher, mortality (19.2% vs. 11.4%, $P = .005$) and MI (10.1% vs. 3.9%, $P = .004$) was significantly higher in the PCI arm. This appeared to be driven primarily by increased rates of repeat revascularization and MI. Cumulative event rates were not significantly different in patients with LM disease who had low or intermediate SYNTAX scores (0 to 22, CABG 31.5% vs. PCI 30.4%, $P = .74$; 23 to 32, CABG 32.3% vs. PCI 32.7%, $P = .88$). In LM patients with the most complex anatomy (SYNTAX score ≥33), the cumulative event rate was significantly increased in PCI-treated patients (CABG 29.7% vs. PCI 46.5%, $P = .003$).[18]

Additionally, at 5-year follow-up, no significant difference was reported in the incidence of Academic Research Consortium (ARC) definite stent thrombosis and ARC-like definite graft occlusion between the two groups (7% vs. 6%, $P = .34$). Whereas stent thrombosis occurred

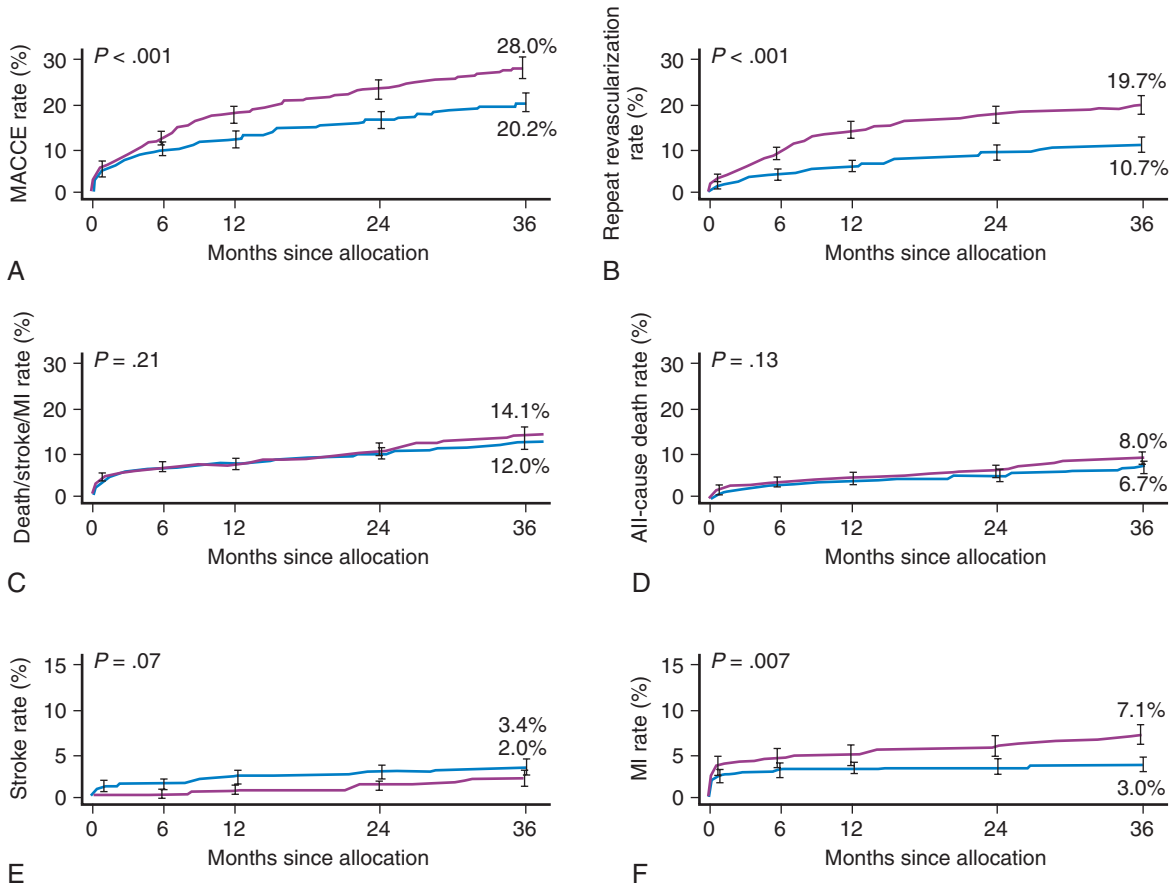


FIGURE 24-5 Outcomes in the SYNTAX trial. *Blue line* shows coronary artery bypass grafting; *purple line* shows percutaneous coronary intervention. *MACCE,* Major adverse cardiac and cerebrovascular event; *MI,* myocardial infarction. (Modified from Kappetein AP, Feldman TE, Mack MJ, et al: Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J* 32(17):2125–2134, 2011.)

more frequently in the proximal coronary vasculature and left main coronary artery, protocol graft occlusion (41 lesions) was more frequent with grafts anastomosed to the distal right coronary artery (17/41, 42%). Although the incidence of stent thrombosis and graft occlusion were not significantly different, stent thrombosis had a stronger association with short- to long-term mortality.[19]

Compared with the first-year results, some interesting observations can be made about the 5-year results of this trial. Overall, the trends in MACCE, death/stroke/MI, cardiac death, and repeat revascularization rates seen in the first year of follow-up were sustained through the 5-year follow-up period. Compared with outcomes after 1 year of follow-up, at 5 years, cardiac death was found to be increased in the overall PCI-treated patient population, largely in those patients with higher SYNTAX scores. Although stroke was significantly increased at 1 year of follow-up for CABG, no difference in stroke was seen during the interval of 1- and 5-year follow-up. A difference in the MI rate between the two treatment groups that favored CABG was also noted after the first year of follow-up. The likely cause of the increased MIs in the PCI arm was felt to be due to restenosis and additional revascularization in those patients with advanced diffuse disease. In addition, whereas the MACCE rates were similar between the intermediate-risk PCI and CABG groups at 1 year, at 5 years the intermediate SYNTAX PCI group demonstrated a significantly increased MACCE rate, likely driven by repeat revascularization and an increased rate of MI.

Based on these observations, it appears that CABG should remain the standard for more complex anatomy. PCI in this trial demonstrated similar outcomes to CABG in patients with less complex disease, measured by lower SYNTAX score for 3VD and lower and intermediate scores for LM disease. This highlights the emerging importance of the SYNTAX score as an effective risk-assessment tool for making decisions about revascularization options.

ARTS II

As mentioned previously, ARTS I was a randomized trial that included 1205 patients with multivessel disease to compare CABG with use of bare-metal stents (BMSs). ARTS II was a multicenter, nonrandomized, open-label trial designed to compare the safety and efficacy of sirolimus-eluting stents (SESs) in patients with de novo multivessel CAD, with the surgical and BMS groups of ARTS I acting as historic controls. The ARTS II trial enrolled 607 patients with an attempt to enroll at least one third of patients with three-vessel disease. At 5 years, the death/stroke/MI event-free survival rate was 87.1% in the ARTS II cohort treated with SESs versus 86% ($P = .1$) and 81.9% ($P = .007$) in the ARTS I cohorts treated with CABG and BMSs, respectively. The 5-year MACCE rate in ARTS II (27.5%) was significantly higher than in the CABG group in ARTS I (21.1%, $P = .02$), and it was lower than in the BMS group in ARTS I (41.5%, $P < .001$). This was largely driven by differences in revascularization rates. During the follow-up period, freedom from revascularization was observed in 91% of the ARTS I CABG group, in 79.2% of the ARTS II SES group, and in 69.1% of the ARTS I BMS group ($P < .001$ for comparisons of DES vs. CABG and DES vs. BMS). Similar to what was observed in the SYNTAX trial, a significant difference in MACCE-free survival was observed when patients were stratified according to SYNTAX score tertiles. When compared with the group with the lowest SYNTAX score (<16), who

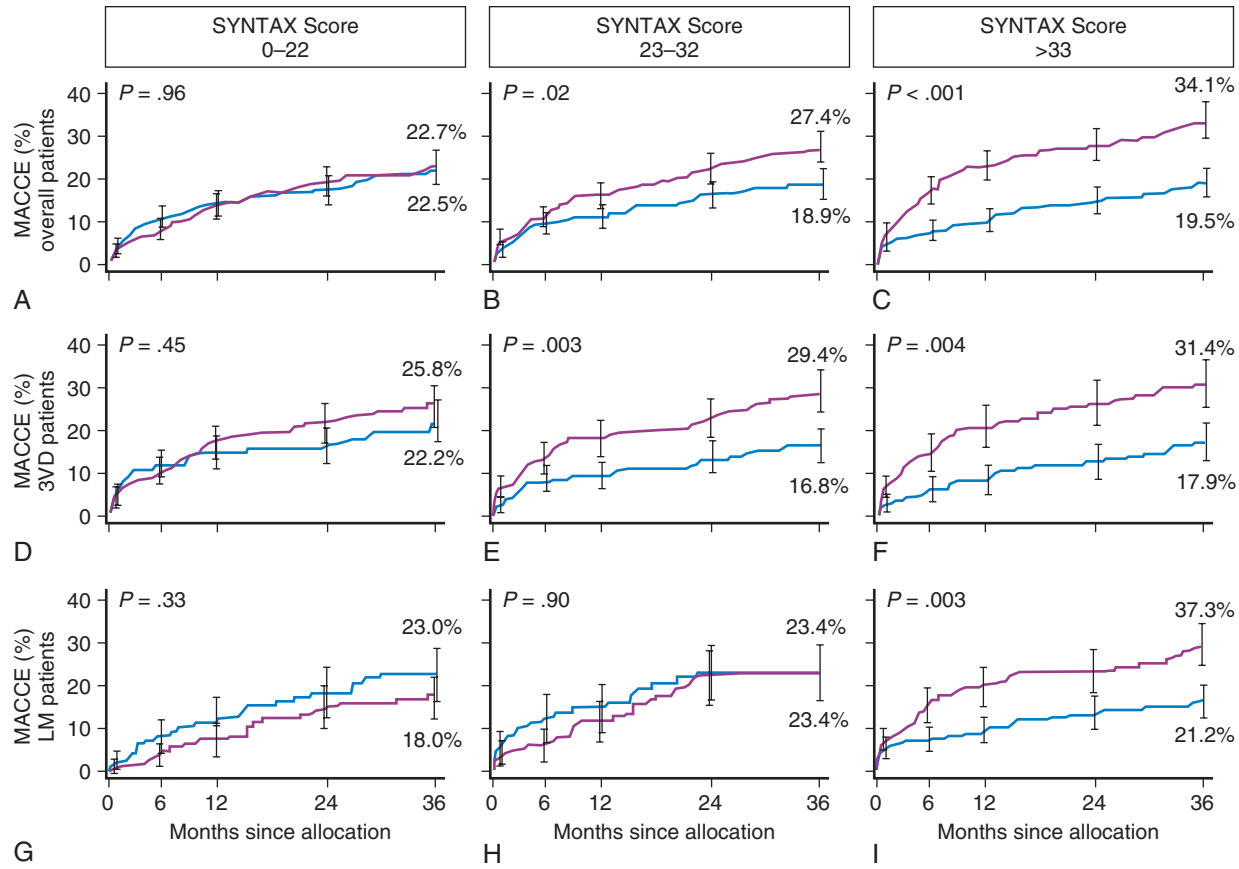


FIGURE 24-6 Major adverse cardiac and cerebrovascular event rates according to the subset, treatment group, and SYNTAX score category. Time-to-event curves in the coronary artery bypass grafting (*blue line*) or percutaneous coronary intervention (*yellow line*) overall cohorts to 3 years according to the low (0-22, **A**), intermediate (23-32, **B**), or high (≥33, **C**) SYNTAX scores. **D** to **F,** Major adverse cardiac and cerebrovascular events in three-vessel disease patients with low, intermediate, or high SYNTAX scores, respectively. **G** to **I,** Major adverse cardiac and cerebrovascular events in patients with left main disease with low, intermediate, or high SYNTAX scores. *P*-value from log-rank test. *3VD,* Three-vessel disease; *LM,* left main; *MACCE,* major adverse cardiac and cerebrovascular event. (Modified from Kappetein AP, Feldman TE, Mack MJ, et al: Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J* 32(17):2125–2134, 2011.)

had a 5-year MACE-free rate of 80.1%, both the intermediate (16 to 24) and high (>24) SYNTAX score groups demonstrated a lower MACE-free survival rate (intermediate 70.1%, log-rank $P = .02$; high 67.1%, $P = .001$).[20]

ERACI III

In the ERACI III trial, 225 patients with multivessel disease who received DESs met clinical and angiographic inclusion criteria for the ERACI II trial and were compared with both ERACI II treatment arms (ERACII–PCI and ERACI II–CABG). At 1 year, freedom from MACCEs was significantly greater in the ERACI III–DES cohort (88%) than in the ERACI II–CABG cohort (80.5%, $P = .038$) and in the ERACI II–PCI cohort (78%, $P = .006$). The ERACI III–DES cohort had freedom from death and acute MI similar to that of the ERACI II–PCI arm but greater than that of the ERACI II–CABG arm. Freedom from repeat revascularization was similar between the ERACI III–DES and the ERACI II–CABG groups (95.1%, *P* = not significant [NS]), but both were significantly better than those in the ERACI II–PCI arm (91.2% and 83%, $P = .002$ and .02, respectively). It was concluded that patients with multivessel disease treated with DESs in ERACI III had better 1-year outcomes than those treated with PCI or CABG in ERACI II.[21] The 3-year MACCE rate was lower in the ERACI III–DES group (22.7%) than in the ERACI II–BMS group (29.8%, $P = .015$), mainly reflecting less target-vessel revascularization (TVR; 14.2% vs. 24.4%, $P = .009$). MACCE rates at 3 years were similar in DES-treated and CABG-treated patients (22.7%, $P = 1.0$), in contrast to results at 1 year (12% vs. 19.6%, $P = .038$). MACCE rates in ERACI III–DES were higher in patients with diabetes (RR, 0.81; 95% CI, 0.66 to 0.99, $P = .018$). Death or nonfatal MI at 3 years trended higher in the DES cohort (10.2%) than in the BMS cohort (6.2%, $P = .08$) and were lower than in the CABG cohort (15.1%, $P = .07$). Subacute or late-stent thrombosis (>30 days) occurred in nine of the DES group and in none of the BMS group ($P = .008$). It therefore appeared that the initial advantage for PCI with DES over CABG observed at 1 year was not apparent by 3 years. Furthermore, despite the continued lower incidence of MACCEs, the initial advantage over BMS appeared to decrease with time.[22]

Coronary Artery Revascularization in Diabetes (CARDia)

The purpose of the CARDia study[23] was to compare the safety and efficacy of PCI with stenting against CABG in patients with diabetes and symptomatic multivessel CAD. The primary outcome was a composite of all-cause mortality, MI, and stroke, and the main secondary outcome included the addition of repeat revascularization to the primary outcome events. A total of 510 patients with diabetes and multivessel or complex single-vessel CAD from 24 centers were randomized to PCI plus stenting or to CABG. BMSs were used initially,

but a switch to an SES (Cypher [Cordis Corporation, Fremont, CA]) was instituted later in the trial. After 12 months of follow-up, the composite rate of death, MI, and stroke was 10.5% in the CABG group and 13% in the PCI group (HR, 1.25; 95% CI, 0.75 to 2.09, $P = .39$); all-cause mortality rates were 3.2% and 3.2%; and the rates of death, MI, stroke, or repeat revascularization were 11.3% and 19.3% (HR, 1.77; 95% CI, 1.11 to 2.82; $P = .02$), respectively. When the patients who underwent CABG were compared with the subset of patients who received DESs (69%), the primary outcome rates were 12.4% and 11.6%, respectively (HR, 0.93; 95% CI, 0.51 to 1.71; $P = .82$).

Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM)

The FREEDOM trial[24] was a multicenter, open-label, prospective, randomized superiority trial of PCI versus CABG in 1900 patients with diabetes in whom revascularization was indicated. Consenting patients with multivessel disease were randomized on a 1:1 basis to either CABG or multivessel stenting using DESs and were observed at 30 days, 1 year, and annually for up to 5 years. 953 patients were randomized to the PCI arm, and 947 patients were randomized to the CABG arm. At the discretion of primary physicians or interventionalists, patients randomized to the PCI-DES arm received any approved DES (either paclitaxel-eluting stents or sirolimus-eluting stents), and in the surgical arm, arterial revascularization was encouraged. Of the entire group, 84% of patients had three-vessel disease with the average SYNTAX score being 26.2% (35% were <22; 45% were 22 to 32, 20% were ≥33). In the CABG arm, the mean number of vessels grafted was 2.9, and surgery was performed off pump in 19% of cases. In the PCI arm, a mean of 3.5 lesions were treated per patient with a mean stent length of 26.1 mm. The primary outcome measure was the composite of all-cause mortality, nonfatal MI, or stroke at 5 years. The 30-day outcome favored PCI (26 vs. 42 events); however, at 2 years, the difference began to appear; and at 5 years, the primary outcome occurred in 26.6% of patients in the PCI arm compared with 18.7% in the PCI arm ($P = .005$). This result appears to be driven by a reduction in all-cause mortality (16.3% vs. 10.9%, $P = .049$) and MI (13.9% vs. 6.0%, $P < .001$). As noted in prior studies, strokes were fewer in the PCI arm (2.4% vs. 5.2%, $P = .03$), and repeat revascularization was more frequent (13% vs. 5%, $P < .0001$). The primary outcome was higher in insulin-dependent diabetes patients versus non–insulin-dependent diabetes patients (29% vs. 19% at 5 years, $P < .001$); however, the superiority of CABG over PCI persisted. This trial reaffirmed that CABG should be the preferred revascularization strategy in most diabetic patients with multivessel disease.

Preventive Angioplasty in Acute Myocardial Infarction (PRAMI)

The PRAMI trial[25] was designed to study the value of additional non–culprit vessel PCI (preventive PCI) in an acute ST-elevation myocardial infarction (STEMI) setting. In this study, 465 patients were enrolled, 234 were randomized to preventive PCI, and 231 were randomized to infarct-related–artery PCI. The primary outcome—cardiovascular death, refractory angina, or nonfatal MI—was found to be significantly lower in the preventive PCI arm at 3 years (9% vs. 23%; HR, 0.35; 95% CI, 0.21 to 0.58; $P < .001$). This led to premature termination of the trial. Significant reductions were also noted in repeat revascularization (6.8% vs. 19.9%, $P < .001$), refractory angina (5.1% vs. 13.0%, $P = .002$), and nonfatal MI (3% vs. 8.7%, $P = .009$). Cardiovascular death was numerically but not statistically lower in the preventive PCI group (4.7% vs. 11.7%, $P = .07$). The results of this study favoring preventive PCI are in contradiction to the current guidelines, which give a class III indication for non–culprit vessel PCI during STEMI in hemodynamically stable patients. This landmark trial demonstrated an impressive 14% absolute risk reduction with up-front multivessel PCI in STEMI patients and has the potential to change practice patterns; however, further studies are clearly needed to support these results.

Complete Versus Culprit-Only Revascularization to Treat Multivessel Disease After Primary Percutaneous Coronary Intervention for STEMI (COMPLETE)

The COMPLETE trial[26] is ongoing with estimated enrollment of 3900 patients and a projected study completion date of December 2018. This study will evaluate whether, in the setting of optimal medical therapy (aspirin and ticagrelor), a strategy of complete revascularization utilizing a staged, preventive PCI approach is superior to culprit-lesion–only primary PCI for STEMI. The primary outcome of interest will be the composite of cardiovascular death or new MI.

Summary

The above studies highlight three notable points:

1. CABG should be the preferred revascularization strategy in diabetic patients with multivessel disease and for patients with complex anatomy.
2. Patients with low SYNTAX scores and less complex anatomy can be revascularized percutaneously with excellent outcomes.
3. Whereas guidelines favor culprit-lesion–only primary PCI, future data may support up-front preventive PCI of nonculprit lesions in hemodynamically stable patients with STEMI.

META-ANALYSIS

A meta-analysis based on ARTS II, CARDIa, ERACI III, and SYNTAX looked at a total of 3895 patients, 1914 in the DES arm and 1981 in the CABG arm. Pooled analysis of data from these four studies showed that in patients treated with a DES, compared with those treated with CABG, the risk of the combined end points of death, MI, and stroke was similar (10.2% vs. 10.8%, respectively; RR, 0.94; 95% CI, 0.77 to 1.116; $P = .56$), but a significantly higher risk of TVR was reported (14.6% vs. 6.8%, respectively; RR, 2.09; 95% CI, 1.72 to 2.55; $P < .001$), and therefore they had a significantly higher risk of MACCEs (21.2% vs. 16.3%, respectively; RR, 1.27; 95% CI, 1.09 to 1.48; $P = .002$). Interestingly, when MACCE rates at 1 year are used, the risk is equivalent between a DES and CABG (14.4% vs. 12.5%, respectively; RR, 1.05; 95% CI, 0.70 to 1.57; $P = .83$).[27] Another more recent meta-analysis that included seven randomized controlled trials and 5835 patients reported lower rates of mortality (RR, 0.70; 95% CI, 0.57 to 0.87), myocardial infarction (RR, 0.47; 95% CI, 0.36 to 0.61), and repeat revascularization (RR, 0.36; 95% CI, 0.24 to 0.52) but an increased stroke risk (RR, 1.72; 95% CI, 1.02 to 2.90) with CABG compared with PCI with a first-generation DES for patients with left main CAD and multivessel disease.[28] In regard to the question of culprit-only versus multivessel PCI for patients with STEMI, a paired meta-analysis of 40,280 patients demonstrated lower short- and long-term mortality with culprit-only PCI followed by staged multivessel PCI compared with up-front multivessel PCI (culprit vessel as well as more than one nonculprit vessel).[29]

Another more recent meta-analysis of 39,390 patients also reported a higher incidence of short-term mortality (OR, 0.50; 95% CI, 0.32 to 0.77; $P = .002$), long-term mortality (OR, 0.52; 95% CI, 0.36 to 0.74; $P < .001$), and risk of renal dysfunction (OR, 0.77; 95% CI, 0.61 to 0.97; $P = .03$) with multivessel PCI compared with culprit-only PCI.[30]

REGISTRY STUDIES

The New York registry study compared 9963 patients receiving DESs and 7437 patients undergoing CABG in terms of death in the hospital; death within 30 days after treatment; and death, MI, and revascularization up to 18 months after treatment. Patients with left main CAD, those who had been previously revascularized, and those within 24 hours of an MI were excluded.[31] No significant differences were found between the two groups in the risk-adjusted rates of in-hospital or 30-day mortality (adjusted odds ratio [OR] 1.29; 95% CI, 0.92 to 1.81; $P = .15$). Of patients who received DESs, 28.4% underwent repeat PCI,

and 2.2% underwent CABG within 18 months. The respective rates for patients undergoing CABG were 5.1% and 0.1%; both differences were statistically significant ($P < .001$). Of patients who received DESs, 12.5% underwent repeat PCI within 30 days and 18.3% underwent repeat PCI within 60 days. The rate of repeat PCI in this registry may be inflated because many patients underwent planned PCI associated with incomplete revascularization during the index admission. Of the 28.4% of patients who underwent repeat PCI during the study period, only a little more than one quarter (7%) underwent TVR. After adjustment for baseline differences, the survival in patients with three-vessel disease was 94% in the CABG group and 92.7% in the PCI group ($P = .03$). In patients with two-vessel disease, overall survival was 96% in the CABG group compared with 94.6% in the PCI group ($P = .003$). A significant difference was also apparent in freedom from MI: it was 92.1% in the CABG group compared with 89.7% in the PCI group ($P = .001$). Among patients with two-vessel disease, 94.5% in the CABG group were free of MI compared with 92.5% in the PCI group ($P = .001$). This study has two key limitations: first, it is subject to the selection bias inherent in the design of registry studies; second, patients were studied at a time that predated the recognition of the importance and implementation of prolonged dual-antiplatelet therapy (DAPT). This may account in part for the relatively higher frequency of MI and death in the DES group. Furthermore, the limited follow-up is unlikely to capture events related to graft failure in the CABG group.

In another registry, 3720 consecutive patients with multivessel disease who underwent isolated CABG surgery or received DESs were identified, and comparisons were made in terms of safety (total mortality, MI, and stroke) and efficacy (TVR) during a 3-year follow-up. Patients who received DESs had considerably higher 3-year rates of TVR. DESs were also associated with higher rates of death (adjusted HR, 1.62; 95% CI, 1.07 to 2.47) and MI (adjusted HR, 1.65; 95% CI, 1.15 to 2.44). The risk-adjusted rate of stroke was similar in the two groups (HR, 0.92; 95% CI, 0.69 to 1.51).[32] In a study by Javaid and associates,[33] 1080 patients were treated for two-vessel disease (196 with CABG and 884 with PCI), and 600 were treated for three-vessel disease (505 with CABG and 95 with PCI). One-year mortality, cerebrovascular events, Q-wave MI, target-vessel failure, and composite MACCEs were compared between the CABG and PCI cohorts. Adjusted outcomes showed increased MACCEs with PCI in patients with two-vessel disease (HR, 2.29; 95% CI, 1.39 to 3.76; $P = .01$) and three-vessel disease (HR, 2.90; 95% CI, 1.76 to 4.78; $P < .001$). Adjusted outcomes for the subpopulation without diabetes demonstrated equivalent MACCE rates with PCI for two-vessel (HR, 1.77; 95% CI, 0.96 to 3.25; $P = .07$) and three-vessel disease (HR, 1.70; 95% CI, 0.77 to 3.61; $P = .19$). Park and colleagues[34] studied 3042 patients with multivessel disease who underwent DES placement ($n = 1547$) or CABG ($n = 1495$). The primary end point was all-cause mortality. After adjustment for baseline differences, the overall risks of death were similar among all patients (HR, 0.85; 95% CI, 0.56 to 1.30; $P = .45$), patients with diabetes (HR, 1.76; 95% CI, 0.82 to 3.78; $P = .15$), and those with compromised ventricular function (HR, 1.39; 95% CI, 0.41 to 4.65; $P = .60$). In the anatomic subgroups, mortality benefit with DES implantation was noted in patients with two-vessel disease with involvement of the nonproximal LAD (HR, 0.23; 95% CI, 0.01 to 0.78; $P = .016$). The rate of revascularization was significantly higher in the DES group than in the CABG group (HR, 2.81; 95% CI, 2.11 to 3.75; $P < .001$). Overall, these registry studies continue to demonstrate a revascularization advantage with CABG. In some studies, there seems to be a higher incidence of death and MI in the PCI arms, and it is not clear whether these differences resulted from issues related to stent thrombosis in the setting of abbreviated antiplatelet therapy.

In a recent publication, a total of nine observational nonrandomized studies were identified and analyzed, including a total of 24,268 patients with multivessel coronary disease who underwent DES-PCI ($n = 13,540$) and CABG ($n = 10,728$). Mean follow-up time was 20 months. Pooled analysis showed that DES-PCI and CABG were comparable in terms of composite occurrence of death, acute MI, and cerebrovascular accidents (HR, 0.94; 95% CI, 0.72 to 1.22; $P = .66$). However, a significantly higher risk of repeat revascularization was present in the DES-PCI group (HR, 4.06; 95% CI, 2.64 to 6.24; $P < .001$), and the overall MACCE rate was higher compared with the that of CABG group (HR, 1.86; 95% CI, 1.36 to 2.54; $P < .001$).[35]

RECOMMENDATIONS FOR CLINICAL PRACTICE

Once multivessel disease is diagnosed with coronary angiography, the clinical data should be reviewed in detail with an interventional cardiologist and the referring cardiologist.

- If the coronary anatomy is complex with an elevated SNYTAX score, the patient should receive bypass surgery, unless comorbidities are significant or the patient refuses.
- If patient factors such as advanced comorbidities would make CABG high risk, PCI should be considered.
- For patients with multivessel disease but with very discrete lesions that would require short segments of stenting (low SYNTAX score), PCI should be preferred because in this situation, the likelihood of a repeat revascularization procedure being needed is lower than with more complex anatomy that requires larger numbers of stents and longer stents.
- Further studies are needed to determine the optimal revascularization strategy (culprit-only, preventive, or staged multivessel PCI) in hemodynamically stable patients with STEMI. However, until more data are available, the current American College of Cardiology (ACC)/American Hospital Association (AHA) guidelines—which advocate culprit-only primary PCI—should be the standard.
- CABG should be the preferred revascularization strategy in most diabetic patients with multivessel disease.
- If clinical circumstances exist in which the patient cannot take DAPT for at least 1 year—typically because of a foreseeable need, an established plan for elective noncardiac surgery, or a known history of poor medical compliance—the option of CABG should be encouraged. However, it is important to note that for many of these patients, PCI with a BMS is a good option, as is the option of abbreviated DAPT with use of newer second-generation DESs. Where appropriate, these options need to be presented to the patient along with the option of CABG.
- Another factor to consider is the age of the patient. When evaluating revascularization strategies for young patients, when CABG and PCI are both technically feasible options, PCI—rather than CABG—should be preferred. Given that the vast majority of vein grafts are expected to occlude over time, clinical problems that result from vein graft disease are very likely to be encountered over a young patient's lifetime. With the use of PCI as the first approach in most cases, the CABG option remains reserved for future use, if necessary; the problems with vein graft disease can be avoided or delayed.
- In the subset of patients in whom the coronary anatomy and other patient factors present a clinical equipoise between both revascularization options, a detailed discussion needs to be held with the patient. A "heart team" approach should be adopted that includes consultation with an interventional cardiologist and a cardiac surgeon. Every effort should be made to ensure that the patient understands the pros and cons of both revascularization approaches. Patient preference is the cornerstone of determining the appropriate management strategy, particularly given that the outcomes of both modalities are similar in terms of the "hard" end points of death and MI. Many patients prefer to undergo PCI in view of the lower short-term morbidity while being aware of the higher risk of the need for a repeat procedure. Such patients are willing to undergo more than one PCI, should the need arise, rather than to undergo CABG with its substantial short-term morbidity. However, many patients prefer to undergo CABG with a view to having a more "durable" outcome, at least in terms of avoiding repeat procedures. Thorough patient education and counseling are instrumental in helping patients and their health care providers in selecting a treatment strategy.

REFERENCES

1. Yusuf S, Zucker D, Peduzzi P, et al: Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 344(8922):563–570, 1994.
2. The final 10-year follow-up results from the BARI randomized trial. *J Am Coll Cardiol* 49(15):1600–1606, 2007.
3. Henderson RA, Pocock SJ, Clayton TC, et al: Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. *J Am Coll Cardiol* 42(7):1161–1170, 2003.
4. Hamm CW, Reimers J, Ischinger T, et al: A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. German Angioplasty Bypass Surgery Investigation (GABI). *N Eng J Med* 331(16): 1037–1043, 1994.
5. King SB, 3rd, Kosinski AS, Guyton RA, et al: Eight-year mortality in the Emory Angioplasty versus Surgery Trial (EAST). *J Am Coll Cardiol* 35(5):1116–1121, 2000.
6. CABRI Trial Participants: First-year results of CABRI (Coronary Angioplasty versus Bypass Revascularisation Investigation). *Lancet* 346(8984):1179–1184, 1995.
7. Rodriguez A, Mele E, Peyregne E, et al: Three-year follow-up of the Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease (ERACI). *J Am Coll Cardiol* 27(5):1178–1184, 1996.
8. Serruys PW, Ong AT, van Herwerden LA, et al: Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol* 46(4):575–581, 2005.
9. Morrison DA, Sethi G, Sacks J, et al: Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. Investigators of the Department of Veterans Affairs Cooperative Study #385, the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). *J Am Coll Cardiol* 38(1):143–149, 2001.
10. Hueb W, Lopes NH, Gersh BJ, et al: Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): A randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 115(9):1082–1089, 2007.
11. Hueb W, Lopes N, Gersh BJ, et al: Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 122(10):949–957, 2010.
12. Booth J, Clayton T, Pepper J, et al: Randomized, controlled trial of coronary artery bypass surgery versus percutaneous coronary intervention in patients with multivessel coronary artery disease: six-year follow-up from the Stent or Surgery Trial (SoS). *Circulation* 118(4):381–388, 2008.
13. Rodriguez AE, Baldi J, Fernández Pereira C, et al: Five-year follow-up of the Argentine randomized trial of coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple vessel disease (ERACI II). *J Am Coll Cardiol* 46(4):582–588, 2005.
14. Daemen J, Boersma E, Flather M, et al: Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation* 118(11): 1146–1154, 2008.
15. Bravata DM, Gienger AL, McDonald KM, et al: Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. *Ann Intern Med* 147(10):703–716, 2007.
16. Serruys PW, Morice MC, Kappetein AP, et al: Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 360(10):961–972, 2009.
17. Kappetein AP, Feldman TE, Mack MJ, et al: Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J* 32(17):2125–2134, 2011.
18. Mohr FW, Morice MC, Kappetein AP, et al: Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 381(9867):629–638, 2013.
19. Farooq V, Serruys PW, Zhang Y, et al: Short-term and long-term clinical impact of stent thrombosis and graft occlusion in the SYNTAX trial at 5 years: Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial. *J Am Coll Cardiol* 62(25):2360–2369, 2013.
20. Serruys PW, Onuma Y, Garg S, et al: 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. *J Am Coll Cardiol* 55(11): 1093–1101, 2010.
21. Rodriguez AE, Grinfeld L, Fernandez-Pereira C, et al: Revascularization strategies of coronary multiple vessel disease in the drug eluting stent era: one year follow-up results of the ERACI III Trial. *EuroIntervention* 2(1):53–60, 2006.
22. Rodriguez AE, Maree AO, Mieres J, et al: Late loss of early benefit from drug-eluting stents when compared with bare-metal stents and coronary artery bypass surgery: 3 years follow-up of the ERACI III registry. *Eur Heart J* 28(17):2118–2125, 2007.
23. Kapur A, Hall RJ, Malik IS, et al: Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. *J Am Coll Cardiol* 55(5):432–440, 2010.
24. Farkouh ME, Domanski M, Sleeper LA, et al: Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 367(25):2375–2384, 2012.
25. Wald DS, Morris JK, Wald NJ, et al: Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 369(12): 1115–1123, 2013.
26. Complete vs Culprit-only Revascularization to Treat Multivessel Disease After Primary PCI for STEMI. ClinicalTrials.gov Identifier: NCT01740479.
27. From AM, Al Badarin FJ, Cha SS, Rihal CS: Percutaneous coronary intervention with drug-eluting stents versus coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis of data from the ARTS II, CARDia, ERACI III, and SYNTAX studies and systematic review of observational data. *EuroIntervention* 6(2):269–276, 2010.
28. Al Ali J, Franck C, Filion KB, Eisenberg MJ: Coronary artery bypass graft surgery versus percutaneous coronary intervention with first-generation drug-eluting stents: a meta-analysis of randomized controlled trials. *JACC Cardiovasc Interv* 7(5):497–506, 2014.
29. Vlaar PJ, Mahmoud KD, Holmes DR, Jr, et al: Culprit vessel only versus multivessel and staged percutaneous coronary intervention for multivessel disease in patients presenting with ST-segment elevation myocardial infarction: a pairwise and network meta-analysis. *J Am Coll Cardiol* 58(7):692–703, 2011.
30. Zhang D, Song X, Lv S, et al: Culprit vessel only versus multivessel percutaneous coronary intervention in patients presenting with ST-segment elevation myocardial infarction and multivessel disease. *PLoS ONE* 9(3):e92316, 2014.
31. Hannan EL, Wu C, Walford G, et al: Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. *N Eng J Med* 358(4):331–341, 2008.
32. Li Y, Zheng Z, Xu B, et al: Comparison of drug-eluting stents and coronary artery bypass surgery for the treatment of multivessel coronary disease: three-year follow-up results from a single institution. *Circulation* 119(15):2040–2050, 2009.
33. Javaid A, Steinberg DH, Buch AN, et al: Outcomes of coronary artery bypass grafting versus percutaneous coronary intervention with drug-eluting stents for patients with multivessel coronary artery disease. *Circulation* 116(11 Suppl):I200–I206, 2007.
34. Park DW, Yun SC, Lee SW, et al: Long-term mortality after percutaneous coronary intervention with drug-eluting stent implantation versus coronary artery bypass surgery for the treatment of multivessel coronary artery disease. *Circulation* 117(16):2079–2086, 2008.
35. Benedetto U, Melina G, Angeloni E, et al: Coronary artery bypass grafting versus drug-eluting stents in multivessel coronary disease. A meta-analysis on 24,268 patients. *Eur J Cardiothorac Surg* 36(4):611–615, 2009.

Intervention for Coronary Chronic Total Occlusions

25

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KEY POINTS

- Chronic total occlusion (CTO) is a common feature in patients with coronary artery disease and is the most common reason for not proceeding with percutaneous coronary intervention (PCI).
- The overwhelming clinical evidence outside of a randomized trial suggests that ischemic reduction from opening of a CTO improves symptoms, ejection fraction (EF), and long-term clinical survival.
- Clinically, a CTO imitates a lesion with a fractional flow reserve (FFR) of .80 or less.
- The success rate of percutaneous recanalization has dramatically improved, and a large number of interventionalists routinely achieve greater than 90% success rates without angiographic exclusions.
- Success rates are still greatly dependent on the operator's experience and CTO-specific training.
- Complications of CTO are slightly greater than those of non-CTO PCI, and some unique complications are related to retrograde techniques.
- The hybrid approach in conjunction with new CTO-specific wires and technologies has provided a dramatic improvement in education and success with CTO PCI.
- Drug-eluting stent patency rates are approximately 90% at 1 year.

Chronic total coronary occlusions, along with major bifurcations (including the left main coronary artery) and long lesions, constitute a lesion type that remains a major technical challenge for interventional cardiologists individually, and they represent a significant limitation for interventional cardiology as a field. PCI is still predicated upon a steerable guidewire spanning the target lesion and acting as a rail over which therapies are delivered and as a "safety line" in case of target-vessel complications. The essential challenge of CTO PCI lies in the initial traversing of the lesion with a guidewire.

In the past 5 years, important advancements have been made in techniques that safely and more predictably overcome this essential challenge.[1] Dissemination of these techniques is accelerating and drawing CTO PCI into mainstream interventional practice. Most major PCI programs now have, or are planning for, specialized competence in contemporary CTO procedures. An understanding of the field has become essential knowledge for all interventionalists and arguably for any cardiologist who advises patients regarding revascularization options. This chapter strives to provide that understanding.

CHRONIC TOTAL CORONARY OCCLUSION

Definition

A CTO is most often defined as an occlusion known to be present for 3 or more months or a newly documented occlusion not attributable to a similarly recent ischemic event. The term *occlusion* is most accurately reserved for a stenosis within which there is neither a continuous visible lumen nor any visible flow that cannot be accounted for by collaterals (thrombolysis in myocardial infarction [TIMI] grade 0).[2] Lesions with trace antegrade lumenal flow (TIMI grade 1) are referred to as *functional* or *subtotal* occlusions. Lesions with a residual lumen but without antegrade flow because of competing collateral flow are referred to as *pseudo-occlusions*. Functional and pseudo-occlusions overlap in practice and may be difficult to distinguish from a true CTO unless imaged with dual-catheter angiography or probed with a guidewire. Finally, spontaneously recanalized CTOs are sometimes identified wherein a long, tortuous microchannel exists within the presumed architecture of a previous occlusion.

Detection of coronary occlusions remains the domain of catheter-based angiography. Current coronary computed tomography (CT) angiography has limited spatial resolution and does not capture the temporal information required to determine flow rate or directionality. As such, it cannot readily be used to distinguish a CTO from a functional or pseudo-occlusion or even reliably from a high-grade stenosis with preserved flow.

Prevalence

Reports that describe the prevalence of CTOs vary widely with respect to defining the cohort studied. Moreover, unless developed specifically for the study of CTOs, angiographic and interventional databases generally do not contain data fields that reliably distinguish subacute from chronic occlusions, true occlusions from subtotal or pseudo-occlusions, or potentially bypassed from nonbypassed occlusions. Thus the literature reveals an inconsistency of methods for determining both denominator and numerator values.

A retrospective study from a large U.S. Veterans Administration (VA) center extracted patients with at least one 70% stenosis (by visual estimate), no prior coronary artery bypass grafting (CABG), and no myocardial infarction (MI) within 3 months from 8004 consecutive patients undergoing cardiac catheterization between 1990 and 2000.[3] Within the derived cohort of 3087 patients, 52% (1612) had a chronic coronary occlusion.

In a prospective study, Fefer and colleagues[4] reported nonacute coronary occlusions present in 14.7% of more than 14,000 patients undergoing nonemergent angiography at three tertiary Canadian centers in 2008 and 2009. Excluding patients with prior CABG, as well as those without significant CAD, left a denominator of 7680, of which 18.4% had at least one nonacute occlusion.

A prospectively collected population-based Swedish registry[5] based upon site-reported, nonacute, 100% visual stenosis coded in a general angiography and PCI registry recently found a similar overall CTO prevalence: 16% of more than 91,000 patients with significant coronary artery disease (CAD). Like the Canadian registry, this prevalence was calculated after exclusion of those with prior CABG. An unexpected finding was a significant decline in CTO prevalence over the 8-year period examined, from 17.2% in 2005 to 15.1% in 2012.

Clinical Profile and Presentation

When compared with a cohort of CAD patients without CTO, cohorts of CAD patients with CTO display important differences in baseline characteristics that point toward more advanced atherosclerosis generally. Patients are on average 1 to 2 years older, more likely to be male, and more likely to report diabetes and hypertension. Multivessel CAD is more commonly present, as is peripheral arterial disease and cerebrovascular disease.

A twofold excess in history of prior MI was observed among CTO patients in both Canadian[4] and Swedish[5] registries (40% vs. 23% and 37% vs. 17%, respectively, $P < .01$ in both). However, the relationship between a CTO, the presence and extent of infarction in the subtended territory, and the degree of left ventricular (LV) dysfunction attributable to the CTO is not well established. Half of the patients in the Canadian registry had a left ventricular ejection fraction (LVEF) less than 50%, but significant Q-waves were present in only 32% of right coronary arteries (RCAs), 13% of left anterior descending (LAD) coronary arteries, and 26% of left circumflex (LCX) artery occlusions. In the VA registry, chronic CAD patients with CTO had a significantly lower LVEF than those without a CTO (LVEF 53% vs. 60%, $P < .0001$) but also had significantly more multivessel CAD (66% vs. 42%, $P < .0001$).

Despite, by definition, the long-standing nature of chronic occlusions, an acute coronary syndrome (ACS) that presumably arises in other coronary segments is a common trigger for CTO detection. ACS immediately preceded CTO detection in 46% of the Canadian cohort[4] and 40% of the Swedish cohort.[5] Conversely, in a prospective single-center registry[6] of nearly 3300 consecutive primary PCI procedures for STEMI, the prevalence of a preexisting CTO was 12.8%. Patients with a CTO detected at primary PCI had significantly worse prognosis than patients with single-vessel CAD (infarct vessel only) or those with multivessel CAD without a CTO.

Pathology

The histopathology of CTOs is an evolving area that has grown from necropsy and ex vivo tissue analyses to include the use of intravascular micro–computed tomography (MCT), micro–magnetic resonance imaging (MMRI), and intravascular ultrasound (IVUS). Studies have aimed to characterize the histology of CTOs and in so doing to characterize the pathologic bases for procedural success and failure.

Most fundamentally, postnecropsy samples of chronically occluded coronaries consistently demonstrate preservation of vessel architecture, including a multilayered structure in which the intima and neointima (including atherosclerotic plaque) is distinguishable from the muscularis and adventitia and, notably, in which the external elastic lamina remains intact. This preservation of gross architecture is the pathologic feature that most enables percutaneous recanalization (Fig. 25-1). Early necropsy studies to examine human CTOs have shown that angiographic characteristics, such as proximal cap morphology, may predict histology. Tapered-tip occlusions contain areas of luminal recanalization with microchannels and loosely packed fibrous tissue. Such occlusions also tend to be shorter.[7] Conversely, lesions with blunt tips are typically composed of densely packed fibrous material and fibrocalcific intimal plaque and tend to be longer.[8]

Studies in mouse, porcine, and rabbit femoral arterial occlusion models have provided experimental insights into the development of CTOs. Recent thrombotic occlusions display an inflammatory infiltrate dominated by neutrophils and mononuclear cells that penetrate the occlusive thrombus. The density of this infiltrate peaks at 2 weeks after occlusion and declines thereafter, as loosely packed collagen extracellular matrix (ECM) infiltrates and replaces the thrombus. This process is accompanied by negative remodeling of the surrounding vessel and variable decay of the internal elastic lamina.[8,9] Proteoglycan-enriched ECM deposition occurs early, between weeks 2 and 6 after occlusion, and it is concentrated at the proximal and distal ends of the lesion. Over time, these areas are replaced by densely packed collagen.[9] These experimental observations may in part explain the clinical paradigm of mechanically resistant proximal and distal caps.

Human and animal necropsy studies and advanced imaging studies have confirmed the frequent presence of recanalization microvascular channels (*microchannels*) within chronically occluded segments. Microchannels within human CTOs were first described by Katsuragawa and colleagues,[7] wherein small vascular channels ranging from 160 to 230 µm in diameter were noted at both proximal and distal lesion segments. This observation led to speculation that microchannels might consistently provide a through-and-through route for fine guidewires to track. Subsequent human and experimental pathologic studies suggested these microchannels are more typically configured as corkscrews or sharply angulated channels that become fragmented and discontinuous as occlusions age and typically do not traverse the full length of an occlusion.[8-10] Thus whereas microchannels are unlikely to provide a continuous channel for guidewire passage, they may still alter local tissue architecture and render a "path of low resistance" through a CTO.

ISCHEMIA, COLLATERAL CIRCULATION, AND LEFT VENTRICLE FUNCTION

The burden of ischemia in a territory subtended by a CTO is presumably determined by the mass of the zone subtended by the occluded segment, the degree of infarction in that zone, the degree of collateralization, and the severity of coronary obstruction, if any, in vessels that supply those collaterals. Because the intracoronary pressure beyond an occlusion is inherently low, the myocardium subtended may be especially vulnerable ischemia exacerbated by elevation of end-diastolic pressure. No systematic study has been done to quantify the degree of ischemia in an unselected cohort of patients with CTO. In a retrospective single-center report drawn from 300 patients selected for CTO PCI and in whom quantitative myocardial perfusion imaging was available before and 1 year following PCI, the ischemic burden at baseline, expressed as a percentage of total LV myocardium, was 13.1% (± 11.9%).

Viability of myocardium distal to a CTO is critically dependent upon collateral circulation. Present in humans from birth, both ischemia and flow-mediated shear stress stimulate collateral development.[11-13] Collateral flow has been characterized functionally by both angiographic and hemodynamic criteria. Rentrop[14] described four collateral grades: (0) no visible filling of any collateral channels, (1) filling of side branches of the occluded artery, (2) partial filling of the recipient main vessel, and (3) complete filling of the epicardial vessel. Although originally described during acute balloon occlusion of the receiving vessel, Rentrop's classification is now used widely to quantitate collaterals in CTO studies. The presence of angiographically visible collaterals conveys positive prognostic information. A recent meta-analysis[15] of 12 studies to examine the association between visible collaterals in acute, subacute, and chronic coronary disease involving 6529 patients found that those with high collateralization had lower risk of death during follow-up (relative risk for all coronary occlusions 0.64; 95% confidence interval [CI], 0.45 to 0.91; $P = .012$; relative risk [RR] for chronic occlusions 0.59; 95% CI, 0.39 to 0.89; $P = .012$).

Hemodynamic quantitation of collateral function most commonly uses the *collateral pressure index* (CPI), defined as mean pressure of collateral circulation (Pw) divided by mean aortic pressure (Pa), each with central venous pressure (CVP) subtracted ([Pw – CVP]/[Pa – CVP]).[16] Both wedge and direct measurements of collateral pressure have been described. Values greater than 0.30 are considered adequate to prevent ischemia at rest but have not been rigorously validated. Threshold CPI values that correspond to provocable ischemia are uncertain, as are the thresholds for pressure-derived fractional flow reserve (FFR) and instantaneous flow reserve (IFR) measured distal to occlusions. In the cases of FFR and IFR, however, reasons are few as to why threshold values established in nonocclusive lesions might not apply. An elegant single-center prospective study of 107 patients undergoing CTO PCI measured CPI (with direct rather than wedge collateral pressure), distal bed postadenosine FFR, and Doppler-based collateral flow velocity reserve (CFVI). Whereas CPI at rest was above 0.3 in 78% of patients, only one patient demonstrated an FFR value above 0.75 (the conventional ischemic threshold), and more than one third of patients had evidence of inducible coronary steal by CFVI.[17]

The relationship among CTO, ischemia, regional and global LV dysfunction, and post-PCI LV recovery is complex and incompletely characterized. Patients with a CTO detected in a non–infarct-related vessel coincident with primary PCI for STEMI are significantly more

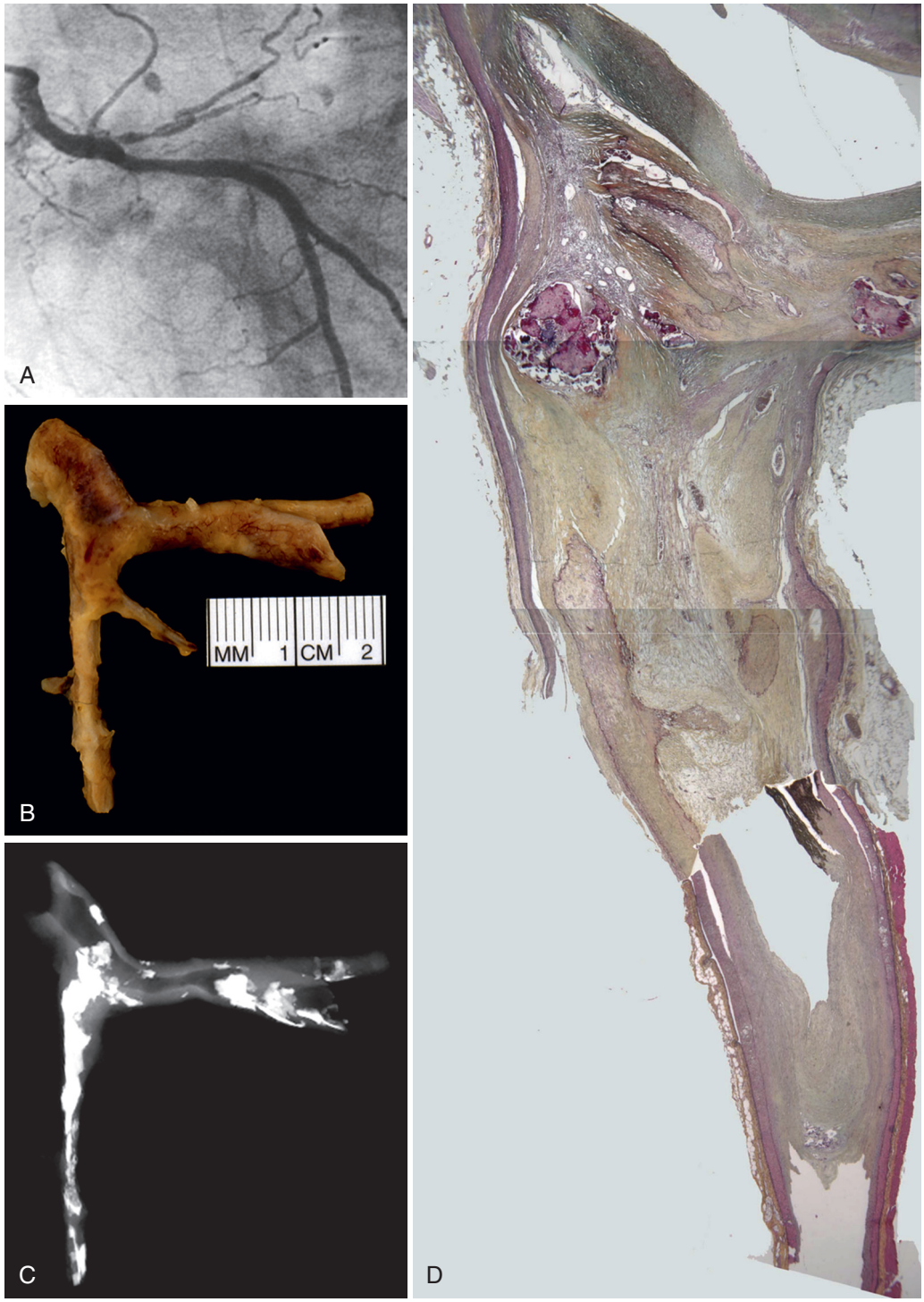


FIGURE 25-1 Postmortem example of a chronically occluded atherosclerotic left anterior descending (LAD) coronary artery. **A,** Ante mortem angiography (left anterior oblique cranial projection) of left coronary demonstrates a flush occlusion of the LAD with small bridge collaterals arising from the left main. The dotted line represents the approximate course of the occluded vessel. **B,** Postmortem, the left main, proximal circumflex, and proximal LAD arteries have been dissected en bloc; apart from negative remodeling, few external cues are present to suggest that the LAD lumen is occluded. **C,** Postmortem radiograph of the specimen emphasizes the extent of dystrophic calcium typical in a chronic occlusion. **D,** Longitudinal histopathology confirms preservation of vessel architecture, including a multilayered structure in which the intima and neointima (and extensive atherosclerotic plaque) is distinguishable from the muscularis and adventitia. Notably, the external elastic lamina remains intact (apparent breaches are due to fixation artifact). The preservation of gross vessel architecture is the pathologic feature that most enables contemporary techniques for percutaneous recanalization.

likely to have moderate or severe LV impairment (28% vs. 17%, $P < .01$) and are more than twice as likely to suffer progressive LV impairment at follow-up (39% vs. 17%, $P < .01$).[6]

The available reports exploring the relationship between CTO revascularization and LV function do not include medically treated comparators. With this important limitation, patients with regional LV dysfunction in whom the abnormal wall segment is subtended by the CTO commonly demonstrate regional LV improvement after CTO PCI.[18] Improvement in global LVEF consequent to CTO PCI is less easily demonstrated in part because more than half of CTO patients have normal baseline ejection fraction (EF). In the Total Occlusion Study of Canada (TOSCA),[19] 244 patients had paired (baseline and 6 mo) core laboratory evaluable LV angiograms, and 106 of these (43%) had an impaired EF at baseline (EF <60%, mean 46% ± 9%). EF did not change at follow-up among those with normal baseline EF but rose 3.8% (± 8.4%) in the cohort with impaired baseline EF ($P < .001$). The direction and magnitude of these EF changes are consistent with those observed in smaller series.[18,20]

An important area for future investigation will be the identification of patients with both a CTO and impaired EF who are most likely to demonstrate EF improvement following CTO recanalization. Large, prospective studies with detailed clinical, electrocardiographic (ECG), angiographic, and imaging variables will likely be necessary.

CLINICAL OUTCOMES

Vast clinical experience and common sense both support the notion that revascularization of severely ischemic viable territories, such as those subtended by many CTOs, provides clinical benefit. Yet the scientific evidence to support this construct remains inconclusive. This knowledge gap is mainly attributable to the absence of an adequately powered randomized clinical trial to compare a strategy of CTO revascularization, especially by PCI, to a strategy of medical therapy. The uncertainty of prognostic benefit provided by CTO PCI is an especially troubling example, in light of the potential for severe ischemia, of the general uncertainty around the prognostic benefit of PCI specifically, and revascularization more generally, in limited stable CAD.[21]

In the absence of prospective randomized data, investigators have focused on retrospective observational analyses drawn from PCI databases, which typically compare long-term cardiovascular outcomes among patients selected for CTO PCI and are grouped according to operator-reported PCI success versus failure. The first such report examined approximately 2000 patients undergoing CTO PCI at a single center over a 20-year period ending in 1999. Ten-year Kaplan-Meier analyses showed PCI success to be associated with an absolute survival advantage of 8.5% when compared with PCI failure (73.5% vs. 65.0%). In a multivariable model for mortality during long-term follow-up, CTO success remained an independently powerful predictor (adjusted hazard ratio [HR] 0.7; 95% CI, 0.5 to 0.8; $P < .001$).[22] In a similarly designed but population-based analysis from the British Columbia Cardiac Registries, PCI success among approximately 1400 CTO PCI procedures was associated with a 9% absolute survival advantage at 6-year follow-up (adjusted HR 0.44; 95% CI, 0.30 to 0.64; $P < .0001$) and a nearly 20% absolute reduction in early and late coronary bypass.[23] Recently the U.K. National Institute for Cardiovascular Outcomes Research examined the data from nearly 15,000 patients who underwent elective PCI between 2005 and 2009 to target one or more CTOs. After adjustment for recorded baseline characteristics, PCI success was powerfully associated with lower all-cause mortality at mean follow-up of 2.7 years (HR 0.71; 95% CI, 0.62 to 0.82; $P < .001$; Fig. 25-2).[24]

Retrospective and nonrandomized analyses cannot demonstrate causality, but two intriguing observations from these nonrandomized analyses suggest a causal relationship between CTO PCI success and better survival. First, Safley and colleagues[25] observed that the association between better survival and CTO PCI success was restricted to LAD procedures. Second, whereas PCI success is associated with lower long-term mortality, it appears *not* to be associated with a lower

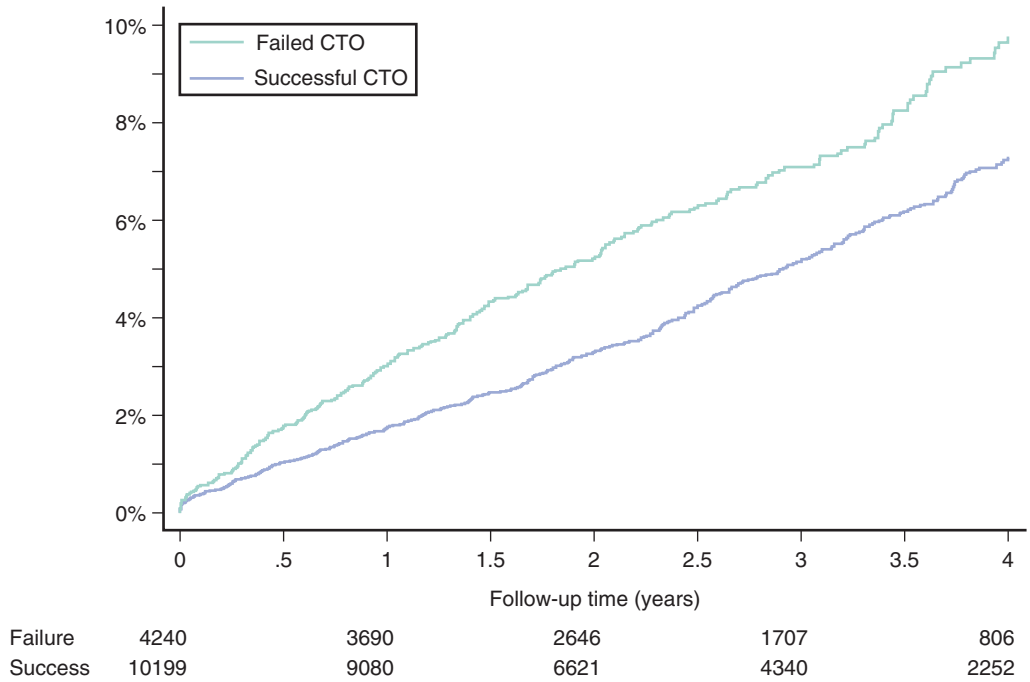


FIGURE 25-2 Kaplan-Meier curve showing differences in mortality between those with failed versus successful percutaneous coronary intervention (PCI) procedures targeting a chronic total occlusion (CTO). Successful intervention was associated with a significant decrease in mortality (hazard ratio 0.71; 95% confidence interval, 0.62 to 0.82; $P < .001$). Data drawn from nearly 15,000 patients enrolled in a population-based U.K. PCI registry. (From British Cardiovascular Intervention Society; National Institute for Cardiovascular Outcomes Research; et al: Long-term follow-up of elective chronic total coronary occlusion angioplasty: analysis from the U.K. Central Cardiac Audit Database. *J Am Coll Cardiol* 64:235-243, 2014.)

incidence of early or late MI.[24,26,27] If CTO PCI success versus failure merely stratifies patients into lower- versus higher-risk cohorts, these heterogeneous effects by both vessel and specific outcome (death vs. MI) beg explanation.

Conversely, patients with successful procedures differ from those with unsuccessful procedures in both known and unknown ways, and these differences may partially or entirely account for differential outcomes. Moreover, patients who undergo failed procedures are exposed to procedural hazards that influence early and perhaps late outcomes, whereas patients managed medically have no such exposure. These effects were demonstrated in a report from the Occluded Artery Trial (OAT), a prospective randomized controlled trial to test routine PCI in subacute, not chronic, coronary occlusions; a post hoc analysis of OAT outcomes identified high- and low-risk subgroups according to PCI success versus failure with significantly different short- and long-term outcomes that in isolation imply a benefit attributable to PCI analogous to the observational data for CTOs. The strategy of PCI, however, was not superior to the strategy of medical therapy in the primary randomized analysis.[28]

Long-term prevention of hard cardiovascular end points cannot be observed by individual clinicians treating individual patients. In contrast, the relief of ischemic symptoms (angina and angina equivalents) following CTO PCI, while admittedly variable, is frequently directly observed and can be striking. Recent dissemination of new CTO techniques and expertise means that symptomatic individuals who have not previously been offered revascularization are now being treated percutaneously and are often rendered asymptomatic after years of functional limitation. Measuring this effect in a randomized trial is challenging, if not impossible, because it is generally viewed as unethical to assign highly symptomatic medically optimized patients to continued medical therapy alone. Moreover, the randomization of minimally symptomatic patients—as in the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches Study (ISCHEMIA) trial,[29] for instance—only serves to underestimate the therapeutic potential of the treatment as it relates to angina relief.

The severity of ischemia downstream from a CTO suggests that revascularization might provide even greater symptom relief on average than treatment of significant but nonocclusive lesions. In Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE),[30] a trial that primarily enrolled patients with nonocclusive coronary stenoses in whom symptom relief attributable to PCI was found to be modest, successful treatment of a CTO was associated with significant improvements in symptom burden and quality of life. In a carefully characterized and prospectively studied cohort from the FlowCardia's Approach to Chronic Total Occlusion Recanalization (FACTOR) trial,[31] successful CTO PCI was associated with significant and clinically important improvements in angina frequency, physical limitations, and quality of life 4 weeks after the procedure as assessed by the Seattle Angina Questionnaire (SAQ). Finally, in a meta-analysis of six other small CTO studies that reported symptoms using various methodologies and follow-up, PCI success was associated with a much higher likelihood of freedom from residual or recurrent angina ($N = 1601$, HR 2.2; 95% CI, 1.5 to 3.3; $P = .0001$).[27] The much less frequent use of early and late coronary bypass surgery after successful CTO PCI that has been observed in numerous reports is concordant with both the effectiveness and durability of symptom relief attributable to these procedures.[23,27]

INDICATIONS FOR REVASCULARIZATION

Published indications for CTO revascularization largely mirror the indications for revascularization in otherwise similar nonocclusive stable CAD. In this regard, the primary indication for CTO PCI in the setting of single-vessel CAD is the relief of ischemic symptoms that persist despite antiischemic medical therapy. However, the frequency with which PCI is offered to patients with a CTO (but otherwise limited CAD not warranting CABG) is much lower than for nonocclusive CAD in practice and moreover varies widely among physicians and PCI centers. Multicenter U.S. registries[32,33] of patients treated in the 1990s indicate that fewer than only 8% to about 15% of patients with a CTO at angiography underwent PCI. A subsequent prospective VA registry[3] found that the presence of a CTO at angiography was a powerful independent predictor of a physician recommending CABG or medical therapy alone over PCI. In the Canadian CTO registry[4] that enrolled patients in 2008 and 2009, PCI was nevertheless undertaken in only 10%. Notably, practice varied enormously by hospital, with as few as 1% and as many as 16% of patients treated with PCI ($P < .001$) despite similar rates of CABG at all centers (22% to 28%, $P =$ NS). The low and variable use of PCI for CTO likely reflects many factors, among them a wide variation in technical expertise and an inconclusive evidence basis for benefits beyond symptom relief. The data do imply, however, that many symptomatic patients with CTOs are not being counseled with respect to contemporary PCI options, nor are they being referred to centers and operators with the special expertise to provide predictable results.

Neither American nor European guidelines distinguish between CTOs and nonocclusive lesions with respect to the threshold for undertaking revascularization, whether by PCI or CABG.[34,35] The European guidelines consider CTO PCI a complex procedure that demands experienced operators at centers with specialized CTO equipment and access to circulatory support and cardiac surgery. Ad hoc treatment (coincident with diagnostic catheterization) is discouraged. The American College of Cardiology (ACC)/American Hospital Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) guidelines state that "(CTO PCI) in patients with appropriate clinical indications and suitable anatomy is reasonable when performed by operators with appropriate expertise" (class IIa, level of evidence B) but do not further define appropriateness. Without clear justification or evidence, the Appropriate Use Criteria provide a somewhat higher threshold for PCI to target CTOs than they do for nonocclusive lesions.[36] Finally, when PCI is chosen as the most suitable mode of revascularization in multivessel CAD, it is generally agreed that complete functional revascularization should be sought (complete revascularization of all viable territories). In this circumstance, therefore, the PCI strategy should include treatment of CTO in vessels subtending substantially viable myocardium.

TECHNIQUES FOR CHRONIC TOTAL OCCLUSION PERCUTANEOUS CORONARY INTERVENTION

The femoral or radial approach can be used for CTO PCI with emphasis on dual angiography to visualize collateral flow, which is key to any approach. The guiding principle of access selection is that operators should use access routes that support their typical and optimal techniques. The relative merits of potentially larger sheath/guide sizes (femoral) can be weighed against the reduction in vascular complications and improved patient comfort (radial).[37,38] When femoral access is used, long (45 cm) sheaths can overcome iliac tortuosity and increase guide catheter support. Guiding catheter size is usually limited to 6 Fr (occasionally 7 Fr) from the radial approach. Good passive support with coaxial alignment is crucial, especially in complex CTO procedures. Although the choice of the guiding catheter shape is generally dictated by personal experience, it is important for operators to seek a guide with optimal back-up support at the onset of the procedure rather than accepting one with merely satisfactory support. The radial operator should be familiar with active guide manipulation to augment the support, and all operators should be versed in balloon anchoring and mother-and-child techniques to improve support when needed.[39]

When the distal vessel is filled by retrograde collaterals, the ipsilateral collaterals can have their flow impaired after wire and catheter advancement, resulting in a collateral or preferential collateral shift to the retrograde collaterals during the procedure. Therefore to achieve the best diagnostic angiography (i.e., to fill the entire collateral bed), contralateral injection should be performed at the start of the procedure if any visible contralateral collaterals are present. Operators from

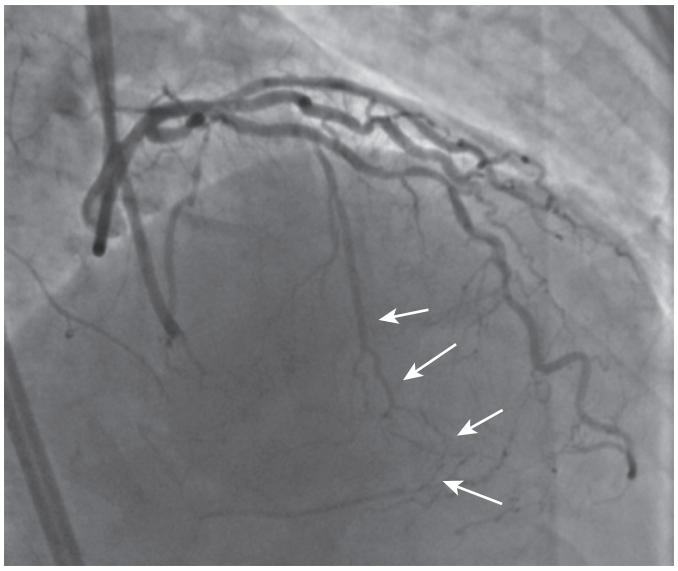


FIGURE 25-3 Typical fine, moderately tortuous transseptal collateral connecting the left anterior descending (LAD) coronary artery to the right posterior descending artery. Transseptals are the most commonly used collaterals for retrograde chronic total occlusion techniques and can serve to access an occluded dominant right coronary artery or dominant left circumflex artery from the LAD, or in the opposite direction, to access an occluded LAD from a dominant right or left circumflex artery. Another transseptal collateral is visible arising from the distal LAD. Because transseptal collaterals are generally contained within septal myocardium, their rupture rarely poses a hazard with respect to tamponade.

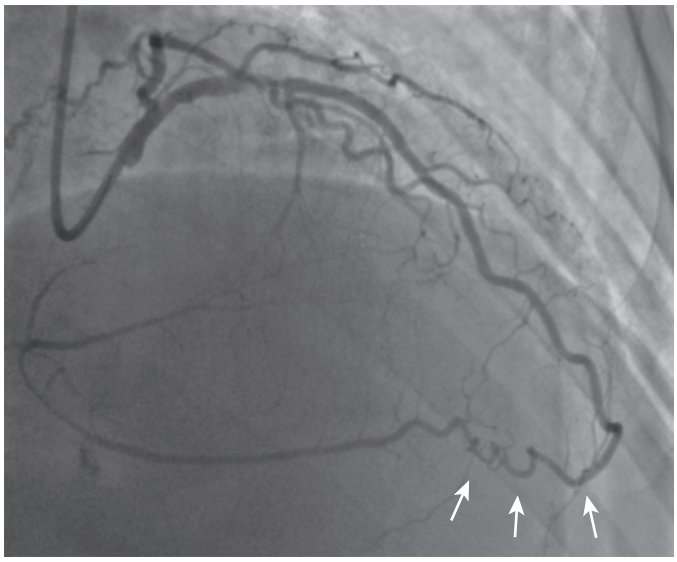


FIGURE 25-4 A large, dominant, tortuous, transapical epicardial collateral supplies the right posterior descending artery from the distal left anterior descending artery. This collateral is likely to become kinked when instrumented with a guidewire or microcatheter, resulting in loss of visualization of the distal target and creating the potential for acute intraprocedural ischemia. Collaterals of this configuration are rarely helpful as conduits for retrograde access.

the EuroCTO Club have used contralateral injection in 62% of their cases,[40] whereas dual injection was used in 78% of cases in a more recent North American series.[41] Dual-injection collateral analysis is best performed using low magnification, so that the entire coronary tree is visualized without panning. Careful study of the collaterals not only provides important information in choosing the most appropriate collateral but will also alert the operator to the risk of ischemia and hemodynamic or electrical instability if the wired collateral becomes occluded. Three typical collateral pathways are demonstrated in Figures 25-3 through 25-5. A careful and detailed review of the angiogram is critical for creating primary and alternative CTO treatment strategies to optimize the efficacy, efficiency, and safety of the procedure.[42]

Anticoagulation during CTO PCI is best achieved with unfractionated heparin (UFH) because it allows for titration of the anticoagulant effect (an activated clotting time [ACT] of >350 seconds is recommended by many operators during retrograde CTO PCI to minimize the risk of donor vessel and guide thrombosis).[43] Bivalirudin requires ongoing flow and exposure to blood to maintain its pharmacotherapeutic effect and therefore has the potential for higher guide catheter thrombotic rates. As with all PCI, preloading with a $P2Y_{12}$ adenosine diphosphate (ADP) receptor inhibitor and aspirin is important to reduce the risk of acute stent thrombosis and periprocedural MI.

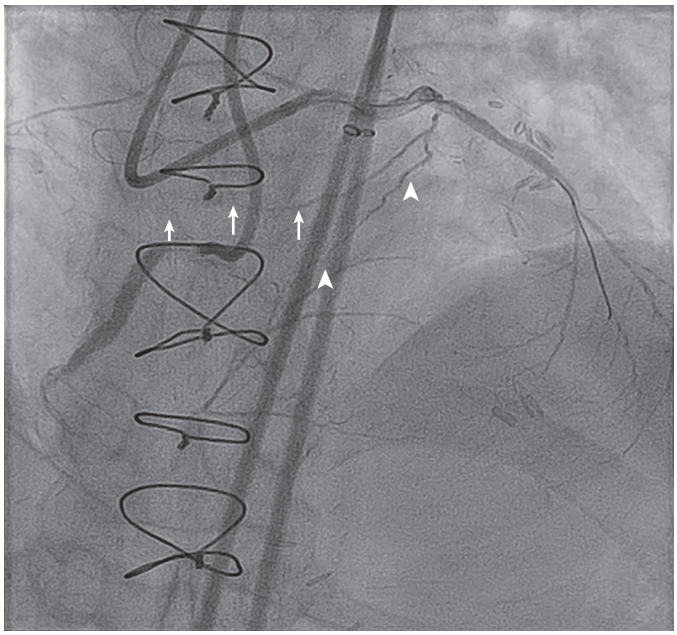


FIGURE 25-5 Two typical atrioventricular groove epicardial collaterals from the circumflex artery to the right posterolateral branch. *Arrowheads* indicate a straight connection; *arrows* show a tortuous connection.

Prediction of Chronic Total Occlusion Crossing Difficulty

Predicting the difficulty of CTO crossing with a guidewire is important for case selection and procedural planning. The Multicentre CTO Registry of Japan (J-CTO) score is determined by assigning one point to each of five variables: (1) previously failed lesion, (2) blunt type of entry, (3) calcification, (4) bending, and (5) occlusion length. Patients are classified into four difficulty groups: *easy* (J-CTO score of 0), *intermediate* (a score of 1), *difficult* (a score of 2), and *very difficult* (a score of 3 or higher). The J-CTO score correlated well with the probability of successful guidewire crossing within 30 minutes (87.7%, 67.1%, 42.4%, and 10.0%, respectively)[44] and was recently validated in an independent single-center Canadian cohort.[45] Recent reports using a hybrid-based CTO algorithm have shown that the J-CTO score predicts an increasing need for retrograde procedures to obtain success (Fig. 25-6).

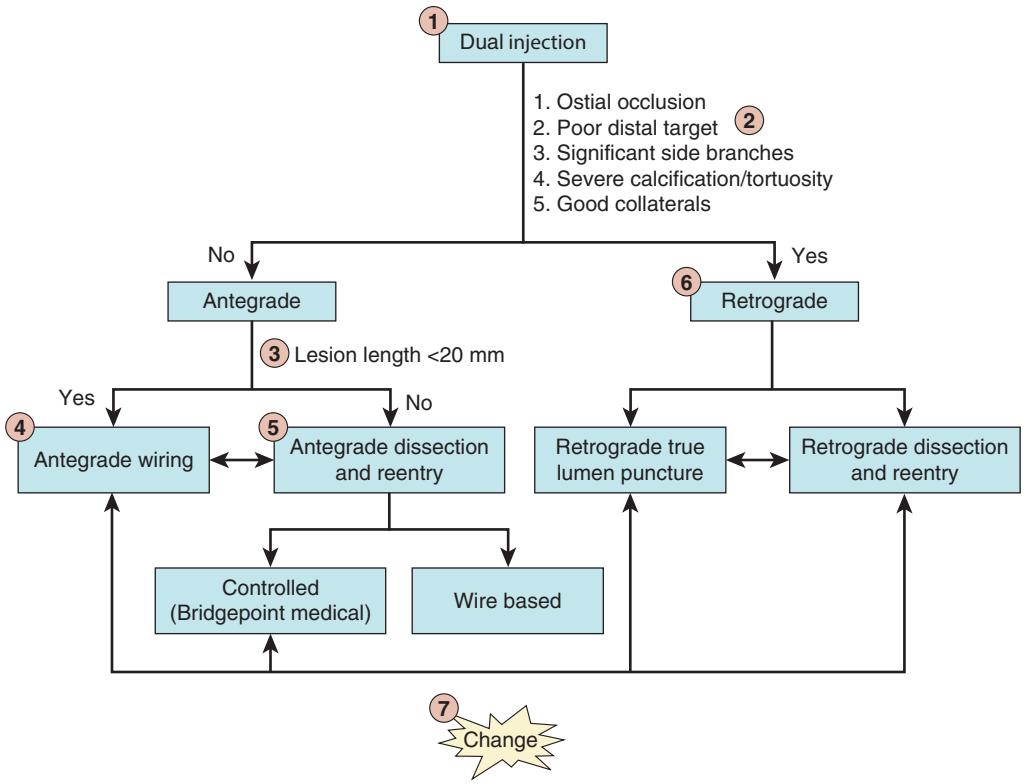


FIGURE 25-6 The hybrid approach to chronic total occlusion (CTO) percutaneous coronary intervention (PCI) uses sentinel features of the coronary anatomy to guide the initial approach to CTO recanalization. Antegrade approaches are favored by a clearly identified nonostial occlusion inlet (proximal cap), a large and well-visualized target segment beyond the distal cap, absence of severe calcification or tortuosity, and absence of an important side branch adjacent to the distal cap that might be excluded during dilation and stenting of a subintimal tract. Retrograde approaches are favored when suitable collaterals or bypass grafts exist through which delivery of PCI equipment to the distal cap appears feasible, particularly when the anatomy does not favor an antegrade approach. An important feature of hybrid CTO procedures is the operator's predisposition to timely changes of strategy when progress toward the goal of recanalization stalls.

Specific Approaches and Techniques

Antegrade Guidewire Approach

Antegrade guidewire-based recanalization of CTOs has been and remains the most common approach worldwide.[46-48] In general, an over-the-wire catheter is delivered to the proximal cap on a workhorse wire, and then CTO-specific techniques and wire shaping are applied. The approach of gradually escalating wire stiffness to achieve crossing has become more nuanced and flexible. Modern step-up/step-down techniques start with soft, tapered polymeric wires but step up promptly to stiff, spring-coil tapered wires to overcome any hard, calcified, or fibrotic segments of the occlusion and then step back down to soft, polymer/hydrophilic wires to continue tracking along the occluded segment and complete the crossing of the CTO.[42,49] A rapidly expanding range of CTO guidewires demands that the CTO specialist have an organized approach to wire choice that keeps pace with evolving global experience and new guidewire designs.[50]

Balloons or catheters should never be advanced over a wire unless it is certain that the wire is in the architecture of the vessel (within the boundary of the external elastic lamina) because wire perforations that occur within the occluded segment are usually benign but can become catastrophic if larger equipment is advanced outside the vessel, thereby enlarging the breach. Moreover, once they access the distal true lumen, the CTO-crossing wires should be exchanged for workhorse wires to avoid distal plaque disruption/dissection and in particular to prevent inadvertent distal perforation of small vessels, causing delayed tamponade.[51]

Antegrade Dissection/Reentry

The primary mode of failure when recanalizing a chronically occluded vessel is failure of the wire to enter the distal true lumen and to instead reside within plaque or within the subintimal plane. Reentering the true lumen from these positions can be extremely challenging with wire-based techniques alone. Recent technologies such as the CrossBoss catheter, Stingray balloon, and Stingray reentry guidewire (Boston Scientific, Natick, MA) have addressed this limitation and have provided a much more reproducible and systematic method for successfully gaining reentry into the coronary lumen. The CrossBoss catheter is a metal-braided, over-the-wire support catheter with a 1-mm rounded distal tip that can be used to support standard guidewire manipulation or can be advanced using rapid rotation, with or without the wire lead (Fig. 25-7). Without the wire lead, this catheter can cross into the distal true lumen in approximately 40% of lesions. Alternatively, it can enter into a side branch, which is important to recognize to avoid perforation, or it can cross within the subintimal space. If the CrossBoss catheter reaches a subintimal position, or if a standard wire strategy leads to subintimal or sublesional wire positioning, coronary reentry can be systematically achieved with Stingray coronary reentry technologies (Boston Scientific). The Stingray balloon is a 1 mm thick, over-the-wire balloon catheter with three exit ports (one distal and two 180-degree diametrically opposed side ports). When the balloon is inflated, it effectively wraps the artery with one of the two exit ports, necessarily directed toward the adventitia, and the other port is directed toward the lumen. Using fluoroscopy and collateral angiography, operators can select the lumen port with

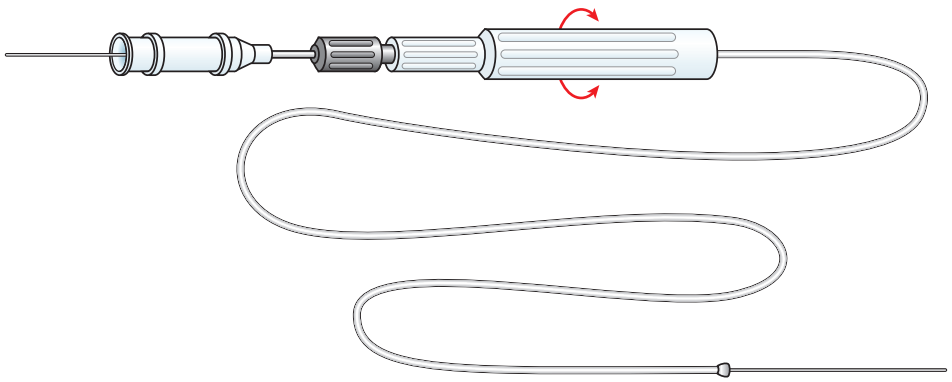


FIGURE 25-7 The CrossBoss catheter is used to make a controlled dissection from the proximal cap to the point of planned reentry with the Stingray balloon. This catheter uses blunt dissection to avoid perforation. Unlike wire-based blunt dissection ("knuckle" wires), the CrossBoss was designed to create a small channel that avoids subintimal hematoma and consequent compression of the reentry zone.

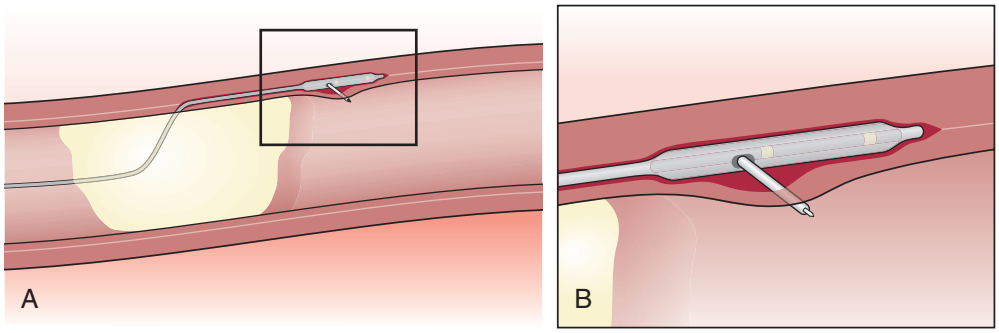


FIGURE 25-8 The BridgePoint (Boston Scientific Corporation, Natick, MA) dedicated antegrade dissection and reentry system. After establishing an antegrade subintimal tract using a CrossBoss (**A**) or other low-profile catheter or small angioplasty balloon, the Stingray balloon (**B**) is delivered and inflated in a position adjacent to the preferred segment for reentry. The flat profile of the Stingray balloon leads to its self-orientation circumferentially within the arterial wall such that *one* of the exit ports inevitably faces the arterial lumen. This port can then be selected using the dedicated steerable Stingray guidewire, designed to facilitate puncture back into the true lumen.

the dedicated Stingray reentry wire to achieve distal lumen control (Fig. 25-8).

Occasionally, subintimal wire entry can cause a subintimal hematoma that can compress the distal true lumen and can thus require decompression through aspiration. The Stingray balloon or other microcatheters can be used for this purpose with a subintimal transcatheter withdrawal (STRAW) technique. These technologies have been highly successful and have had low complication rates, even in early experiences and refractory cases.[52,53]

The Retrograde Approach

In 2005, Katoh and colleagues pioneered the modern era of retrograde CTO recanalization by introducing new techniques such as targeted septal or epicardial collateral crossing, retrograde lesion crossing, and management of the subintimal space through the use of balloon dilation for connecting antegrade and retrograde channels.[53] Currently, retrograde procedures account for 15% to 34% of specialist CTO PCI procedures recorded in dedicated European and U.S. registries.[40,54-56] These methods require access to the distal CTO vessel from a collateral (or occasionally a bypass graft) vessel with successful placement of a support catheter into the distal target vessel.[57]

Retrograde Wire Crossing

The term *retrograde wire crossing* refers to lesion crossing in the distal-to-proximal cap direction with successful true lumen access to the proximal vessel; it is successful in less than 30% of retrograde procedures.[43] The standard approach after successful retrograde wire manipulation includes placing the wire and then the microcatheter into the antegrade guide catheter and then exchanging those for a long wire to be externalized from the antegrade guide.[58] The externalized wire—such as the ViperWire Advance (CSI, St. Paul, MN), R350 (Vascular Solutions, Minneapolis, MN), or RG3 (Asahi Intecc, Nagoya, Japan)—is then used as the interventional platform to complete the PCI procedure.[59] It is important for the portion of the retrograde guidewire that is traversing fine collaterals to remain covered by a microcatheter to protect the collateral vessel from laceration and perforation. Equally important is careful attention to guide movement to prevent guide-induced donor vessel injury.

Retrograde Dissection and Reentry Techniques

Controlled antegrade and retrograde subintimal tracking (CART; Fig. 25-9) with intentional dissection followed by reentry has become the dominant retrograde technique for successful crossing of CTOs. The principle of this technique is to create a subintimal dissection with limited extension only at the CTO site, thereby facilitating antegrade or retrograde wire crossing. The current evolution of this technique, termed *reverse CART*, uses retrograde delivery of a microcatheter within the CTO segment either with traditional wire or knuckle-wire techniques. An antegrade wire is then advanced distal to the retrograde equipment followed by dilation of the occlusion segment with a balloon delivered over the antegrade wire. This tears (dissects) together the two spaces occupied by antegrade and retrograde equipment to create a single, common space that is in continuity with the proximal true lumen; the retrograde wire can then be advanced into the true lumen.

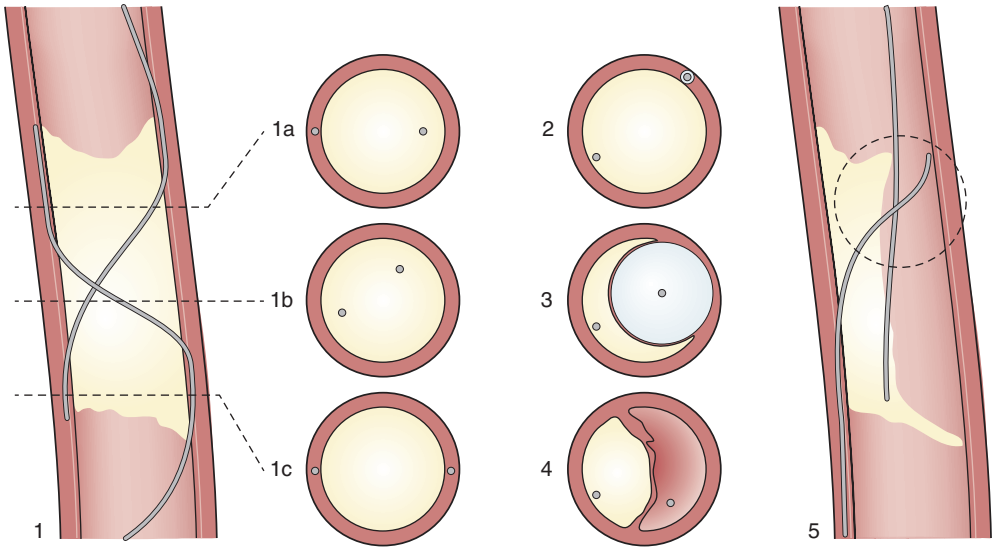


FIGURE 25-9 Controlled antegrade-retrograde tracking (CART). Through directed penetration or knuckling, antegrade and retrograde guidewires are brought into overlap within the occluded segment [1]; wires may be on opposite sides of the internal elastic lamina (one subintimal, the other within the occluded true lumen [1a]; both within the occluded true lumen [1b]; or both in a subintimal plane [1c]). Regardless, a balloon is advanced over one of the wires [2]; it is inflated and deflated [3]; and it is then withdrawn, leaving behind iatrogenic dissection that often includes breaches of the internal elastic lamina within the occluded segment [4] that allow the retrograde wire to be moved into a plane common with the antegrade wire and then advanced into the patent proximal true lumen [5] and ultimately externalized. CART was originally described with the balloon positioned on the retrograde wire; the term *reverse CART* refers to the now common practice of positioning the balloon on the antegrade wire.

Ultrasound observations suggest this maneuver is easiest when both the antegrade and retrograde guidewire are on the same side of the internal elastic lamina, either both within the subintimal space or both within the original true lumen. The most common reason for failure of this technique is use of undersized balloons, a problem overcome with experience and use of IVUS for optimal balloon sizing and positioning.[60] After the retrograde wire is advanced into the antegrade guide, externalization of the retrograde wire is performed as described earlier. The use of an antegrade daughter catheter such as a GuideLiner (Vascular Solutions) positioned immediately proximal to the reverse-CART segment can expedite retrograde wire capture and externalization.

Hybrid Strategy for Chronic Total Occlusion Percutaneous Coronary Intervention

Contemporary antegrade, retrograde, and dissection and reentry techniques are complementary and necessary for the full spectrum of CTO PCI. Exploring sequential CTO crossing options can increase success, shorten procedure times, and reduce radiation exposure. The CTO expert operator needs broad skill sets, versatility, and flexibility to accommodate the wide range of anatomic scenarios for chronic occlusion that will be present in patients with strong indications for revascularization.[61] Although significant variability exists among many operators with respect to procedural approaches, the "hybrid method" for CTO PCI is an effort to standardize initial and provisional technique selection based on patient anatomy (see Fig. 25-6).[42] The implementation of the hybrid method requires skill-set development in optimal wire manipulation, dissection/reentry strategies, and retrograde techniques. The development and adoption of only one or two of these skill sets will ultimately limit the experienced operator who wishes to approach all patients with appropriate indications for revascularization. Failure to develop all three skill sets will likely lead to underutilization of revascularization in patient subgroups who may derive the greatest benefit from these techniques.

Treatment of Lesions Resistant to Dilation

Although less common than failure to cross a CTO lesion with a guidewire, occasionally a coronary lesion cannot be crossed with a balloon or cannot be dilated with a balloon. It is important to confirm that the guidewire is in the vessel architecture or in the distal true lumen before proceeding with any over-the-wire catheter or before applying various dilation strategies. The vessel architecture can usually be determined fluoroscopically by observing calcium deposits or other signs of the vessel outline moving or "dancing" in sync with the interventional guidewire. The distal true lumen can be determined by contralateral angiography. After maximizing guide catheter support with either guide extension or anchor balloon, attempts to pass the initial over-the-wire system should be attempted. In general, if a Corsair microcatheter (Asahi Intecc) will not cross the lesion, the initial step is to advance and inflate to high pressure a small (1.2 to 1.5 mm in diameter, 14 to 16 atm) balloon as deeply as possible within the lesion to modify the proximal cap. When using small balloons, it is important to use longer balloons (15 to 20 mm) because the largest profile of these balloons is at the midshaft marker, and thus the balloon tip will often penetrate the occlusion more readily. If this fails to allow passage of larger balloons, the next maneuver is to intentionally rupture the small balloon so as to modify with barotrauma the morphology of the proximal vessel and cap. If this fails to enable crossing, the Tornus catheter (Asahi Intecc) may be useful.[61] If these maneuvers fail, more aggressive techniques such as the use of coronary laser[62] or rotational atherectomy[63] can be used. Rotational atherectomy and laser can be used even when the wire is not in the distal lumen, provided it is still within the vessel architecture. The advantage of the excimer laser (e.g., the .9 mm Turbo Elite; Spectranetics, Colorado Springs, CO) is that it may be used on any 0.014-inch guidewire. However, rotational atherectomy requires exchanging the guidewire to a dedicated rotowire, and this may not be feasible when a resistant lesion prevents distal placement of any microcatheter. In situations where the distal true lumen has not been reached, the last 2 cm of the radiopaque wire tip can be removed

prior to placement in the artery, thereby providing further reach with the burr (part of the radiopaque portion of the wire should be preserved to prevent the burr from going off the guidewire). Alternatively, the wire can be looped further down the vessel prior to atherectomy. Rotational atherectomy in the subintimal space should be attempted only by very advanced CTO operators with extensive experience assessing wire position in relation to vessel architecture. Performing rotational atherectomy in this situation demands the use of small 1.25 to 1.5 mm burrs, maintenance of a high number of revolutions per minute (>170,000 rpm), and scrupulous avoidance of stalling and thus trapping the device in a distal subintimal position. If all of these techniques fail to achieve balloon crossing and/or balloon dilation of the lesion, success can often be achieved by deliberately entering the subintimal space proximal to the anatomic cap, effectively moving the functional cap proximally and bypassing the point of resistance. This is done in an antegrade direction using a prolapsed guidewire or CrossBoss catheter with reentry of the true lumen prior to major branches or using a retrograde approach with retrograde dissection and reentry to go around the uncrossable or undilatable lesion.

CONCLUSION

With the development of a multitude of new techniques and technologies, the ability to revascularize ischemic/hibernating myocardium via percutaneous techniques is achievable. This opens a new era of research and patient care to evaluate optimal percutaneous treatment.

REFERENCES

1. Brilakis ES, Grantham JA, Rinfret S, et al: A percutaneous treatment algorithm for crossing coronary chronic total occlusions. *JACC Cardiovasc Interv* 5:376–379, 2012.
2. The TIMI Study Group: The Thrombolysis in Myocardial Infarction (TIMI) Trial: Phase I findings. *N Eng J Med* 33:523–530, 1984.
3. Christofferson RD, Lehmann KG, Martin GV, et al: Effect of chronic total coronary occlusion on treatment strategy. *Am J Cardiol* 95:1088–1091, 2005.
4. Fefer P, Knudtson ML, Cheema AN, et al: Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. *J Am Coll Cardiol* 59:991–997, 2012.
5. Råmunddal T, Hoebers L, Henriques JP, et al: Chronic total occlusions in Sweden: a report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *PLoS ONE* 9(8):e103850, 2014.
6. Claessen BE, Van der Scheaff RJ, Verouden NJ, et al: Evaluation of the effect of a concurrent chronic total occlusion on long-term mortality and left ventricular function in patients after primary percutaneous coronary intervention. *JACC Cardiovasc Interv* 2:1128–1134, 2009.
7. Katsuragawa M, Hisayoshi F, Masami M, et al: Histologic studies in percutaneous transluminal coronary angioplasty for chronic total occlusion: comparison of tapering and abrupt types of occlusion and short and long occlusion segments. *J Am Coll Cardiol* 21:604–611, 1993.
8. Srivatsa SS, Edwards WD, Boos CM, et al: Histologic correlates of angiographic chronic total coronary artery occlusions. Influence of occlusion duration on neovascular channel patterns and intimal plaque composition. *J Am Coll Cardiol* 29:955–963, 1997.
9. Thind AS, Leung G, Munce NR, et al: Investigation of microultrasound for microvessel imaging in a model of chronic total occlusion. *Ultrason Imaging* 29:167–181, 2007.
10. Munce NR, Strauss BH, Qi X, et al: Intravascular and extravascular microvessel formation in chronic total occlusions: a micro-CT imaging study. *JACC Cardiovasc Imaging* 3(8):797–805, 2010.
11. Seiler C: The human coronary collateral circulation. *Eur J Clin Invest* 40(5):465–476, 2010.
12. Meier P, Schirmer SH, Lansky AJ, et al: The collateral circulation of the heart. *BMC Med* 11(1):143, 2013.
13. Pung YF, Sam WJ, Hardwick JP, et al: The role of mitochondrial bioenergetics and reactive oxygen species in coronary collateral growth. *Am J Physiol Heart Circ Physiol* 305(9):H1275–H1280, 2013.
14. Rentrop KP, Cohen M, Blanke H, Phillips RA: Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol* 5(3):587–592, 1985.
15. Meier P, Hemingway H, Lansky AJ, et al: The impact of the coronary collateral circulation on mortality: a meta-analysis. *Eur Heart J* 33(5):614–621, 2012.
16. Van Liebergen RA, Piek JJ, Koch KT, et al: Quantification of collateral flow in humans: a comparison of angiographic, electrocardiographic and hemodynamic variables. *J Am Coll Cardiol* 33(3):670–677, 1999.
17. Werner GS, Surber R, Ferrari M, et al: The functional reserve of collaterals supplying long-term chronic total coronary occlusions in patients without prior myocardial infarction. *Eur Heart J* 27(20):2406–2412, 2006.
18. Werner GS, Surber R, Kuethe F, et al: Collaterals and the recovery of left ventricular function after recanalization of a chronic total coronary occlusion. *Am Heart J* 149(1):129–137, 2005.
19. Buller CE, Dzavik V, Carere RG, et al: Primary stenting versus balloon angioplasty in occluded coronary arteries: the Total Occlusion Study of Canada (TOSCA). *Circulation* 100:236–242, 1999.
20. Kirschbaum SW, Baks T, van den Ent M, et al: Evaluation of left ventricular function three years after percutaneous recanalization of chronic total coronary occlusions. *Am J Cardiol* 101:179–185, 2008.
21. Hachamovitch R, Hayes SW, Friedman JD, et al: Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 107:2900–2907, 2003.
22. Suero JA, Marso SP, Jones PG, et al: Procedural outcomes and long-term survival among patients undergoing percutaneous coronary intervention of a chronic total occlusion in native coronary arteries. *J Am Coll Cardiol* 38:409–414, 2001.
23. Ramanathan K, Gao M, Nogareda GJ, et al: Successful percutaneous recanalization of a non-acute occluded coronary artery predicts clinical outcomes and survival (abstract). *Circulation* 104:II–415, 2001.
24. British Cardiovascular Intervention Society, National Institute for Cardiovascular Outcomes Research, et al: Long-term follow-up of elective chronic total coronary occlusion angioplasty: analysis from the U.K. Central Cardiac Audit Database. *J Am Coll Cardiol* 64(3):235–243, 2014.
25. Safley DM, House JA, Marso SP, et al: Improvement in survival following successful percutaneous coronary intervention of coronary chronic total occlusion: variability by target vessel. *JACC Cardiovasc Interv* 1:295–302, 2008.
26. Multinational Chronic Total Occlusion Registry: Long-term outcome of percutaneous coronary intervention for chronic total occlusions. *JACC Cardiovasc Interv* 4:952–961, 2011.
27. Joyal D, Afilalo J, Rinfret S, et al: Effectiveness of recanalization of chronic total occlusions: a systematic review and meta-analysis. *Am Heart J* 160:179–187, 2010.
28. Buller CE, Rankin JM, Carere RG, et al: Percutaneous coronary intervention in occluded artery trial: procedural success, hazard, and outcomes over 5 years. *Am Heart J* 158(3):408–415, 2009.
29. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches Study (ISCHEMIA), ClinicalTrials.gov identifier NCT01471522.
30. Borgia F, Vicconte N, Ali O, et al: Improved cardiac survival, freedom from MACE and angina quality of life after successful percutaneous coronary intervention of coronary chronic total occlusions. *Int J Cardiol* 161(1):31–38, 2012.
31. Grantham JA, Jones PG, Cannon L, Spertus JA: Quantifying the early health status benefits of successful chronic total occlusion recanalization: results from the FlowCardia's Approach to Chronic Total Occlusion Recanalization (FACTOR) trial. *Circ Cardiovasc Qual Outcomes* 3:284–290, 2010.
32. Anderson HV, Shaw RE, Brindis RG, et al: A contemporary overview of percutaneous coronary interventions: the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *J Am Coll Cardiol* 39(1):1096–1103, 2002.
33. Wiliams DO, Holubkov R, Yeh W: Percutaneous coronary intervention in the current era compared with 1985-1986: the National Heart, Lung, and Blood Institute registries. *Circulation* 102:2945–2951, 2000.
34. Wijns W, Koln P, Danchin N, et al: Guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association of Cardiothoracic Surgery (EACTS) European PCI guidelines. *Eur Heart J* 31:2501–2555, 2010.
35. Levine GN, Bates ER, Blankenship JC, et al: 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv* 79(3):453–495, 2012.
36. Patel MR, Dehmer GJ, Hirshfeld JW, et al: ACCF/SCAI/STS/AATS/ASNC 2009 appropriateness criteria for coronary revascularization. *J Am Coll Cardiol* 53(6):530–553, 2009.
37. Hamon M, Mehta S, Steg PG, et al: Impact of transradial and transfemoral coronary interventions on bleeding and net adverse clinical events in acute coronary syndromes. *EuroIntervention* 7:91–97, 2011.
38. Cantor WJ, Mahaffey KW, Huang Z, et al: Bleeding complications in patients with acute coronary syndrome undergoing early invasive management can be reduced with radial access, smaller sheath sizes, and timely sheath removal. *Catheter Cardiovasc Interv* 69:73–83, 2007.
39. Di Mario C, Ramasami N: Techniques to enhance guide catheter support. *Catheter Cardiovasc Interv* 72:505–512, 2008.
40. Galassi AR, Tomasello SD, Reifart N, et al: In-hospital outcomes of percutaneous coronary intervention in patients with chronic total occlusion: insights from the ERCTO (European Registry of Chronic Total Occlusion) registry. *EuroIntervention* 7:472–479, 2011.
41. Michael TT, Mogabgab O, Fuh E, et al: Application of the "hybrid approach" to chronic total occlusion interventions: a detailed procedural analysis. *J Interv Cardiol* 27:36–43, 2014.
42. Brilakis ES, Grantham JA, Rinfret S, et al: A percutaneous treatment algorithm for crossing coronary chronic total occlusions. *JACC Cardiovasc Interv* 5:367–379, 2012.
43. Brilakis ES, Grantham JA, Thompson CA, et al: The retrograde approach to coronary artery chronic total occlusions: a practical approach. *Catheter Cardiovasc Interv* 79:3–19, 2012.
44. Morino Y, Abe M, Morimoto T, et al: Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. *JACC Cardiovasc Interv* 4:213–221, 2011.
45. Nombela-Franco L, Urena M, Jerez-Valero M, et al: Validation of the J-chronic total occlusion score for chronic total occlusion percutaneous coronary intervention in an independent contemporary cohort. *Circ Cardiovasc Interv* 6:635–643, 2013.
46. J-CTO Registry Investigators: In-hospital outcomes of contemporary percutaneous coronary intervention in patients with chronic total occlusion insights from the J-CTO Registry (Multicenter CTO Registry in Japan). *JACC Cardiovasc Interv* 3:143–151, 2010.
47. Sianos G, Werner GS, Galassi AR, et al: Recanalisation of chronic total coronary occlusions: 2012 consensus document from the EuroCTO club. *EuroIntervention* 8:139–145, 2012.
48. Rathore S, Matsuo H, Terashima M, et al: Procedural and in-hospital outcomes after percutaneous coronary intervention for chronic total occlusions of coronary arteries 2002 to 2008: impact of novel guidewire techniques. *JACC Cardiovasc Interv* 2:489–497, 2009.
49. Brilakis ES, Karmpaliotis D, Patel V, Banerjee S: Complications of chronic total occlusion angioplasty. *Intervent Cardiol Clin* 1:373–389, 2012.
50. Buller CE: Coronary guidewires for chronic total occlusion procedures: function and design. *Interv Cardiol* 5(5):533–540, 2013.
51. Whitlow PL, Burke MN, Lombardi WL, et al: Use of a novel crossing and re-entry system in coronary chronic total occlusions that have failed standard crossing techniques: results of the FASTCTOs (Facilitated Antegrade Steering Technique in Chronic Total Occlusions) trial. *JACC Cardiovasc Interv* 5:393–401, 2012.
52. Werner GS, Schofer J, Sievert H, et al: Multicentre experience with the BridgePoint devices to facilitate recanalisation of chronic total coronary occlusions through controlled subintimal re-entry. *EuroIntervention* 7:192–200, 2011.
53. Surmely JF, Tsuchikane E, Katoh O, et al: New concept for CTO recanalization using controlled antegrade and retrograde subintimal tracking: the CART technique. *J Invasive Cardiol* 18:334–338, 2006.
54. Karmpaliotis D, Michael TT, Brilakis ES, et al: Retrograde coronary chronic total occlusion revascularization: procedural and in-hospital outcomes from a multicenter registry in the United States. *JACC Cardiovasc Interv* 5:1273–1279, 2012.
55. Michael TT, Karmpaliotis D, Brilakis ES, et al: Procedural outcomes of revascularization of chronic total occlusion of native coronary arteries (from a Multicenter United States Registry). *Am J Cardiol* 112:488–492, 2013.
56. El Sabbagh A, Patel VG, Jeroudi OM, et al: Angiographic success and procedural complications in patients undergoing retrograde percutaneous coronary chronic total occlusion interventions: a weighted meta-analysis of 3482 patients from 26 studies. *Int J Cardiol* 174:243–248, 2014.
57. Tsuchikane E, Katoh O, Kimura M, et al: The first clinical experience with a novel catheter for collateral channel tracking in retrograde approach for chronic coronary total occlusions. *JACC Cardiovasc Interv* 3:165–171, 2010.
58. Galassi AR, Tomasello SD, Costanzo L, Tamburino C: Retrograde approach for chronic total occlusion percutaneous revascularization. *Interv Cardiol* 2:391–403, 2010.

59. Rathore S, Katoh O, Tuschikane E, et al: A novel modification of the retrograde approach for the recanalization of chronic total occlusion of the coronary arteries intravascular ultrasound-guided reverse controlled antegrade and retrograde tracking. *JACC Cardiovasc Interv* 3:155–164, 2010.
60. Thompson CA: Percutaneous revascularization of coronary chronic total occlusions: the new era begins. *JACC Cardiovasc Interv* 3:152–154, 2010.
61. Fang HY, Lee CH, Fang CY, et al: Application of penetration device (Tornus) for percutaneous coronary intervention in balloon uncrossable chronic total occlusion: procedure outcomes, complications, and predictors of device success. *Catheter Cardiovasc Interv* 78:356–362, 2011.
62. Shen ZJ, Garcia-Garcia HM, Schultz C, et al: Crossing of a calcified "balloon uncrossable" coronary chronic total occlusion facilitated by a laser catheter: a case report and review recent four years' experience at the Thoraxcenter. *Int J Cardiol* 145:251–254, 2010.
63. Pagnotta P, Briguori C, Mango R, et al: Rotational atherectomy in resistant chronic total occlusions. *Catheter Cardiovasc Interv* 76:366–371, 2010.

26 Bypass Graft Intervention

JOHN S. DOUGLAS, JR.

KEY POINTS

- Early postoperative ischemia (<30 days) is often due to graft occlusion or stenosis, and percutaneous coronary intervention (PCI) is frequently feasible.
- Unstable angina (UA) or ST-segment–elevation myocardial infarction (STEMI) years after coronary artery bypass grafting (CABG) is most often due to a saphenous vein graft (SVG) lesion; in such cases, native vessel PCI is preferred whenever possible.
- Embolic protection halves the risk of atheroembolic myocardial infarction during SVG PCI and should be used routinely in the treatment of de novo SVG lesions that occur years after CABG.
- Multiple diseased or occluded SVGs, reduced left ventricular (LV) function, and available arterial conduits favor repeat CABG; a patent left internal mammary artery (LIMA) to the left anterior descending coronary artery (LAD) favors PCI.
- Drug-eluting stents reduce restenosis in SVGs and native coronary arteries and have become the default strategy for many operators in spite of reduced efficacy in SVGs compared with native vessels.

THE SCOPE OF THE PROBLEM

CABG is a commonly performed surgical procedure whose efficacy has been enhanced by the use of arterial grafts, off-bypass procedures, and minimally invasive surgical techniques; in addition, attempts have been made to improve graft longevity with antiplatelet agents and lipid-lowering therapy. However, the temporary nature of the palliative effect of CABG remains a significant health care problem. Severe myocardial ischemic syndromes occur in 3% to 5% of patients immediately after surgery; thereafter, recurrent ischemic symptoms appear in 4% to 8% of post-CABG patients annually. SVG attrition, the most common cause, is up to 40% during the first year; 1% to 2% of grafts occlude annually 1 to 5 years after surgery, and 4% to 5% occlude each year over the next 5 years. At 10 years, one half of all SVGs are occluded, and half of the patent SVGs are diseased.

In early experience at Emory University Hospital and the Cleveland Clinic, reoperation was required in about 3% of patients by 5 years, 15% by 10 years, and 30% by 15 years. For reoperation, even in the most experienced centers, the risk of in-hospital death and nonfatal Q-wave myocardial infarction (MI) is triple that of the initial operation. In the state of New York, in-hospital mortality was 4.1% for initial operations but 11%, 25%, and 39% for first, second, and third reoperations, respectively.[1] In addition to being more risky, reoperative surgery was associated with less complete anginal relief and reduced graft patency, probably attributable to more advanced disease and poorer graft conduits. These factors have promoted a conservative approach to reoperation and have favored the use of PCI.[2-5] In addition, many symptomatic patients who are candidates for percutaneous methods would not be considered for reoperation because of jeopardy to a limited amount of myocardium, risk to patent grafts, lack of suitable conduits, poor LV function, advanced age, or coexisting medical problems. Recently published data from the Society of Thoracic Surgery (STS) national database showed that among patients aged 65 years and older who survived following an initial CABG operation, rates of repeat revascularization at 1, 5, 10, and 18 years were 2%, 8%, 16%, and 25%, respectively, and that the mode of revascularization was mostly PCI (93%).[6] Factors associated with a higher rate of repeat revascularization included female sex, diabetes, prior PCI, dialysis, and incomplete revascularization. In the past decade at Emory, approximately 15% of the patients who underwent PCI had had a prior CABG, and bypass graft intervention was the most common indication. It is in this difficult group of patients, those who require bypass graft intervention, that decision making is particularly critical owing to the increased risk and reduced long-term benefit of such intervention.

INDICATIONS FOR INTERVENTION

Patients who experience recurrent ischemia after coronary bypass surgery have diverse anatomic problems; therefore selection for PCI must be based on careful analysis of the probabilities of outcomes compared with competing strategies. The status of the LAD and its graft significantly influences revascularization choices because of its impact on long-term outcome and the lack of survival benefit of reoperative surgery to treat non–LAD-related ischemia.[7,6] Factors that favor surgical revascularization include multiple-vessel involvement, severe vein graft disease, poor LV function, total occlusions of native coronary arteries, and the availability of arterial conduits.[8] Because the choice among percutaneous methods and the relative effectiveness of each are often influenced by the time elapsed since surgery, indications are considered relative to this factor.

Early Postoperative Period

The performance of routine intraoperative angiography at the conclusion of CABG at one center and three recent trials in which routine angiography was performed at 12 months to assess graft patency have provided sobering insights regarding contemporary CABG.[9-12] Among 366 consecutive patients who underwent intraoperative completion angiography, Zhao and colleagues[9] found that 12% of bypass grafts had defects important enough to require intervention (open surgical revision, 3.4%; open-chest PCI, 6%; and minor adjustment, 2.8%). In a randomized trial in over 100 high-volume U.S. centers that included over 3000 patients in whom modern surgical techniques and medications were utilized, graft failure at 1 year occurred in 40% to 50% of SVGs.[10] In the PRAGUE-4 trial, angiographic follow-up at 1 year revealed that 40% of SVGs and 9% of LIMA grafts were occluded.[11] In the Veterans Affairs Randomized On/Off Bypass (ROOBY) study, 23% of SVGs and 11% of LIMA grafts performed off pump failed at 1 year.[12] Graft failure was associated with death, new MI, or repeat revascularization in 26% of patients.[10] Recurrent ischemia within days of surgery is usually related to acute vein graft thrombosis due to endothelial damage during harvesting and initial exposure to arterial pressure. However, stenosis may exist at proximal or distal anastomoses (Fig. 26-1); a bypass graft may be kinked; the wrong vessel may have been bypassed; or the revascularization may have been rendered incomplete as a result of diffuse disease, stenoses distal to graft insertion, or inaccessible intramyocardial position of a recipient artery. To determine the cause of severe early postoperative myocardial ischemia and define therapeutic options, coronary arteriography has been carried out within a few hours of surgery in 3% to 4% of patients in some

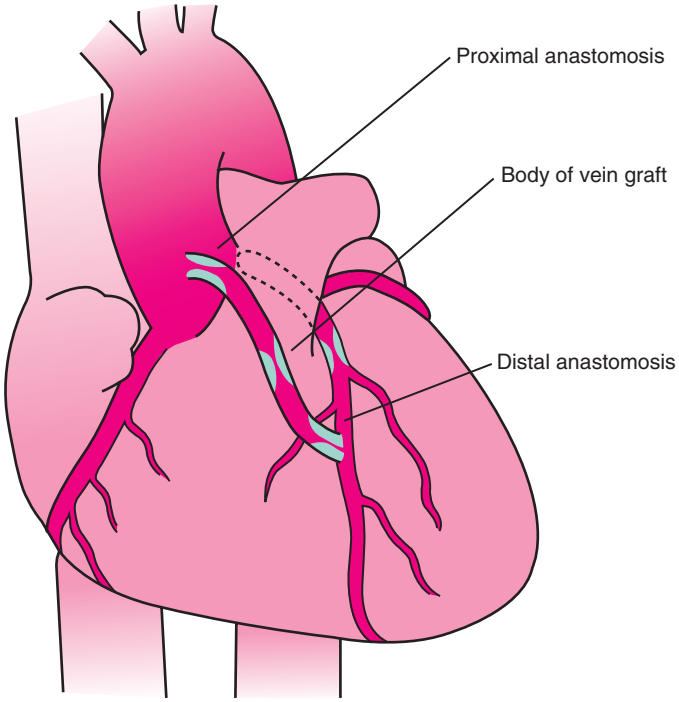


FIGURE 26-1 Sites of saphenous vein graft stenoses. All lesions between the proximal and distal anastomoses are considered midgraft lesions.

centers,[13-15] and this strategy is recommended. PCI in patients with early ischemia after CABG is a class I indication in the American College of Cardiology(ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) 2005 PCI guidelines and the 2010 European guidelines on revascularization.[16,17] Although 44 of 145 patients (30%) catheterized because of ischemia early after surgery had no apparent cause for ischemia, most patients had correctable problems; 30 patients had emergency reoperation, and 44 underwent PCI.[13-15] In a more recent report, emergency coronary angiography was performed in 118 of 5427 CABG patients of whom 57% had graft failure and 60% underwent repeat revascularization.[18] Graft occlusion or stenosis was present in about 60% of catheterized patients. In seven patients, focal stenosis was present in a venous or arterial graft distal anastomosis, and balloon dilation across suture lines was safe in these patients.[13-15] However, in our experience (Fig. 26-2) and in that of others, extreme care is warranted within a few hours after surgery to ensure an intracoronary position of the steerable guidewire, indicating that the guidewire has not penetrated a suture line. In addition, balloon sizing should be conservative; we are aware of unreported cases of suture-line disruption and severe hemorrhagic complications. It is noteworthy that European guidelines advise against PCI of a graft anastomosis early after CABG because of this risk of perforation.[17] Immediate access to a covered stent is essential, should suture line perforation occur. Mild to moderate imperfections at the anastomosis should not be dilated because they frequently disappear on subsequent angiography, suggesting the presence of edema,[19] although some attribute these observations to the reparative ability of the LIMA.[20] If a thrombosed graft is discovered, PCI of the native coronary artery is recommended, but mechanical thrombectomy can be attempted—or a return to the operating room may be considered—if the jeopardized vessel is of significant importance. Use of thrombolytic agents or glycoprotein (GP) IIb/IIIa inhibitors in the early postoperative period carries substantial risk of bleeding. Patients at increased risk for early postoperative ischemia include those undergoing minimally invasive and "off-bypass" techniques and those who receive non–internal mammary artery (IMA) grafts.

When ischemia recurs 1 to 12 months after surgery, perianastomotic stenoses are among the most common problems (Fig. 26-3). Stenotic lesions of the distal anastomosis of saphenous vein or arterial grafts can be successfully dilated with balloon angioplasty at this time with little morbidity and good long-term patency in 80% to 90% of patients without stent implantation.[3,21] Among 34 patients with distal anastomosis lesions reported from our early experience, 25 (74%) presented within 1 year of CABG.[3] Thirty-two were successfully dilated, and three of four restenosis lesions redilated. A total of 30 of 32 patients were asymptomatic at 10 months. Stenoses, or in some cases total occlusions, of the middle or distal portions of the IMA or radial artery grafts may be dilated successfully (Fig. 26-4), especially when the presence of a short occlusion can be documented. Stenotic lesions of mid-SVGs that occur within a year of surgery are usually the result of intimal hyperplasia; these lesions can be dilated with balloon angioplasty and/or stented with little risk of distal embolization, but recurrence has been noted in about 50% of cases in our experience, and periprocedural graft perforation has been observed. Stents, directional coronary atherectomy (DCA), and excimer laser angioplasty have all been tried for the treatment of proximal anastomotic lesions that occur within a year of surgery with excellent initial results but significant rates of restenosis. Data are sparse regarding use of drug-eluting stents at this site.

One to Three Years After Surgery

Patients with recurrent ischemia 1 to 3 years after surgery frequently have new stenoses in graft conduits and native coronary arteries that are amenable to percutaneous intervention. Whenever possible, native coronary lesions are targeted. The ACC/AHA/SCAI 2005 PCI guidelines consider focal ischemia–producing graft lesions in patients 1 to 3 years after CABG with preserved LV function to be a class IIa indication ("conflicting evidence, weight of evidence/opinion in favor of usefulness").[16]

More Than Three Years After Surgery

Beginning about 3 years after implantation, atherosclerotic lesions appear in vein grafts with increasing frequency. Unstable ischemic syndromes are common, and aggressive invasive evaluation and therapy are indicated. In over 70% of post-CABG patients who present with an acute coronary syndrome (ACS), the culprit lesion is located in an SVG.[22] Atherosclerotic plaques in vein grafts contain foam cells, cholesterol crystals, blood elements, and necrotic debris, with less fibrocollagenous tissue and calcification than are present in native coronary arteries (Fig. 26-5). Consequently, the plaques in older vein grafts may be softer and more friable, as well as being larger than those observed in native coronary arteries, and they frequently have associated thrombus formation (Fig. 26-6).[23] Recently published optical coherence tomography (OCT) studies of SVGs in patients with ACSs revealed the enormous complexity of SVG lesions (Fig. 26-7).[24] Atheroembolism related to graft intervention may have catastrophic consequences. Consequently, bulky vein graft lesions (those with a large potential atheroma mass) should be avoided if possible, with embolic protection utilized if not. Improved initial outcome has been reported with stent placement compared with balloon dilation in SVGs. However, long-term results in SVGs, even with stents, have been disappointing. Data on long-term outcomes with drug-eluting stents in SVGs are limited (see "Drug-Eluting Stents in Vein Grafts" section), and the role of percutaneous techniques in totally occluded SVGs is controversial. Whereas successful recanalization of totally occluded SVGs is possible, the risk of distal debris embolization is considerable.

Acute ST-Segment–Elevation Myocardial Infarction

After coronary bypass surgery, approximately 3% of patients experience acute MI (AMI) annually. Because these patients were excluded from early reperfusion trials, therapy has been based on clinical

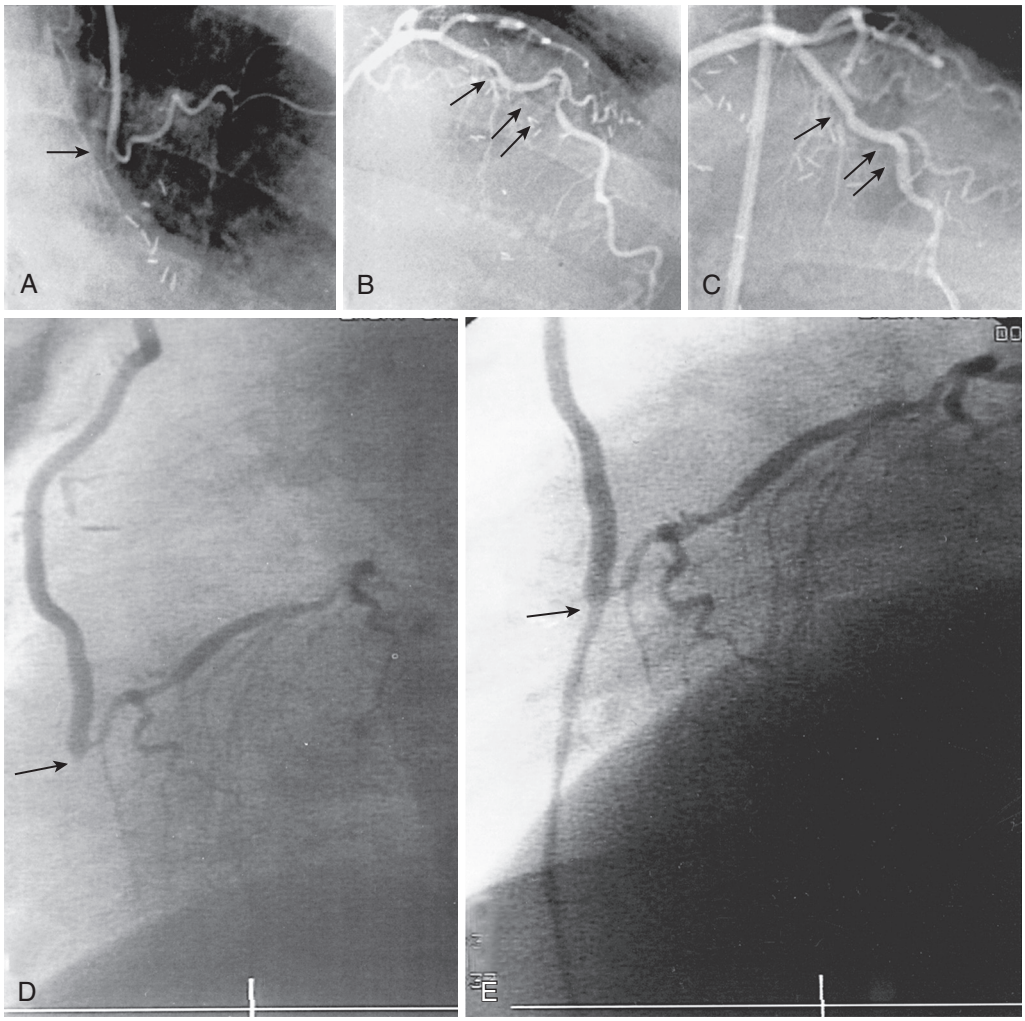


FIGURE 26-2 Two cases of failure of minimally invasive coronary artery bypass graft treated with percutaneous catheter-based intervention. *Case 1:* A 78-year-old woman underwent left internal mammary artery (LIMA) to left anterior descending (LAD) coronary artery surgery through a left fourth intercostal incision without cardiopulmonary bypass because of refractory angina and a long stenosis of a tortuous LAD. Angina at rest recurred within a few hours after surgery, and angiography on the second postoperative day revealed occlusion of the LIMA graft about 4 cm from its insertion into the LAD (**A,** *arrow*). The LAD was tortuous, with multiple, severe stenoses (**B,** *arrows*); left ventricular function was normal. Angioplasty and stent implantation in the native vessel yielded an excellent angiographic result (**C,** *arrows*) and favorable short-term follow-up. *Case 2:* Because of disabling angina and a long proximal LAD stenosis, a 60-year-old man underwent minimally invasive LIMA to LAD. About 2 hours after surgery, an electrocardiogram showed anterior ST-segment elevation, and emergency coronary arteriography revealed occlusion of the distal LAD at the graft insertion (**D,** left lateral view, *arrow*). Balloon angioplasty through the LIMA graft was successful (**E,** *arrow*), and the patient remained asymptomatic at 6-month follow-up.

experience and remains controversial. In a majority of patients, the culprit vessel has been found to be a vein graft, and considerable lesion-associated thrombus was a common accompaniment (see Fig. 26-6). Intravenous thrombolytic therapy is relatively ineffective in SVGs.[25] Most investigators currently favor emergency coronary arteriography if feasible and the option of more specific intervention, including thrombectomy and mechanical recanalization. Kahn and associates[26] reported their experience with 72 postbypass patients who underwent direct PCI without antecedent thrombolytic therapy. No urgent bypass operations, strokes, or transfusions were reported, and in-hospital survival was 90%. However, more recent reports indicate that both acute and long-term results of PCI in SVGs for treatment of STEMI are inferior to those of native vessel PCI for STEMI. In a study of 2240 consecutive patients with STEMI, Brodie and colleagues[27] observed that patients who underwent SVG PCI were sicker (had poorer LV function, more three-vessel disease, and prior MI) than patients who underwent native vessel PCI. Patients with SVG occlusion had lower rates of Thrombolysis in Myocardial Infarction (TIMI) grade 3 blood flow, higher in-hospital mortality (21% vs. 8%, $P = .0004$), and worse 10-year survival (49% vs. 76%, $P < .0001$). SVG patency was 64% at 1 year. Similar poor long-term outcomes were reported by other investigators.[28] In the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial, 90-day death was higher in patients who underwent SVG PCI (19% vs. 5.7%, $P = .05$).[29] In the Mayo Clinic STEMI experience, treatment of an SVG was independently associated with adverse cardiac events.[30] In a report of 192 post-CABG patients with acute MI, 30-day mortality with SVG PCI was significantly higher than that with native vessel PCI (14.3% vs. 8.4%, $P = .03$).[31] The ACC/AHA Task Force Report on Early Management of Acute Myocardial Infarction classified PCI for vein graft recanalization as a class IIa intervention: "acceptable, of uncertain efficacy and may be controversial; weight of evidence in favor of usefulness/efficacy."[32]

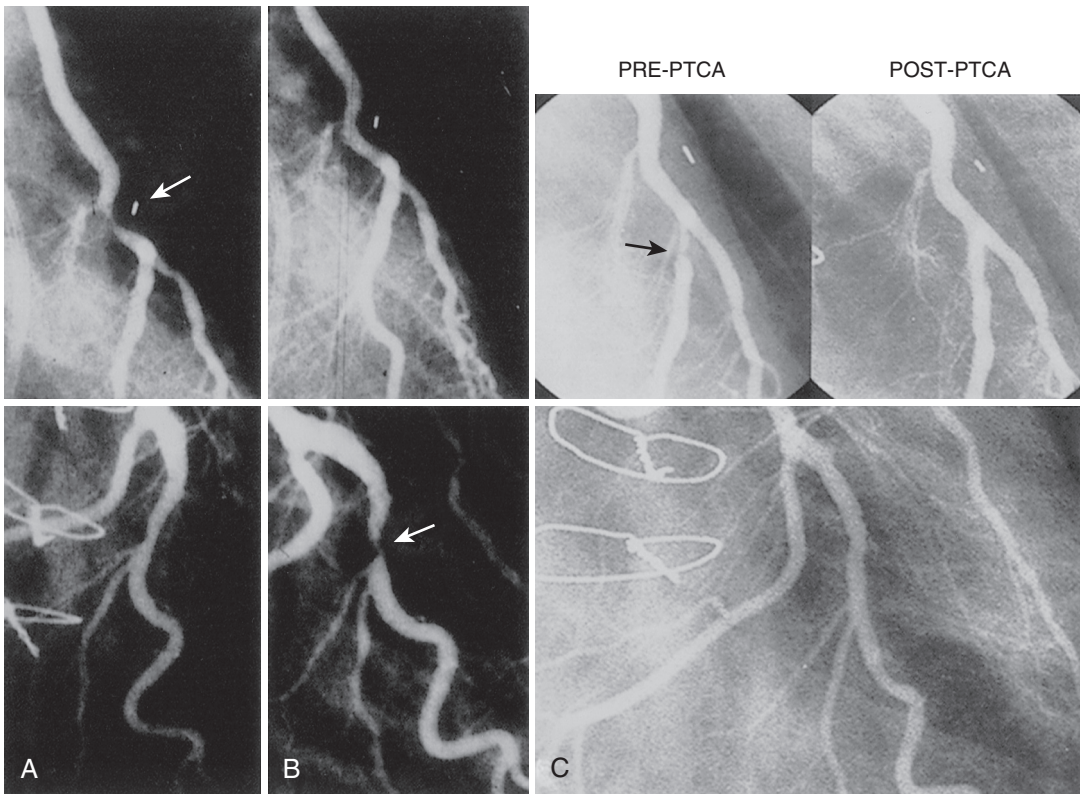


FIGURE 26-3 A 37-year-old woman had placement of saphenous vein grafts (SVGs) to the left anterior descending (LAD) and posterior descending coronary arteries. Unstable angina recurred 3 months later, and high-grade stenosis was present at the junction of the SVG to the LAD (**A,** *top: arrow*). The circumflex coronary artery had minimal disease (**A,** *bottom*). The SVG to the posterior descending coronary artery was patent, and balloon angioplasty of the distal anastomosis was successful. Disabling angina recurred 9 months following coronary artery bypass grafting (CABG). Coronary arteriography (**B,** *top*) showed a widely patent distal anastomosis but high-grade stenosis of the circumflex coronary artery (**B,** *bottom: arrow*) that was unresponsive to nitroglycerin. Balloon angioplasty of the circumflex stenosis was successful (residual stenosis 5%). Twelve years following CABG, angina recurred and recatheterization showed high-grade stenosis of the mid-LAD just beyond the takeoff of a large diagonal (**C,** *top left: arrow*); the vein graft to the posterior descending coronary artery was occluded. Previous percutaneous transluminal coronary angioplasty (PTCA) sites at the distal anastomosis of the vein graft to the LAD and the circumflex artery (**C,** *bottom*) were widely patent. Balloon angioplasty of the mid-LAD was successful. The patient remained asymptomatic for 4.5 years, when a new thrombotic stenosis in the midportion of the SVG to the LAD led to replacement of this graft with a left internal mammary artery (LIMA) graft. All prior PTCA sites were patent, and surgical benefit was extended over 16 years with three percutaneous procedures.

TECHNICAL STRATEGY

The postoperative patient offers unique challenges to the PCI operator. The selection of a guide catheter to achieve coaxial alignment and provide adequate back-up support is often the key to success. Figure 26-8 illustrates the shapes of guide catheters commonly used for vein graft interventions; 7-Fr catheters are favored for many vein graft procedures (for optimal visualization, to facilitate stenting, and to accommodate large balloons, stents, and embolic protection devices); covered stents are needed to treat bypass graft perforations. Although some have recommended routine use of slightly oversized balloons and stents for vein graft procedures, it is prudent to size balloons and stents no larger than the normal reference segment. This is especially true in older vein grafts, in which vein graft rupture has been reported with modest oversizing. In addition, Iakovau and colleagues[33] reported no benefit of oversizing with respect to target-vessel revascularization (TVR; 31% vs. 26%, $P = 0.3$), and MI was increased (29% vs. 17%, $P < 0.05$). Notably, Hong and colleagues[34] have reported favorable outcomes using undersized stents in SVGs. In general, most experienced operators stent from "normal to normal." When vein grafts that encircle the heart are encountered, or in the case of IMA grafts to far distal locations, balloon catheters with extra-long (145-cm) shafts or shorter guide catheters may be needed, or the guide catheter can be shortened and a flared, short sheath one size smaller can be used to close the cut end of the catheter. Embolic protection strategies, a class I indication in PCI guidelines for de novo SVG lesions, have been shown to reduce atheroembolic MI by approximately 50% (see below) and should be used routinely in PCI of de novo SVG lesions.

RESULTS OF INTERVENTION

Percutaneous Coronary Intervention Versus Reoperation

At Emory University between 1980 and 1994, a total of 2613 postbypass patients underwent catheter-based myocardial revascularization.[35] Compared with 1561 patients treated with reoperative surgery, in-hospital outcomes were more favorable for mortality (1.1% vs. 6.9%; $P < .001$), Q-wave infarction (1.4% vs. 5.4%; $P < .001$), stroke (0% vs. 2.8%; $P = .27$), length of stay (3.0 vs. 10.5 days; $P < .001$), and cost

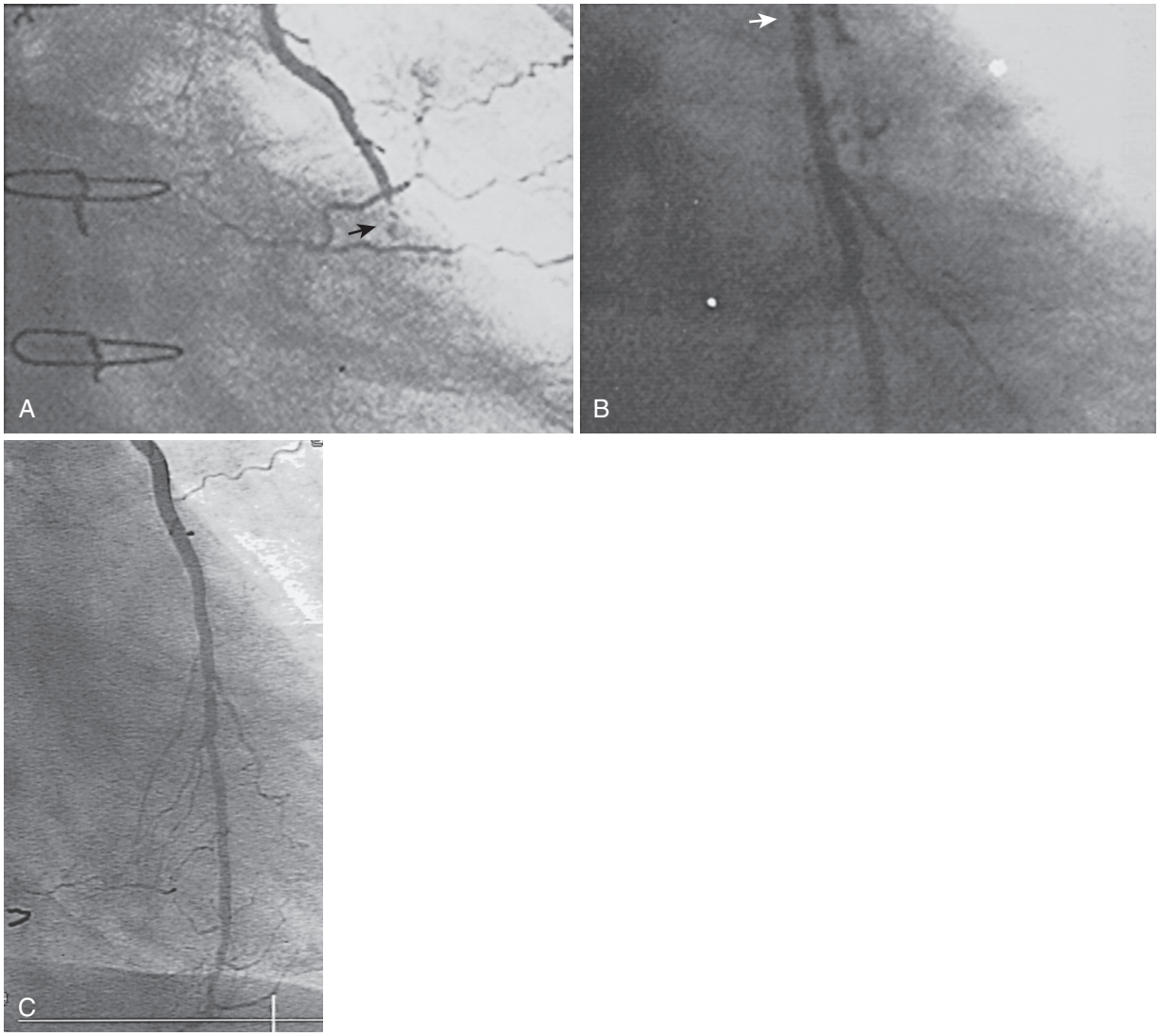


FIGURE 26-4 A 52-year-old man experienced recurrence of angina 5 months after triple coronary bypass. Coronary arteriography revealed total occlusion of the left internal mammary artery (LIMA) 1 to 2 cm proximal to insertion into the left anterior descending (LAD) coronary artery (**A,** *arrow*), severe stenosis of a large diagonal, and patent grafts to the obtuse marginal and right coronary arteries. The LIMA was recanalized by use of an 8-Fr internal mammary artery (IMA) guide catheter for good backup, progression to a relatively stiff guidewire to punch across the total occlusion, and a 2-mm over-the-wire balloon (result after percutaneous transluminal coronary angioplasty [PTCA]: **B,** *arrow*). The diagonal was successfully dilated. The patient presented again 5 years later with recurrent angina and was found to have an occluded saphenous vein graft to the obtuse marginal artery; the native obtuse marginal artery was successfully dilated. The LIMA-to-LAD anastomosis was widely patent (**C**), as was the diagonal, 5 years after recanalization.

($8500 vs. $24,200; $P < .01$); in-hospital CABG was required in 2.9% of angioplasty patients. Ten-year survival was better in the angioplasty group. By 5 years, approximately 50% of the angioplasty patients required either repeated PCI or CABG, and survival was better in patients who underwent native vessel, compared with graft, interventions—an observation *not* confirmed in the Mayo Clinic experience after correction for baseline differences.[5] In 2191 post-CABG patients who underwent multivessel revascularization at the Cleveland Clinic between 1995 and 2000, a total of 1487 had reoperation and 704 had PCI.[8] Initial outcomes were more favorable with PCI for completeness of revascularization, 30-day mortality, periprocedural Q-wave infarction, and stroke. At 5 years, unadjusted survival was 79% for CABG and 75% for PCI ($P = .008$). The only randomized comparison of PCI and CABG in postbypass patients was reported by Morrison and colleagues,[36] who randomized 143 patients (67 to PCI and 75 to CABG). At 3 years, survival was approximately 75%, comparable to the 5-year survival in the Cleveland Clinic study; no significant advantage of one procedure over the other was apparent. An Emory University experience with 1712 diabetic patients who required repeat revascularization between 1985 and 1999 (1123 with PCI, 589 with reoperation) indicated relatively poor long-term outcomes. Survival at 5 years with PCI and reoperation was about 60%.[37] Data from the STS registry shows an increasing use of PCI as the revascularization strategy of choice as the patient's age increases.[6]

Vein Graft Intervention

Although the benefit of PCI for native vessel stenoses has been firmly established and even enhanced with drug-eluting stents, conduit lesion interventions have been more controversial. Guideline statements[16,17]

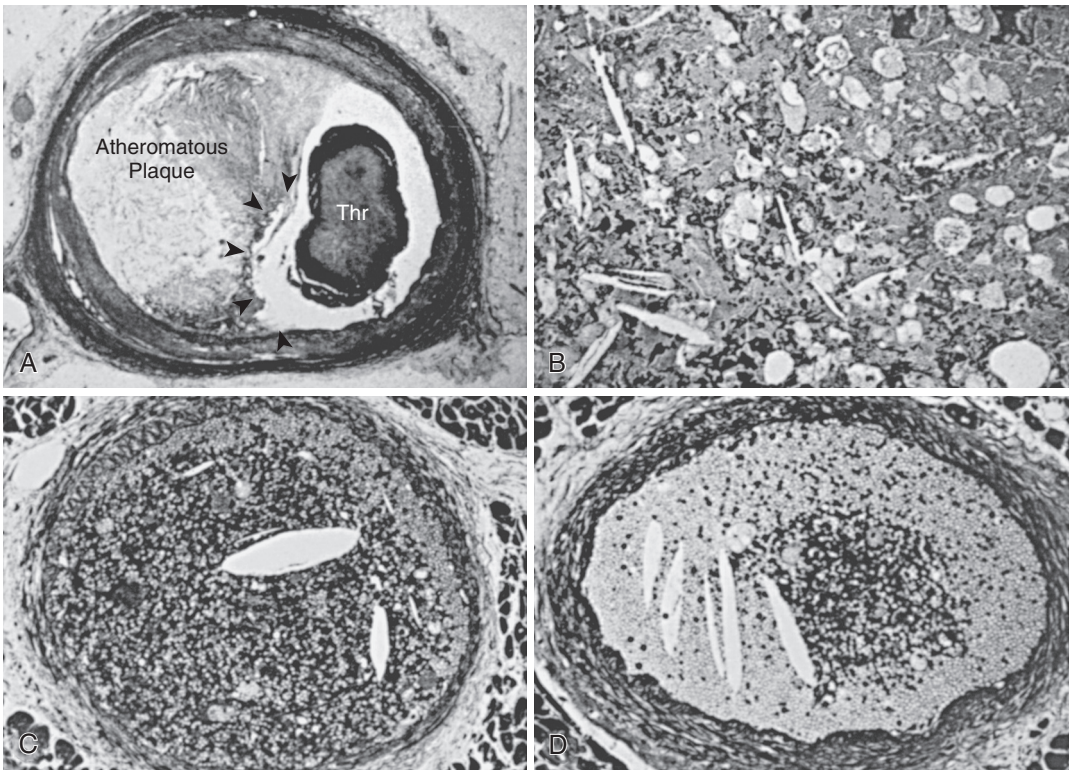


FIGURE 26-5 Vein graft. **A,** Low-power photomicrograph shows rupture (*arrowheads*) of atheromatous plaque caused by balloon angioplasty and secondary thrombosis (Thr). Sections taken at adjacent sites were involved by such extensive disruption that luminal boundaries were obliterated. **B,** High-power photomicrograph demonstrates the nature of the plaque, with foam cells, cholesterol clefts, blood elements, and necrotic debris. **C** and **D,** Intramural coronary artery branches. Atheromatous emboli obstruct vessels in anterolateral (**C**) and inferoseptal (**D**) walls of left ventricle (compare with **B**). (From Saber RS, Edwards WD, Holmes DR Jr, et al: Balloon angioplasty of aortocoronary saphenous vein bypass grafts: a histopathologic study of six grafts from five patients, with emphasis on restenosis and embolic complications. *J Am Coll Cardiol* 1988;12: 1501-1509.)

and appropriate use criteria[38] encourage the use of PCI in early graft failure but are less supportive of PCI in vein grafts in place for more than 3 years because of the risk of embolic MI and poor durability. Vein graft intervention is a class IIa indication for patients with severe symptoms, good LV function, and patent arterial grafts and for patients who are poor candidates for reoperation. Criteria for determining whether a vein graft stenosis is "significant" are similar to those for native vessel lesions, but the use of fractional flow reserve (FFR) has not been studied in this setting. Because progression of atherosclerosis in SVGs exceeds that in native coronary arteries, some operators have been more aggressive in SVGs. Two observations support this line of thinking. Ellis and colleagues[39] noted that patients with moderate, untreated stenoses in SVGs had a much higher late cardiac event rate than patients without (45% vs. 2%). And in a pilot trial of 57 patients randomized to drug-eluting stent implantation in intermediate SVG lesions (30% to 60%) or medical therapy alone, Rodes-Cabau and associates[40,41] reported a lower rate of adverse cardiac events out to 3 years in stent-treated patients. A larger, prospective randomized trial is currently in progress to test this hypothesis.

Bare-Metal Stents Versus Balloon Angioplasty in Vein Grafts

In the first reports of balloon angioplasty in SVGs, Grüntzig noted a higher than expected restenosis rate,[2] and subsequent experiences confirmed this finding.[3,4] Initial success rates of balloon angioplasty were higher in relatively ideal SVG lesions that were discrete and free of thrombus, but non–Q-wave MI occurred in 13% of 599 consecutive patients at Emory. Restenosis occurred in 68% of proximal lesions, 61% of mid-vein graft lesions, and 45% of distal lesions.

Many different stent designs have been used in SVGs. In early experience, the self-expanding Wall stent resulted in successful deployment in more than 95% of patients, but stent thrombosis was reported in up to 10% and restenosis in up to 50%. Use of the Palmaz-Schatz coronary stent in SVGs was reported in observational registries, nonrandomized comparative studies, and a randomized trial comparing balloon angioplasty with stents. A total of 220 patients with new SVG lesions and angina pectoris or objective evidence of myocardial ischemia were randomly assigned to implantation of Palmaz-Schatz stents or standard balloon angioplasty in the Saphenous Vein De Novo (SAVED) trial.[42] Patients with lesion length greater than two stents, MI within 7 days, or evidence of intragraft thrombus were excluded. Stented patients received warfarin anticoagulation. Patients assigned to stenting had a higher rate of procedural efficacy, defined as a reduction of stenosis to less than 50% of the vessel diameter with the assigned therapy, than did those assigned to angioplasty (Fig. 26-9), but they experienced more hemorrhagic complications resulting from warfarin anticoagulation. In-hospital complications were otherwise similar in the two groups, although a trend was observed toward fewer non–Q-wave infarctions in the stent group. Whether stents have a significant effect in reducing particulate matter embolization is not certain, but it is a possible explanation for this trend. Restenosis occurred in 37% of the stented patients and in 46% of the angioplasty group ($P = 0.24$). Late lumen loss was significantly greater in patients who received high-pressure (≥16 atm) stent expansion, suggesting that routine high pressure may be undesirable in an SVG stenting. The outcome in the

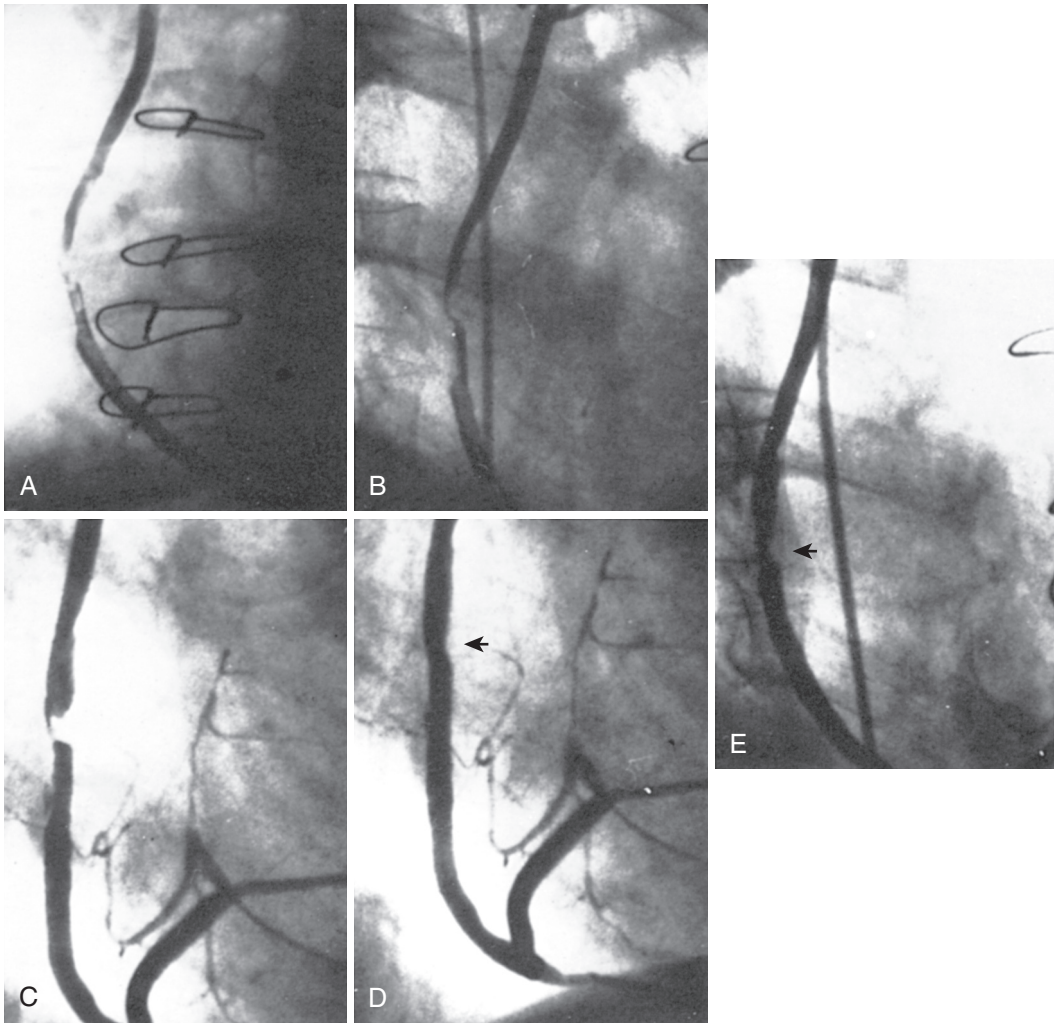


FIGURE 26-6 A 59-year-old man developed unstable angina 10 years after coronary bypass surgery. **A,** Coronary arteriography revealed high-grade stenosis with thrombus and poor flow in a sequential saphenous vein graft (SVG) to the posterior descending and circumflex coronary arteries. No narrowing was present in the left anterior descending coronary artery, diagonal, and large anterior marginal systems. The inferior left ventricular wall was moderately hypokinetic. **B,** After infusion of thrombolytic agent into the graft for approximately 1 hour, flow improved and thrombus was diminished. The patient was maintained on intravenous heparin for 5 days. **C,** Coronary arteriography then showed that an eccentric, high-grade focal stenosis was present in the proximal SVG to the right coronary artery without thrombus. **D,** After placement of a 4.0-mm stent (*arrow*), the patient became asymptomatic. **E,** Recatheterization 6 months later revealed excellent patency of the SVG with mild narrowing of approximately 40% at the stent site (*arrow*). At last follow-up 10 months after intervention, the patient remained asymptomatic. The current availability of thrombectomy and embolic protection make a more direct approach with thrombectomy appealing in some similar patients with extensive SVG thrombus.

SAVED trial with respect to freedom from death, MI, repeated bypass surgery, or revascularization was significantly better in the stent group (73% vs. 58%; $P = .03$). The lack of a significant difference in restenosis rates in the treatment groups was due to the greater late lumen loss in the stent group and the small sample size.

Several centers have reported outcomes of more contemporary SVG interventions, but these studies were performed prior to embolic protection and drug-eluting stents. Comparing outcomes of patients from 1990 through 1994 with those from 1995 through 1998, Hong and colleagues[43] reported similar initial success rates but improved 1-year event-free survival in the more recent experience (71% vs. 59%; $P < .0001$) and lower late mortality (6.1% vs. 11.3%; $P < .0001$) and a protective effect of stent implantation in both time periods. Five-year outcome data from Emory University in 2556 patients who underwent PCI of SVGs emphasized the poorer outcome of diabetic compared with nondiabetic patients with respect to both survival and event-free survival (Fig. 26-10, *A* and *B*).[44] When only the patients who received bare-metal stents were considered, in-hospital outcomes among diabetic and nondiabetic patients were not significantly different, but survival was worse in diabetic patients. Kaplan-Meier survival curves for bare-metal stenting are shown in Figure 26-10, *C*.

Drug-Eluting Stents in Vein Grafts

Although bare-metal stents improve the initial and intermediate-term outcomes of SVG PCI, the impact is modest owing to restenosis and disease progression. A number of published reports of the use of drug-eluting stents (DESs) in SVGs have shown conflicting results, leading some to question their use for this indication.[45] In the first of three randomized comparisons of DESs with bare-metal stents (BMSs) in

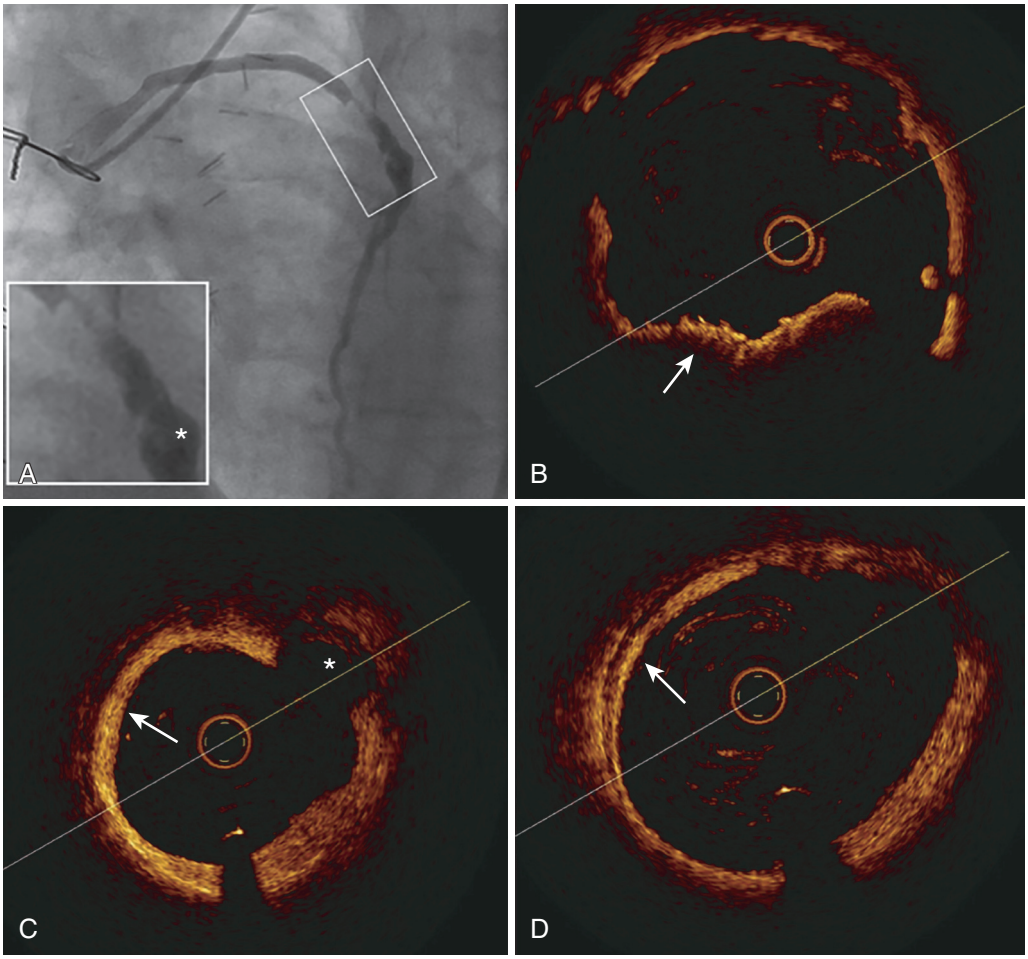


FIGURE 26-7 Angiography and optical coherence tomography (OCT) of a saphenous vein graft (SVG) lesion in a patient with non–ST-segment–elevation myocardial infarction. **A,** Angiography of an SVG to left anterior descending (LAD) coronary artery with severe narrowing and thrombus (*white box*). Plaque ulceration with a flap is shown in the magnification (*). **B,** OCT at the site of the lesion reveals red thrombus (*arrow*). **C,** Intimal rupture with a large cavity underneath (*) is also apparent. In **C** and **D,** *arrows* point to a signal-rich layer, under which a signal-free layer is evident that separates the former from the SVG wall. In all OCT frames, fibrofatty composition of the intima is evident. (From Davlouros, P, Damelou A, Karantolis V, et al: Evaluation of culprit saphenous vein graft lesions with optical coherence tomography in patients with acute coronary syndromes. *J Am Coll Cardiol Interv* 4:683-693, 2011.)

SVGs, Vermeersch and coworkers[46] implanted sirolimus-eluting stents (SESs) in 38 patients and BMSs in 37. At 6 months, patients who received SESs had less restenosis (14% vs. 33%, $P = .03$) and target-lesion revascularization (TLR; 5% vs. 22%, $P = .047$) but similar rates of death and MI. At a median follow-up of 32 months, "late catch-up" had occurred, and TVR rates were comparable.[47]

A second randomized trial compared the outcomes of 41 patients treated with paclitaxel-eluting stents (PESs) with 39 treated with BMSs. Angiographic restenosis at 1 year occurred in 57% of BMS-treated SVGs and in 11% of PES-treated SVGs ($P < .0001$), and TLR was significantly less common with a PES at 1.5 years (5% vs. 28%, $P = .003$).[48] Several observational registries have reported outcomes of SVG stenting in larger groups of patients followed for up to 3 years. These reports suggest that DESs are safe in SVGs but that benefit in terms of reduced restenosis and need for repeat revascularization during the first year may be lost at 2 to 3 years. In the largest of these studies, the benefit of lower TVR rates at 9 months was confined to patients with an SVG diameter less than 3.5 mm.[49] Several meta-analyses that have compared the use of DESs and BMSs in saphenous vein grafting have also been published. One summarized 20 studies of over 5000 patients and reported a 36% decrease in major adverse cardiac events (MACEs) related to DES use.[50]

The third randomized comparison of DES and BMS use in saphenous vein grafting, the Drug-Eluting Versus Bare-Metal Stents in Saphenous Vein Graft Lesions (ISAR-CABG) study, is the first powered for clinical end points.[51] In this superiority trial, 610 patients were randomly assigned to receive a BMS or one of three DESs. The primary end point—the combined incidence of death, MI, and TVR at 1 year—was reduced significantly by DES use (15% vs. 22%, $P = .02$) as was TLR (7% vs. 13%, $P = .01$). No differences were observed in death, MI, or stent thrombosis (Fig. 26-11). Seventy-two percent of patients underwent routine follow-up angiography at a median of 6.7 months, and less restenosis (15% vs. 29%, $P < .0001$) and graft occlusion (6% vs. 12%, $P = .008$) were noted in DES-treated patients. Of interest, the 36% reduction in the 1-year MACE rate reported in this study was the same as that reported in the cited meta-analysis[50] and large registry.[49] Clearly, longer-term follow-up of the ISAR-CABG randomized patients will be important. A recently published study from the Western Denmark Registry indicated that at 3 years, DES use in SVGs showed no benefit compared with BMS use with respect to death or stent

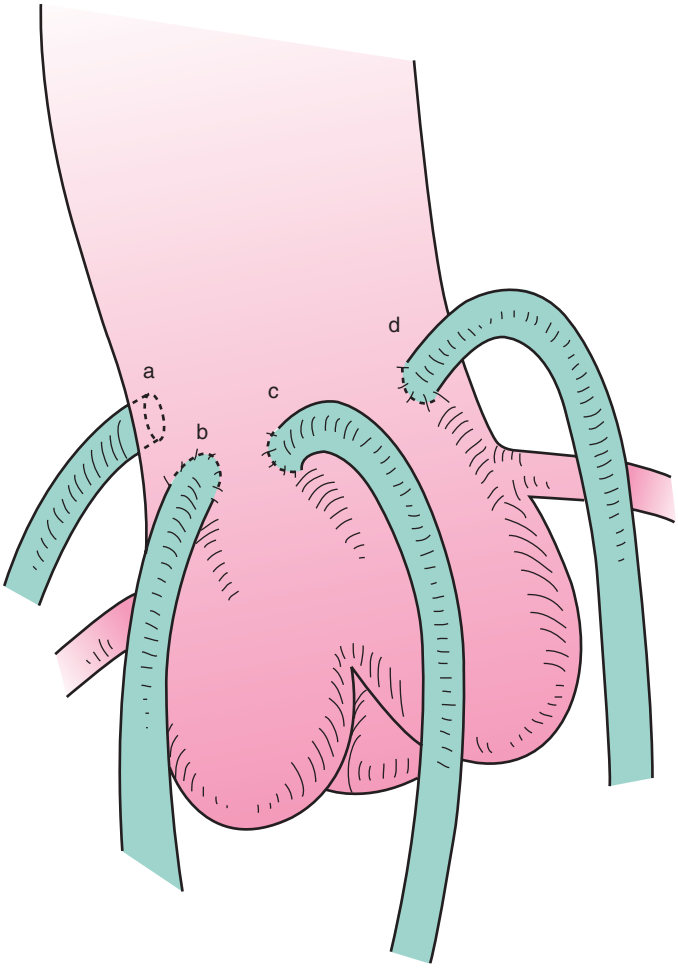


FIGURE 26-8 Selection of guide catheters in vein graft angioplasty: *a,* multipurpose shape; *b,* multipurpose, right Judkins; *c,* hockey stick, left Amplatz, right Judkins; *d,* hockey stick, left Amplatz. Obtaining adequate backup becomes more difficult in positions c and d.

failure.[52] It has been suggested that the delayed healing observed following DES implantation compared with BMS use in SVGs may contribute to a higher rate of late cardiac events or a "catch up" with DES.[53]

The clinical and pathology studies noted earlier relate to the use of first-generation DESs, whereas virtually all DESs implanted in SVGs today are second-generation DESs that have been shown to be superior in native coronary arteries. Few data are currently available regarding outcomes following use of second-generation DESs in SVGs. In a single-center observational study, Kitabata and associates[54] compared the outcomes of 88 patients treated with second-generation everolimus-eluting stents (EESs) with 243 patients treated with sirolimus-eluting stents (n = 212) or PESs (n = 105). Two-year outcomes were better in EES-treated patients with respect to MACEs (18% vs. 35%, P = .003), TVR (6.8% vs. 25%), P < .001), and TLR (1% vs. 12%, P = .005). DES type was an independent predictor of MACEs. Nevertheless, the nonrandomized nature of this study, inherent selection bias, possible underreporting of outcomes, lack of power for clinical outcomes, and temporal differences in entry time limit the value of these observations.

The data at present indicate that DESs in SVGs are safe; the occurrence of death or MI is equal or less than with BMSs, and no difference is apparent in the rate of stent thrombosis. The 2011 PCI guidelines support the use of DESs in SVGs.[55] Choosing DESs over BMSs for the treatment of SVG stenoses must depend on the ensurance of reliable dual-antiplatelet therapy (DAPT) and must be favored in SVGs less than 3.5 mm in diameter and in patients at high risk for restenosis (those with long lesions or diabetes). A survey published in 2012 found that about two thirds of interventionalists preferred DESs in SVGs.[56] The significant occurrence of adverse cardiac events after SVG stenting (annual mortality of 5% to 10%, SVG occlusion in 15%) indicates a need for native vessel PCI whenever possible.

Embolic Protection

Recent attention has refocused on the importance of periprocedural elevations of creatine kinase myocardial band (CK-MB) and troponin, which indicate myocardial necrosis most often as a result of atheroembolism. Even when mostly straightforward, single-lesion, single-stent SVG PCI procedures were carried out prior to the availability of embolic protection, significant CK elevations were noted in 20% of patients (see Fig. 26-5). The rate of MI and procedural risk were shown to increase with lesion complexity, length, and estimated plaque volume.[57] In over 1000 patients who underwent SVG stenting, CK-MB elevation was the most powerful predictor of late mortality. The key role played by atheroembolization and confirmation of effective protective strategies were the products of several observational and randomized studies.[58] The GuardWire system (Medtronics, Minneapolis, MN [no longer available]) utilized a hollow 0.014-inch wire incorporating a compliant, inflatable distal occlusion balloon. During inflation of the distally placed balloon, flow in the graft was interrupted; the stent was then implanted, followed by aspiration of the graft using a special monorail catheter and deflation of the balloon to restore flow. The effectiveness of this strategy in a broad range of patients was confirmed in the Saphenous Vein Graft Angioplasty Free of Emboli Randomized (SAFER) trial,[59] in which 801 patients were randomly assigned to stent implantation with or without use of the GuardWire distal protection device. This study is the only randomized controlled trial of embolic protection. Thirty-day MACEs were reduced by 42% with use of embolic protection (16.5% to 9.6%, P = .004) primarily because of the lower rates of MI. This system, frequently applicable even in the presence of severe stenosis owing to its relatively low profile, captured small particles and soluble vasoactive agents such as endothelin, serotonin, and a variety of coagulation components that have been shown to be liberated during SVG PCI.[60] Analysis of the benefit of embolic protection in relation to lesion length in SAFER showed that even with lesions less than 10 mm in length, a 77% reduction in 30-day MACEs was experienced (2.2% vs. 8.1%). The use of this system increased costs at 30 days by less than $650 per patient, with a cost-effectiveness ratio of $3700 per year of life, making it highly cost-effective. Disadvantages of this form of embolic protection include the need to completely occlude the target SVG during stent deployment and aspiration (not always well tolerated), a requirement for a relatively long "parking" segment distal to the lesion, inability to protect side branches, and the complexity of the system.

A variety of filters have been applied to SVG interventions, and filters have become the only form of embolic protection currently available (Fig. 26-12). In a 651-patient randomized multicenter trial, the FilterWire (Boston Scientific, Natick, MA) was compared with the GuardWire. The 30-day MACE rate, the primary end point, was similar—9.9% with the FilterWire compared with 11.6% with the GuardWire—and no difference was seen in rates of death or MI.[61] Some of the advantages of filters include ease of use, avoidance of ischemia because of preserved coronary flow, and good visualization. Disadvantages include the need to cross the lesion with a somewhat bulky filter, which may require predilation and could cause embolization; these sequelae have been shown to increase the occurrence of Q-wave MI. In addition, some material may not be captured, including particles smaller than the 100-micron pore size and soluble agents. The former may not be relevant based on studies reporting that filtering was just as efficient as balloon occlusion in particle capture despite pore sizes larger than the majority of embolic particles. Other problems with filters include the long distal parking segment required and the

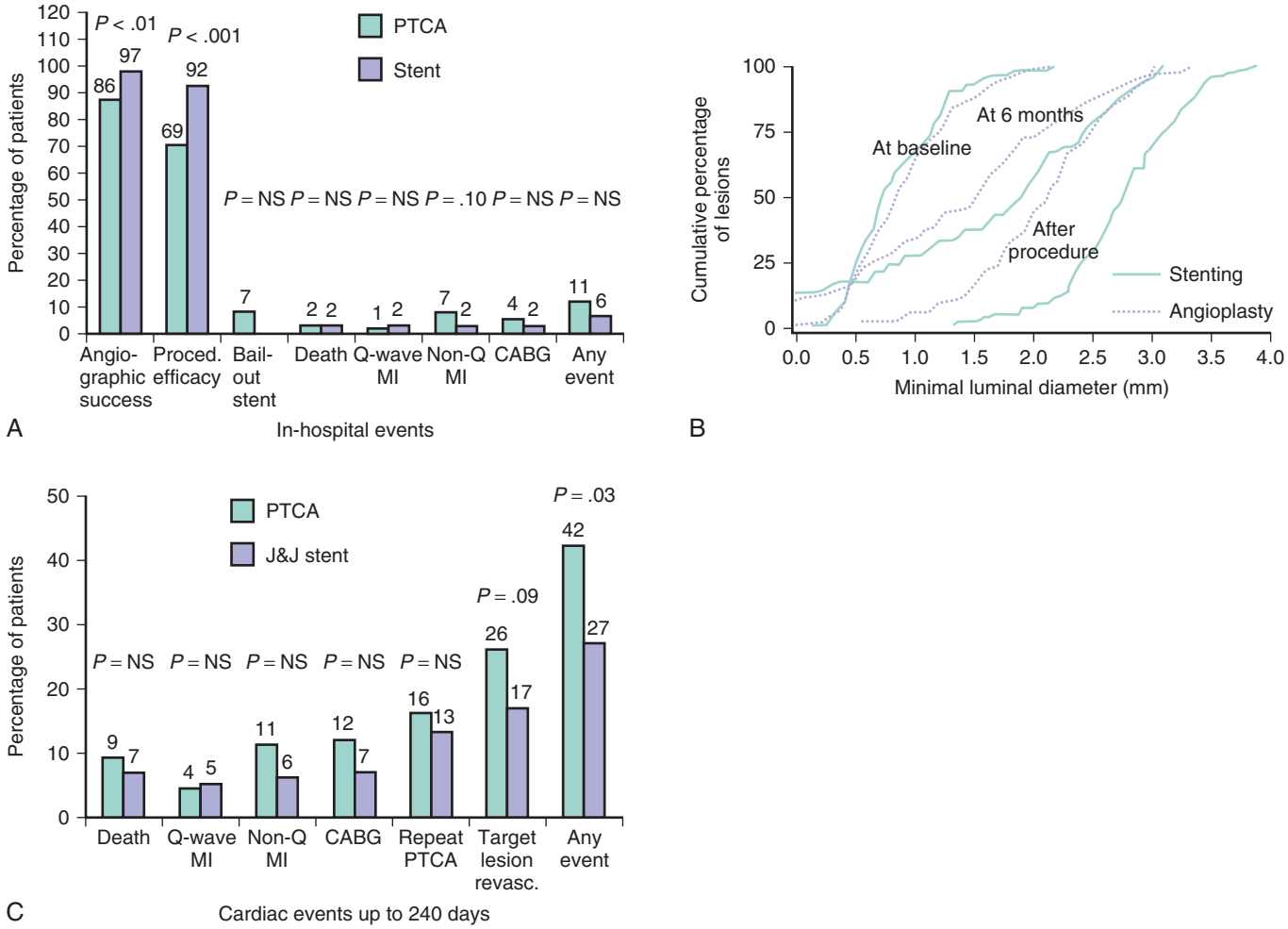
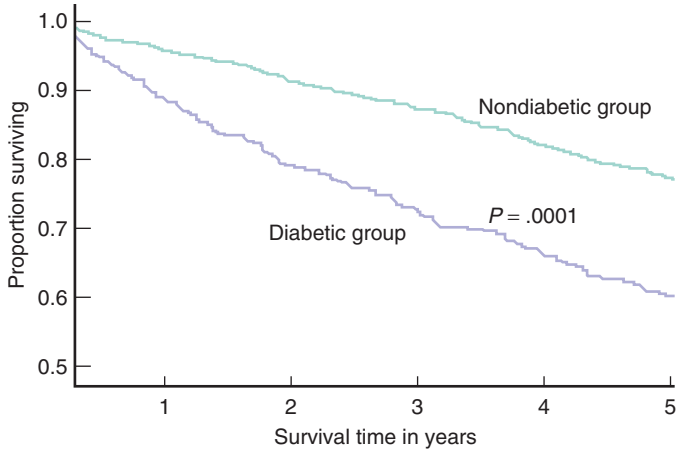


FIGURE 26-9 Results from the SAVED trial, a randomized comparison of Palmaz-Schatz stenting and standard balloon angioplasty. **A,** Stents were associated with a higher procedural success rate, whereas other in-hospital events were similar. **B,** The minimal luminal diameter at 6 months was larger in the stent group (1.73 vs. 1.49 mm; $P = .01$). **C,** Late cardiac events were significantly more common in patients in the percutaneous transluminal coronary angioplasty (PTCA) group. *CABG,* Coronary artery bypass grafting; *MI,* myocardial infarction. (From Savage MP, Douglas JS Jr, Fischman DL, et al: Stent placement compared with balloon angioplasty for obstructed coronary bypass grafts. Saphenous Vein De Novo Trial Investigators. *N Engl J Med* 337:740-747, 1997.)

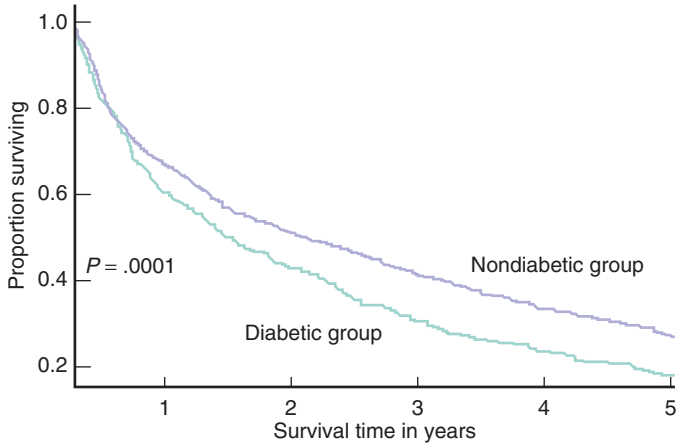
potential for overwhelming the filter, resulting in diminished antegrade flow that mimics the no-reflow phenomenon. Should this occur, the optimal strategy is to aspirate the stagnant dye column—which may contain suspended debris—followed by filter removal and replacement if more interventional work is needed. Unfortunately, a proximal protection device, applicable in patients with an inadequate "landing zone" beyond the lesion, is no longer available. When proximal protection was compared with either the FilterWire or GuardWire in a randomized trial, the rate of MACEs was comparable (9.2% vs. 10%, P = nonsignificant [NS]).[62] A number of filters are currently available that appear to be equally effective.

Expanding on the work of Liu and colleagues,[57] in an analysis of SVG stenting in 3958 patients from six studies, angiographic variables were found to be potent predictors of 30-day MACEs.[58] SVG degeneration score and large estimated plaque volume were the most potent predictors; thrombus, advanced patient age, and active tobacco use also contributed. When the occurrence of MACEs was analyzed relative to degeneration score or plaque volume, the use of embolic protection had similar relative treatment benefit across all categories of risk. The almost halving of MACE associated with embolic protection across all risk strata strongly supports its routine use in all PCIs of old SVGs. This contrasts sharply with the observation that embolic protection was used in only 22% of almost 20,000 patients who underwent SVG PCI in the National Cardiovascular Data Registry (NCDR) in spite of a class I indication for the use of embolic protection in SVGs in the PCI guidelines statements.[16,17,55,63] It is of interest that in the important ISAR-CABG study, in which 610 patients underwent SVG stenting, embolic protection was used in a minority of patients (<5%), and the 30-day MACE rate was low (4%).[51] The very selective use of embolic protection with favorable outcomes suggests that patient selection and management strategies and more effective pharmacotherapy may all be contributing. The fact that 40% of patients in the control arm of SAFER underwent postdilation with a mean balloon size of 4.2 mm (mean reference vessel diameter of the entire group was 3.4 mm) may be one example of a change in technique that has occurred. Clinical scenarios in which embolic protection may be expected to have little impact include lesions with very little plaque volume, in-stent restenosis lesions in which neointimal hyperplasia is the predominant pathology, and lesions that occur less than 3 years after CABG. The use of filters during stent implantation in ostial SVG lesions has been associated with serious complications due to difficulty in filter retrieval.[64] (see Chapter 29 for more information on embolic protection).



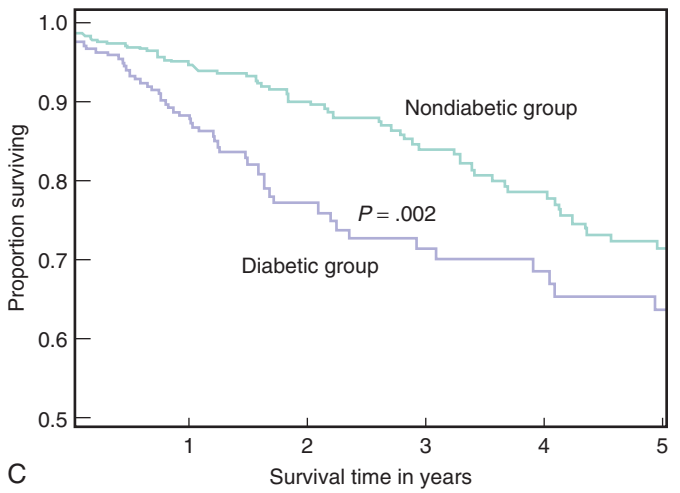
A

Survival time	1-yr	2-yr	3-yr	4-yr	5-yr
Diabetic group	0.88	0.80	0.73	0.68	0.63
Nondiabetic group	0.95	0.91	0.87	0.83	0.79



B

Survival time	1-yr	2-yr	3-yr	4-yr	5-yr
Diabetic group	0.58	0.45	0.33	0.28	0.23
Nondiabetic group	0.64	0.53	0.43	0.37	0.31



C

FIGURE 26-10 **A,** Kaplan-Meier curves show survival free of death in 2556 patients who underwent percutaneous coronary intervention (PCI) at Emory University Hospital, comparing 5-year outcomes of patients without diabetes with those with treated diabetes. **B,** Kaplan-Meier curves show survival free of death, myocardial infarction (MI), or repeat revascularization. **C,** Kaplan-Meier curves show survival free of death in 1045 patients who underwent bare-metal stent implantation in saphenous vein grafts. (From Ashfaq S, Ghazzal Z, Douglas JS, et al: Impact of diabetes on five-year outcomes after vein graft intervention performed prior to the drug-eluting stent era. *J Invasive Cardiol* 18:100-105, 2006.)

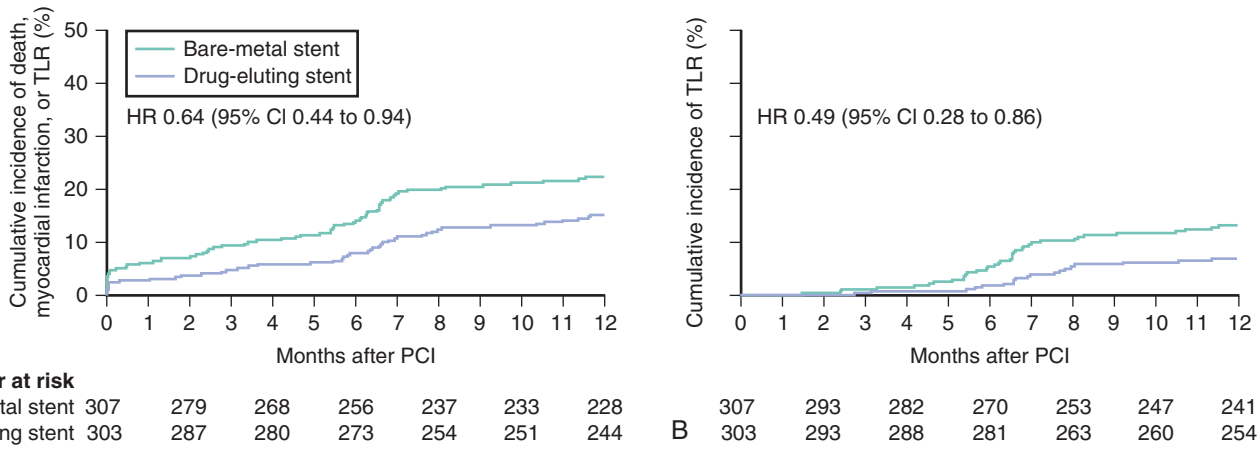
Adjunctive Pharmacotherapy

Accepted adjunctive therapy during PCI of native vessels and SVGs includes antithrombotic measures—aspirin, antithrombin, other antiplatelet agents—and vascular dilators as needed for the prevention and treatment of slow or no reflow. Unfractionated heparin was used in the vast majority of SVG studies reported. Among the 403 SVG patients in the first and second Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE) trials randomized to heparin or bivalirudin, logistic regression analysis revealed no difference in the combined end point—death, MI, urgent revascularization, or major bleeding—but less minor bleeding was observed with bivalirudin.[65] A somewhat increased risk of perforation with SVGs makes the use of bivalirudin, which is not reversible, less appealing in this group of patients; however, bivalirudin may be the best choice in certain patients with high bleeding risk. Optimal dosing and duration of DAPT following SVG PCI have not been well studied. Most operators recommend a bolus of 600 mg of clopidogrel prior to SVG PCI followed by a dose of 75 mg daily for at least a year. A recently published cohort study of 411 post-SVG PCI patients who were event free at the time of clopidogrel cessation revealed a clustering of death or MI within 90 days. The cumulative 5-year event rate was lowest in patients treated with clopidogrel for more than 2 years ($P < .001$), which supports long-term DAPT following SVG PCI.[66]

The relatively large embolic burden encountered in SVG procedures provides some explanation of the failure of GP IIb/IIIa platelet receptor inhibitors to prevent periprocedural MI in these patients.[57-60,67,68] When data from five large trials—Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC), Evaluation of Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome With Abciximab GP IIb/IIIa Blockade (EPILOG), Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT), Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT II), and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT)—with a total of over 600 SVG PCI patients and data from the Cleveland Clinic registry were analyzed, there was no apparent benefit from GP IIb/IIIa inhibitors.[68] In a trial of filter-based embolic protection, use of GP IIb/IIIa inhibitors was associated with lower MACE rates but increased bleeding.[69] In spite of the class III recommendation in the 2011 PCI guidelines for the use of GP IIb/IIIa inhibitors in SVG PCI, selective use in certain patients with significant thrombus burden may be indicated.[55] The use of microvascular dilators to treat no or slow reflow following PCI, or their use prophylactically before the procedure, has not been well studied but is an important strategy in SVG PCI (see the discussion of the no-reflow phenomenon in that section below).

Restenosis Lesions in Saphenous Vein Grafts

The management of patients with restenosis of SVG stent sites is a topic of considerable interest and a significant clinical problem. As is true in native coronary intervention, treatment of in-stent restenotic lesions in SVGs is safer than treatment of de novo SVG lesions primarily



Number at risk

A	Bare-metal stent	307	279	268	256	237	233	228
	Drug-eluting stent	303	287	280	273	254	251	244
B	Bare-metal stent	307	293	282	270	253	247	241
	Drug-eluting stent	303	293	288	281	263	260	254

FIGURE 26-11 One-year cumulative rates of outcomes in patients assigned to receive drug-eluting or bare-metal stents. Kaplan-Meier curves are shown. **A,** The primary end point: composite of death, myocardial infarction, and ischemia-driven target-lesion revascularization (TLR). **B,** The secondary efficacy end point of ischemia-driven TLR. *CI,* Confidence interval; *HR,* hazard ratio; *PCI,* percutaneous coronary intervention. (From Mehili, J, Pache J, Abdel-Wahab, et al: Drug-eluting versus bare-metal stents in saphenous vein graft lesions [ISAR-CABG]: a randomized controlled superiority trial, *Lancet* 378:1071-1078, 2011.)

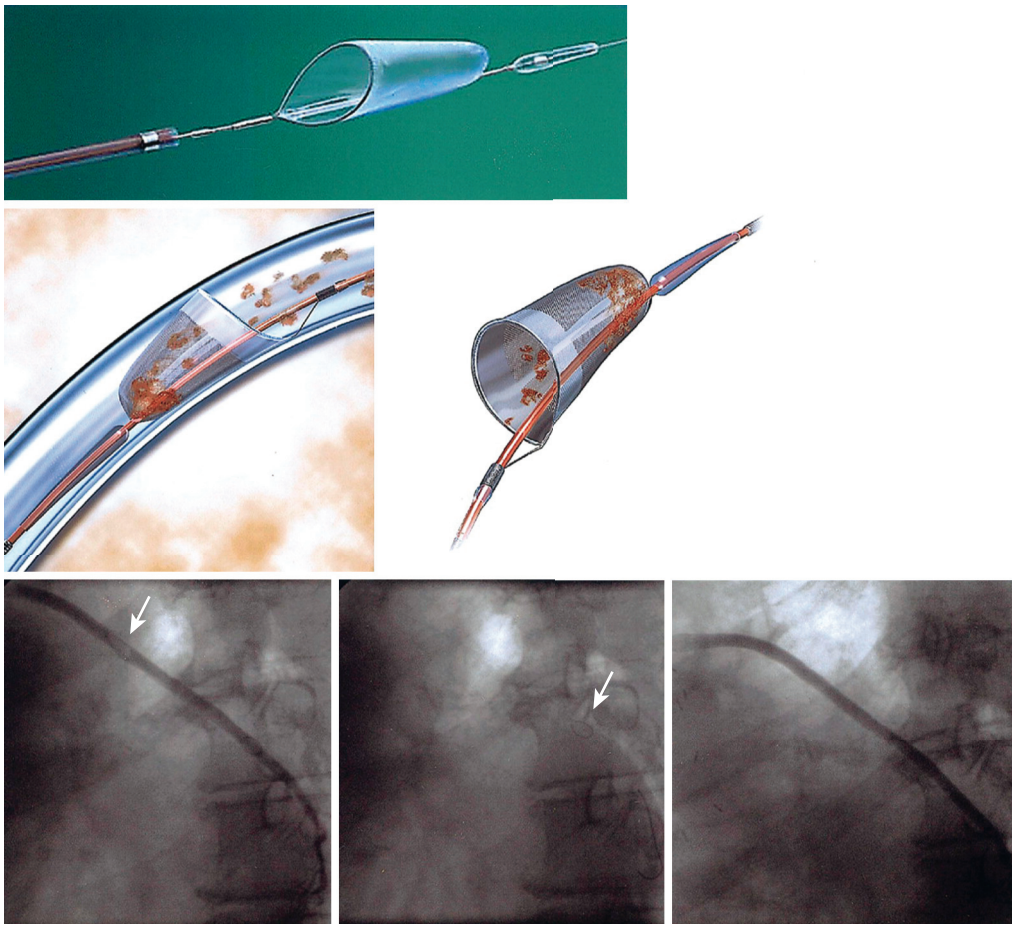


FIGURE 26-12 The FilterWire. *Top panel:* The polyurethane nonocclusive filter with 110-micron pore size mounted on a nitinol loop fixed to a guidewire. *Middle, left panel:* The filter is deployed distal to the lesion and the nitinol is expanded to the size of the vessel (3.0 to 5.5 mm). *Middle, right panel:* Filter is removed with a large embolic load. *Bottom, left panel:* Thrombus containing saphenous vein graft (SVG) lesion. *Bottom, middle panel:* Deployed filter. *Bottom, right panel:* Excellent result after stenting. (From Gorog DA, Foale RA, Malik I, et al: Distal myocardial protection during percutaneous coronary intervention. When and where? *J Am Coll Cardiol* 46:1434-1445, 2005.)

because of reductions in slow or no reflow and periprocedural MI. In-stent restenosis lesions are a subset in which embolic protection can often be omitted because the pathology is mostly neointimal hyperplasia. In a double-blind randomized trial that included 120 patients with in-stent restenosis who received gamma radiation with Iridium-192 or placebo, Waksman[70] reported significantly lower restenosis in the irradiated group at 6 months compared with the control group and noted a 79% reduction in the need for repeat intervention. However, intracoronary brachytherapy is not currently available in most centers, and DESs have become the default strategy in spite of a paucity of data to support this application.

Total Occlusion of Saphenous Vein Grafts

Considering the relatively poor results of PCI in SVGs with focal stenoses, it is not surprising that complete occlusion with attendant large clot burden is hugely problematic. In the setting of STEMI and newly formed thrombus, results are suboptimal (see above); and as acuity wanes, thrombus resistance heightens, making revascularization extremely challenging. In the subacute setting, thrombectomy (aspiration or rheolytic) with or without balloon angioplasty plus a strategy to dissolve thrombus (local or systemic GP IIb/IIIa or lytic agents, prolonged anticoagulation) achieved reasonable initial success in small cohort studies. Delaying stent implantation for days or weeks until the thrombus burden had largely resolved was the principal strategy in most reports,[71-72] and use of embolic protection and undersized stents was noted to avoid the consequences of embolization.[73]

Although intervention in chronic total SVG occlusion received a class III recommendation in the 2011 PCI guidelines,[55] successful PCI was recently reported in about 70% of almost 100 patients, with 1- to 3-year cardiac mortality of 4.2%, MI in 14%, and TVR in about 30%.[74] Considering the narrow risk-benefit relationship, most experienced PCI operators do not attempt chronic total SVG occlusion.[75]

Internal Mammary Artery Grafts

Favorable results have been reported with balloon dilation of IMA graft stenoses. Lesions at the anastomoses of arterial grafts with the native coronary artery behave much like distal anastomotic lesions of SVGs. They usually occur within a few months of surgery and often respond to low-pressure balloon inflations. Successful dilation and stenting of ostial or extremely proximal IMA graft lesions is infrequently required. In a report of PCI of 32 IMA graft lesions, 12 were in the midportion of the artery and 20 were at the anastomosis.[76] Gruberg and colleagues[77] reported outcomes of 174 patients with LIMA PCI (63% had lesions at the anastomosis) with 97% procedural success and TLR of 7% at 1 year. Success was achieved in over 90% of approximately 1000 patients in over 20 reports in the literature. Complications were infrequent, the most common being IMA dissection and spasm. No very large series or long-term data are available regarding stenting in IMA grafts or PCI in gastroepiploic or radial artery grafts.

COMPLICATIONS

Improved techniques, and especially stents, have made PCI safer, but complications still occur. Fortunately, the need for emergency surgery for failed PCI has plummeted from the 3.5% reported for 1263 post-CABG patients in the 1980s to less than 1%.[78] The most common complications are atheroembolic MI, bleeding, no reflow, and graft perforation. Embolic MI is minimized by avoidance of bulky SVG lesions by performing native vessel PCI, using embolic protection in SVGs when possible, using direct stenting and slight stent undersizing, and avoiding postdilation of stents in SVGs. In every case, the interventionalist is balancing risks and benefits: for instance, significant undersizing of a stent could lead to stent thrombosis or undesirable interactions between the stent and other equipment such as intravascular ultrasound (IVUS) catheters or filters, which can become "entangled" by the unopposed stent edge. Bleeding is a major issue in elderly post-CABG patients and in women, and it is reduced by avoidance of GP IIb/IIIa inhibitors, use of radial access, and selective use of bivalirudin. Graft perforation and no-reflow phenomenon are discussed below.

Perforation

Coronary artery perforation is a potential complication of all coronary interventions. It has been attributed to vessel wall penetration with guidewires, inflation of a balloon in a subintimal location, overexpansion of a coronary artery or graft, atheroablative techniques, and stent implantation. SVG perforation is a rare but greatly feared complication. Prolonged balloon inflation and reversal of anticoagulation are effective in stabilizing most patients. However, in spite of the absence of pericardium and the scarring present after bypass surgery, vessel perforation may result in extensive hemorrhage, vessel occlusion, and cardiac tamponade, necessitating emergency surgery. Covered stents have had an increasing role in the treatment of perforation. In one report of 35 perforations, a polytetrafluoroethylene (PTFE)-covered stent was successful in sealing 100%.[79] Because of their large diameter, SVGs are favorable conduits for use of this strategy for sealing perforations. Although the use of oversized balloons has been advocated for vein graft dilations, older vein grafts may rupture with only modest oversizing Because of this potential risk, it seems wise to size balloons and stents to the normal adjacent vessel or slightly smaller, to plan ahead by having a covered stent of proper size available, and by using a guide catheter capable of delivering the device.

No-Reflow Phenomenon

The cause of slow or no reflow following SVG PCI is multifactoral and includes vasospasm and embolization of atheromatous debris and thrombus. The importance of microvascular spasm is suggested by the observation that vasoconstrictors are released during SVG stent procedures, by the relief in no-reflow phenomenon when a calcium channel blocker is administered before SVG PCI, by the apparent treatment effect of small vessel dilators (calcium channel blockers, adenosine, nitroprusside), and by the lack of benefit of nitroglycerin.[80-84] When no reflow occurs or is expected, intracoronary administration of these agents is frequently effective. It is noteworthy that one study reported that aspiration of the stagnant dye column retrieving plaque gruel, and probably soluble vasoconstrictors liberated during SVG PCI,[82] was more effective than calcium channel–blocking agents in relieving no reflow. The dominant role of atheroembolism is apparent from the studies of embolic protection and pathology (see Fig. 26-5).[57-59]

THE FUTURE OF BYPASS GRAFT INTERVENTION

Thorny issues related to bypass graft intervention occupy both ends of the temporal spectrum. Intraoperative angiography has identified significant bypass graft imperfections, the treatment of which may enhance graft patency, improve clinical outcomes, and reduce the need for subsequent ischemia-driven repeat revascularization. It is not clear whether the information gained by routine intraoperative angiography is worth the added cost. Late-term SVG PCI is encumbered by atheroembolic MI and a high number of subsequent cardiac events due to restenosis and progressive vein graft disease. However, embolic protection strategies documented to be beneficial across the entire range of risk strata are markedly underutilized. Will physician education be sufficient to change this practice, or are technical improvements necessary before wide-scale use can occur? Are DESs sufficiently effective in SVGs to warrant the increased cost associated with their use? Is one DES more effective than others? The data are not compelling. And finally, can disease progression in nontarget sites be forestalled? Will the use of "plaque sealing" of moderate SVG lesions by DES implantation, which appeared promising in a pilot trial, be tested in the multicenter study required to corroborate these findings? In the future of bypass graft intervention, questions will outnumber answers.

REFERENCES

1. Hannan EL, Kilburn H, O'Donnell JF, et al: Adult open heart surgery in New York State. *JAMA* 264:2768–2774, 1990.
2. Grüntzig AR, Senning A, Siegenthaler WE: Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med* 301:61–68, 1979.
3. Douglas JS, Jr, Gruentzig AR, King SB, 3rd, et al: Percutaneous transluminal coronary angioplasty in patients with prior coronary bypass surgery. *J Am Coll Cardiol* 2:745–754, 1983.
4. Douglas JS, Jr, King SB, 3rd, Roubin GS: Percutaneous transluminal coronary angioplasty in patients with prior coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 93:272–275, 7, 1987.
5. Mathew V, Clavell AL, Lennon RJ, et al: Percutaneous coronary interventions in patients with prior coronary bypass surgery: changes in patient characteristics and outcome during two decades. *Am J Med* 108:127–135, 2000.
6. Subramanian S, Sabik JF, 3rd, Houghtaling PL, et al: Decision-making for patients with patent left internal thoracic artery grafts to left anterior descending. *Ann Thorac Surg* 87:1392–1400, 2009.
7. Fosbol E, Zhao Y, Shahian DM, et al: Repeat coronary revascularization after coronary artery bypass surgery in older adults. The Society of Thoracic Surgeons' National Experience, 1991–2007. *Circulation* 127:1656–1663, 2013.
8. Brener SJ, Lytle BW, Casserly IP, et al: Predictors of revascularization method and long-term outcome of percutaneous coronary intervention or repeat coronary bypass surgery in patients with multivessel coronary disease and previous coronary bypass surgery. *Eur Heart J* 27:413–418, 2006.
9. Zhoa DX, Leacche M, Balaguer JM, et al: Routine intraoperative completion angiography after coronary artery bypass grafting and 1-stop hybrid revascularization: results from a fully integrated hybrid catheterization laboratory/operating room. *J Am Coll Cardiol* 53:232–241, 2009.
10. Mehta RH, Ferguson TB, Lopes RD, et al: Saphenous vein grafts with multiple versus single distal targets in patients undergoing coronary artery bypass surgery. One-year graft failure and five-year outcome from the Project of Ex-Vivo Vein Graft Engineering via Transfection (PREVENT) IV Trial. *Circulation* 124:280–288, 2011.
11. Widimsky P, Straka Z, Stros P, et al: One-year coronary bypass graft patency: a randomized comparison between off-pump and on-pump surgery angiographic results of the PRAGUE-4 trial. *Circulation* 110:3418–3423, 2004.
12. Shroyer AL, Grover FL, Hattler B, et al: On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med* 361:1827–1837, 2009.
13. Reifart N, Haase J, Störger H, et al: Interventional standby for cardiac surgery. *Circulation* 94(Suppl 1):1–86, 1996.
14. Rasmussen C, Thiis JJ, Clemmensen P, et al: Management of suspected graft failure in coronary artery bypass grafting. *Circulation* 94(Suppl I):I–413, 1996.
15. Cutlip DE, Dauerman HL, Carrozza JP: Recurrent ischemia within thirty days of coronary artery bypass surgery: angiographic findings and outcome of percutaneous revascularization. *Circulation* 94(Suppl I):I–249, 1996.
16. Smith SC, Jr, Feldman TE, Hirschfeld JW, et al: ACC/AHA/SCAI 2005 guideline update for percutaneous intervention: a report of the American College of Cardiology/American Heart Association Task Force on the Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol* 47:1–121, 2006.
17. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS): Guidelines in myocardial revascularization. *Eur Heart J* 31:2501–2555, 2010.
18. Thielmann M, Massoudy P, Jaeger BR, et al: Emergency re-revascularization with percutaneous coronary intervention, reoperation or conservative treatment in patients with acute perioperative graft failure following coronary artery bypass surgery. *Eur J Cardiothorac Surg* 30:117–125, 2006.
19. Izumi C, Hayashi H, Ueda Y, et al: Late regression of left internal thoracic artery graft stenosis at the anastomotic site without intervention therapy. *J Thorac Cardiovasc Surg* 130:1661–1667, 2005.
20. Kitamura S: Does the internal thoracic artery graft have self-reparative ability? *J Thorac Cardiovasc Surg* 130:1494–1495, 2005.
21. Shimshak TM, Giorgi LV, Johnson WL, et al: Application of percutaneous transluminal coronary angioplasty to the internal mammary artery graft. *J Am Coll Cardiol* 12:1205–1214, 1988.
22. Chen L, Theroux P, Lesperance J, et al: Angiographic features of vein grafts versus ungrafted coronary arteries in patients with unstable angina and previous bypass surgery. *J Am Coll Cardiol* 28:1493–1499, 1996.
23. Motwani JG, Topol EJ: Aortocoronary saphenous vein graft disease: pathogenesis, predisposition and prevention. *Circulation* 97:916–931, 1998.
24. Davlouros P, Damelou A, Karantalis V, et al: Evaluation of culprit saphenous vein graft lesions with optical coherence tomography in patients with acute coronary syndromes. *JACC Cardiovasc Interv* 4:683–693, 2011.
25. Grines CL, Booth DC, Nissen SE, et al: Mechanism of acute myocardial infarction in patients with prior coronary artery bypass grafting and therapeutic implications. *Am J Cardiol* 65:1292–1296, 1990.
26. Kahn JK, Rutherford BD, McConahay DR, et al: Usefulness of angioplasty during acute myocardial infarction in patients with prior coronary artery bypass grafting. *Am J Cardiol* 65:698–702, 1990.
27. Brodie BR, VerSteeg DS, Brodie MM, et al: Poor long-term patient and graft survival after primary percutaneous coronary intervention for acute myocardial infarction due to saphenous vein graft occlusion. *Catheter Cardiovasc Interv* 65:504–509, 2005.
28. Hoffmann R, Nitendo G, Deserno V, et al: Follow-up results after interventional treatment of infarct-related saphenous vein graft occlusion. *Coron Artery Dis* 21:61–64, 2010.
29. Welsh RC, Granger CB, Westerhout CM, et al: Prior coronary artery bypass graft patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *J Am Coll Cardiol Interv* 3:343–351, 2010.
30. Suwaidi JA, Velianou JL, Berger PB, et al: Primary percutaneous coronary interventions in patients with acute myocardial infarction and prior coronary artery bypass grafting. *Am Heart J* 142:452–459, 2001.
31. Gaglia MA, Torguson R, Xue Z, et al: Outcomes of patients with acute myocardial infarction from a saphenous vein graft culprit undergoing percutaneous coronary intervention. *Catheter Cardiovasc Interv* 78:23–29, 2011.
32. Ryan TJ, Anderson JL, Antman EM, et al: ACC/AHA guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol* 28:1328–1428, 1996.
33. Iakovau I, Dangas G, Mintz GS, et al: Relation of final lumen dimensions in saphenous vein grafts after stent implantation to outcome. *Am J Cardiol* 93:963, 2004.
34. Hong YJ, Pichard AD, Mintz GS, et al: Outcome of undersized drug-eluting stents for percutaneous coronary intervention of saphenous vein graft lesions. *Am J Cardiol* 105:179–185, 2010.
35. Weintraub WS, Jones EL, Morris DC, et al: Outcome of reoperative coronary bypass surgery versus coronary angioplasty after bypass surgery. *Circulation* 95:868–877, 1997.
36. Morrison DA, Sethi G, Sacks J, et al: Percutaneous coronary intervention versus repeat bypass surgery for patients with medically refractory myocardial ischemia: AWESOME randomized trial and registry experience with post-CABG patients. *J Am Coll Cardiol* 40:1951–1954, 2002.
37. Cole JH, Jones EL, Craver JM, et al: Outcomes of repeat revascularization in diabetic patients with prior coronary surgery. *J Am Coll Cardiol* 40:1968–1975, 2002.
38. Patel MR, Dehmer GJ, Hirshfeld JW, et al: ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation and Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 53:530–553, 2009.
39. Ellis SG, Brener SJ, DeLuca S, et al: Late myocardial ischemic events after saphenous vein graft intervention: importance of initially "non-significant" vein graft lesions. *Am J Cardiol* 79:1460–1464, 1997.
40. Rodes-Cabau J, Bertrand OF, Larose E, et al: Comparison of plaque sealing with paclitaxel-eluting stents versus medical therapy for the treatment of moderate non-significant saphenous vein graft lesions: the Moderate Vein Graft Lesion Stenting with the Taxus Stent and Intravascular Ultrasound (VELETI) pilot trial. *Circulation* 120:978–986, 2009.
41. Rodes-Cabau J: Plaque scaling with paclitaxel-eluting stents for the treatment of moderate non-significant saphenous vein graft lesions. Three-year follow-up of the VELETI (moderate vein graft lesion stenting with the Taxus stent and intravascular ultrasound) trial. Presented at i2 Summit; Atlanta, GA, 14 March 2010.
42. Savage MP, Douglas JS, Jr, Fischman DL, et al: Stent placement compared with balloon angioplasty for obstructed bypass grafts. Saphenous Vein De Novo Trial Investigators. *N Engl J Med* 337:740–747, 1997.
43. Hong MK, Mehran R, Dangas G, et al: Are we making progress with percutaneous saphenous vein graft treatment? *J Am Coll Cardiol* 38:150–154, 2001.
44. Ashfaq S, Ghazzal Z, Douglas JS, et al: Impact of diabetes on five-year outcomes after vein graft intervention performed prior to the drug-eluting stent era. *J Invasive Cardiol* 18:100–105, 2006.
45. Douglas JS, Jr: Are our patients better off with drug-eluting stents in saphenous vein grafts? *JACC Cardiovasc Interv* 2:1113–1114, 2009.
46. Vermeersh P, Pierfrancesco A, Verheye S, et al: Randomized double-blind comparison of sirolimus-eluting stent versus bare-metal stent implantation in diseased saphenous vein grafts: six-month angiographic, intravascular ultrasound, and clinical follow-up of the RRISC trial. *J Am Coll Cardiol* 48:2423–2431, 2006.
47. Vermeesch P, Agostoni P, Verheye S, et al: Increased late mortality after sirolimus-eluting stents versus bare-metal stents in diseased saphenous vein grafts: results from the randomized DELAYED RRISC Trial. *J Am Coll Cardiol* 50:261–267, 2007.
48. Brilakis ES, Lichtenwalter C, de Lemos JA, et al: A randomized-controlled trial of a paclitaxel-eluting stent versus a similar bare-metal stent in saphenous vein graft lesions: the SOS (Stenting of Saphenous Vein Grafts). *J Am Coll Cardiol* 53:919–928, 2009.
49. The STENT Group: Outcomes with drug-eluting versus bare-metal stents in saphenous vein graft intervention: results from the STENT (Strategic Transcatheter Evaluation of New Therapies) Group. *J Am Coll Cardiol Interv* 2:1105–1112, 2009.
50. Mamas MA, Foley J, Nair S, et al: Comparison of drug-eluting stents versus bare-metal stents in saphenous vein graft PCI outcomes: a meta-analysis. *J Interv Cardiol* 24:172–180, 2011.
51. Mehili J, Pache J, Abdel-Wahab M, et al: Drug-eluting versus bare-metal stents in saphenous vein graft lesions (ISAR-CABG): a randomized controlled superiority trial. *Lancet* 378:1071–1078, 2011.
52. Hougaard M, Thayssen P, Kaltoft A, et al: Long-term outcome following percutaneous coronary intervention with drug-eluting stents compared with bare-metal stents in saphenous vein graft lesions: from Western Denmark Heart Registry. *Catheter Cardiovasc Interv* 83:1035–1042, 2014.
53. Yazdani SK, Farb A, Nakano M, et al: Pathology of drug-eluting versus bare-metal stents in saphenous vein bypass graft lesions. *J Am Coll Cardiol Interv* 5:666–674, 2012.
54. Kitabata H, Loh JP, Pendyala L, et al: Two-year follow-up of outcomes of second-generation everolimus-eluting stents versus first-generation drug-eluting stents for stenosis of saphenous vein grafts used as aortocoronary conduits. *Am J Cardiol* 112:61–67, 2013.
55. Levine GN, Bates ER, Blankenship JC, et al: 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 58:e44–e122, 2011.
56. Mahmood A, Khair T, Abdel-karim AR, et al: Contemporary approaches to saphenous vein graft intervention: a survey of 275 interventional cardiologists. *Catheter Cardiovasc Interv* 79:834–842, 2012.
57. Liu MW, Douglas JS, Jr, Lembo NJ, et al: Angiographic predictors of a rise in serum creatine kinase (distal embolization) after balloon angioplasty of saphenous vein coronary artery bypass grafts. *Am J Cardiol* 72:514–517, 1993.
58. Coolong A, Baim DS, Kuntz RE, et al: Saphenous vein graft stenting and major adverse cardiac events. A predictive model derived from a pooled analysis of 3,958 patients. *Circulation* 117:790–797, 2008.
59. Baim DS, Wahr D, George B, et al: Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. *Circulation* 105:512–590, 2002.
60. Sallam J, Tharpe C, Vaughan D, et al: Release and elimination of soluble vasoactive factors during percutaneous intervention of saphenous vein grafts: analysis using the PercuSurge GuardWire distal protection device. *J Invasive Cardiol* 17:575–579, 2005.
61. Stone GW, Rogers C, Hermiller J, et al: Randomized comparison of distal protection with a filter-based catheter and a balloon occlusion and aspiration system during percutaneous intervention of diseased saphenous vein aorto-coronary bypass grafts. *Circulation* 108:548–553, 2003.
62. Mauri L, Cox D, Hermiller J, et al: The PROXIMAL trial: Proximal protection during saphenous vein graft intervention using the Proxis Embolic Protection System: a randomized perspective, multicenter clinical trial. *J Am Coll Cardiol* 50:1442–1449, 2007.
63. Mehta SK, Frutkin AD, Milford-Beland S, et al: Utilization of distal embolic protection in saphenous vein graft intervention (an analysis of 19,546 patients in the American College of Cardiology-National Cardiovascular Data Registry). *Am J Cardiol* 100:1114–1118, 2007.
64. Abdel-Karim A, Papayannis AC, Mahmood A, et al: Role of embolic devices in ostial saphenous vein graft lesions. *Catheter Cardiovasc Interv* 80:1120–1126, 2012.
65. Kao J, Lincoff AM, Topol EJ, et al: Direct thrombin inhibition appears to be a safe and effective anticoagulant for percutaneous bypass graft interventions. *Catheter Cardiovasc Interv* 68:352–356, 2006.
66. Sachdeva A, Bavisetty S, Beckham G, et al: Discontinuation of long-term clopidogrel therapy is associated with death and myocardial infarction after saphenous vein graft percutaneous coronary intervention. *J Am Coll Cardiol* 60:2357–2363, 2012.
67. Mathew V, Grill DE, Scott CG, et al: the influence of abciximab use on clinical outcomes after aortocoronary vein graft interventions. *J Am Coll Cardiol* 34:1163–1169, 1999.
68. Roffi M, Mukherjee D, Chew DP, et al: Lack of benefit from intravenous platelet glycoprotein IIb/IIIa receptor inhibition as adjunctive treatment for percutaneous interventions of aorto-coronary bypass grafts: a pooled analysis of five randomized clinical trials. *Circulation* 106:3063–3067, 2002.
69. Jonas M, Stone GW, Mehran R, et al: Platelet glycoprotein GP IIb/IIIa receptor inhibition as adjunctive treatment during saphenous vein graft stenting: differential effects after randomization to occlusion or filter-based embolic protection. *Eur Heart J* 27:920–928, 2006.
70. Waksman R: Intracoronary gamma radiation for in-stent restenosis in saphenous vein grafts. *J Am Coll Cardiol* 38:597, 2001.

71. Ozkan M, Sag C, Yokusoglu M, et al: The effect of tirofiban and clopidogrel pretreatment on outcome of old saphenous vein graft stenting in patients with acute coronary syndromes. *Tohoku J Exp Med* 206:7–13, 2005.
72. Florina C, Megliga E, Chizzola G, et al: Early experience with a new approach for percutaneous intervention of totally occluded saphenous vein graft: Is the flow the best thrombolytic? *EuroIntervention* 6:461–466, 2010.
73. Maluenda G, Alfonso F, Pichard AD, et al: Percutaneous intervention of a thrombotic-occluded saphenous vein graft successfully treated using the undersized stent approach to prevent distal embolization. *Catheter Cardiovasc Interv* 80:1120–1126, 2012.
74. Garg N, Hakeem A, Gobal F, Uretsky BF: Outcomes of percutaneous coronary intervention of chronic total saphenous vein graft occlusions in the contemporary era. *Catheter Cardiovasc Interv* 83:1025–1032, 2014.
75. Heuser R: Moualla SK: Choose your battles wisely! Saphenous vein graft chronic total occlusion interventions, a path less traveled, a frontier to be mostly avoided. *Catheter Cardiovasc Interv* 83:1033–1034, 2014.
76. Shimshak TM, Giorgi LV, Johnson WL, et al: Application of percutaneous transluminal coronary angioplasty to the internal mammary artery graft. *J Am Coll Cardiol* 12:1205–1214, 1988.
77. Gruberg L, Dangas G, Mehran R, et al: Percutaneous revascularization of the internal mammary artery graft: short- and long-term outcomes. *J Am Coll Cardiol* 35:944–948, 2000.
78. Weintraub WS, Cohen CL, Curling PE, et al: Results of coronary surgery after failed elective coronary angioplasty in patients with prior coronary surgery. *J Am Coll Cardiol* 16:1341–1347, 1990.
79. Lansky AJ, Stone GW, Grube E, et al: A multicenter registry of the JoStent PTFE stent graft for the treatment of arterial perforations complicating percutaneous coronary interventions. *J Am Coll Cardiol* 35:26A, 2000.
80. Leineweber K, Bose D, Vogelsang M, et al: Intense vasoconstriction in response to aspirate from stented saphenous vein aorto-coronary bypass grafts. *J Am Coll Cardiol* 47:981–986, 2006.
81. Hillgrass WB, Dean DA, Liao L, et al: Treatment of no-reflow and impaired flow with the nitric oxide donor nitroprusside following percutaneous coronary interventions: initial human clinical experience. *J Am Coll Cardiol* 37:1335–1343, 2001.
82. Salloum J, Tharpe C, Vaughan D, et al: Release and elimination of soluble vasoactive factors during percutaneous intervention of saphenous vein grafts: analysis using the PercuSurge GuardWire distal protection device. *J Invasive Cardiol* 17:575–579, 2005.
83. Jaffe R, Dick A, Strauss BH: Prevention and treatment of microvascular obstruction-related myocardial injury and coronary no-reflow following percutaneous coronary intervention: a systematic approach. *JACC Cardiovasc Interv* 3:695–704, 2010.
84. Fischell TA, Subraya RG, Ashraf K, et al: "Pharmacologic" distal protection using prophylactic, intragraft nicardipine to prevent no-reflow and non-Q-wave myocardial infarction during elective saphenous vein graft intervention. *J Invasive Cardiol* 19:58–62, 2007.

The Thrombus-Containing Lesion

27

ON TOPAZ

KEY POINTS

- A thrombus is made of a conglomerate of platelets, red blood cells, vasoconstrictors, and procoagulants anchored to a scaffolding matrix of crisscrossing fibrin fibers.
- Thrombus-containing lesions represent active, unstable plaques that account for acute coronary syndromes.
- Thrombus is a predictor of hazards related to percutaneous coronary intervention (PCI), including resultant major adverse cardiovascular events (MACEs), early and late development of stent thrombosis, increased rate of in-hospital complications, recurrent myocardial infarction (MI), and death.
- The most common imaging modalities used for thrombus detection in the cardiac catheterization suite include angiography, intravascular ultrasound (IVUS), and optical coherence tomography (OCT).
- Thrombus grading systems should quantify the thrombus burden as they assist in the planning of tailored interventions.
- Ruptured plaques, heavy thrombus burden, distal embolizations, infarct-related vessels, degenerated old bypass grafts, chronic total occlusions (CTOs), left main lesions, vessels that contain several thrombi, and multivessel thrombosis are among the most challenging thrombotic lesions.
- The mainstay pharmacologic treatments for thrombus-containing lesions include aspirin, heparin, glycoprotein (GP) IIb/IIIa platelet receptor antagonists, thienopyridines, direct thrombin inhibitors, and thrombolytic agents.
- The main contemporary technologies for mechanical thrombus extraction are manual aspiration catheters, power-sourced thrombectomy devices, ultrasound sonication, and embolic protection systems.
- The most popular tool for thrombus management during PCI is the aspiration catheter.
- A useful strategy for the management of a heavy thrombus burden combines adjunct pharmacotherapy and mechanical thrombus removal. The route of administration; the dosing of the thrombolytic agent, platelet receptor, and/or thrombin inhibitor; and the selection of a dedicated device are tailored to the location of the thrombus and the burden of thrombosis and its resistance to mechanical force by balloons and stents.
- Dedicated thrombus-capturing or thrombus-displacement stents provide an option for the management of selected thrombus-containing lesions.

Thrombus-containing lesions represent active, unstable atherosclerotic plaques commonly found in patients with an acute coronary syndrome (ACS). In the past four decades, PCI has increasingly targeted complex lesions and has enhanced the treatment of urgent cases with a remarkably high success rate.[1] Despite this progress, the thrombus-containing plaque remains a considerable revascularization challenge and continues to serve as a predictor of PCI-related MACEs, more myocardial damage, stent thrombosis, and increased in-hospital complications, 6-month recurrent MI, and death.[2-7] Consequently, thrombus exerts a major impact on the performance, results, long-term outcome, and cost of primary and rescue interventions (Table 27-1)[8]; yet the optimal treatment of thrombotic lesions is still enigmatic and controversial. The aim of this chapter is to present the role of intracoronary (IC) thrombus in the pathophysiology of ACSs, illustrate its complex morphology, and describe its impact on interventions and outcomes. This chapter also covers the imaging modalities for thrombus identification and delineates specific pharmacotherapy, techniques, and technology incorporated in dedicated thrombus-removal strategies. A specific set of challenging thrombus-containing lesions and corresponding management options are highlighted.

PATHOPHYSIOLOGY OF THROMBUS

Understanding the structure of thrombus and its multifaceted physical characteristics is crucial for making proper management choices in revascularization of atherosclerotic lesions and vessels.[9] The formation of thrombotic lesions occurs when the fibrous cap of an atherosclerotic plaque develops structural defects.[10] Significant adverse morphologic changes in the plaque are manifested by erosion, fissure, or rupture. Such weakening of the plaque's integrity exposes the inside necrotic core, a deleterious step that enables the transfer of plaque material into the arterial lumen. Cholesterol crystals inside the plaque also perforate the tunica intima and trigger further disruption, and the crystal content has been identified as an independent predictor of thrombus and clinical events.[11] The ensuing contact of exposed, disrupted, and highly thrombogenic subendothelial matrix and plaque with circulating platelets and white blood cells activates the coagulation cascade. The resultant platelet adhesion and aggregation leads to thrombus formation (Fig. 27-1). Furthermore, released tissue factor from the arterial injury directly activates the extrinsic coagulation cascade and promotes fibrin formation. Activated platelets release powerful promoters of vasoconstriction and aggregation including serotonin, adenosine diphosphate (ADP), thromboxane A2 (TXA_2), oxygen-derived free radicals, endothelin, and platelet activating factor.[12] As the thrombus accumulates to form a critical obstacle (Fig. 27-2), impaired flow dynamics along and distal to the thrombotic lesion develop, frequently accompanied by vasoconstriction with resultant clinical ischemic events.[13] During PCI, thrombus frequently exhibits structural variability as it adheres either loosely—or at times, quite firmly—to the underlying plaque and to the vessel wall. Consequently, and unpredictably, it exhibits either marked friability or unyielding rigidity in response to the mechanical forces generated by balloon and stent deployment. These contradictory physical properties stem from the cumulative effects of an assortment of intrathrombus components. Structurally, the thrombus is held by a scaffolding platform made of fibrin fibers.[14] Two distinct types of branching fibrin fibers are organized in a three-dimensional (3-D) network within the thrombus. Dense, thin fibers resist deforming mechanical forces and are poorly dissolved by thrombolytic agents. Thick fibrin fibers, on the other hand, are susceptible to the effects of external mechanical forces and are readily dissolved by thrombolytic therapy.[15] Platelets, red blood cells (RBCs), vasoconstrictors, and procoagulant compounds are anchored to the matrix of the crisscrossing fibers (Fig. 27-3). Abnormalities in platelet function can persist and are predictive of clinical events following PCI.[16] Typically, in patients who present with ACS, the clot-adhering platelets exert a significant increase in contractile force, leading to increased platelet aggregation, with the entire thrombus exhibiting increased elastic modulus.[17] The platelets

sustain and amplify the coagulant response at the plaque site and release procoagulant platelet–derived microparticles.

Various biochemical processes and interactions among activated platelets, RBCs, fibrinogen, vasoconstrictors, atherosclerotic material, and the vessel wall all produce a substantial impact on the fibrin network. These constituents account for the thrombus's level of activity, stability, or instability and for the overall "aggressiveness" of the thrombus as encountered during intervention. The presence and ratio of the aforementioned components determine formation of distinct thrombus types, each with unique rheolytic and mechanical properties. The two most prominent are the red and white thrombi, which can be detected by angioscopy (Fig. 27-4),[18] and their angiographic characteristics correlate with the histology of extracted thrombi.[19] The red thrombus contains dense surface with a loose inner core. Transmission or scanning electron microscopy demonstrates loosely packed fibrin and many interspersed RBCs. The white thrombus consists of a dense structure that lacks loose inner spaces yet contains a high concentration of platelets with fibrin and only few RBCs.[20] Based on histopathologic analysis of aspirated thrombotic content, erythrocyte-rich red thrombus is found in about 35% of patients, predominately in those who present with low Thrombolysis in Myocardial Infarction (TIMI) grade flow. The platelet-rich white thrombus is identified in 65% of cases, especially in the early hours of acute myocardial infarction (AMI).[21] Noteworthy, however, in many patients is that the occlusive thrombus is a mixture of red and white clot, and the frequent resistance upon extraction attempts suggests that certain clots contain layer upon layer of one thrombus type interspersed with the other.[22,23]

TABLE 27-1 The Impact of Thrombus on Percutaneous Coronary Intervention

- Requires targeted treatment, which increases costs and may prolong procedures
- Adverse effect on lesion, vessel, and clinical outcome during and after interventions
- Increased intervention-related risk of distal embolization, no-reflow phenomenon, acute thrombotic occlusion, periprocedural myocardial infarction, postprocedural myocardial infarction, need for emergency bypass surgery, and death
- Predictor of major adverse coronary events, early and late stent thrombosis, in-hospital complications, risk of 6-month recurrent myocardial infarction, and death
- Predictor of success in selected cases of chronic total occlusion

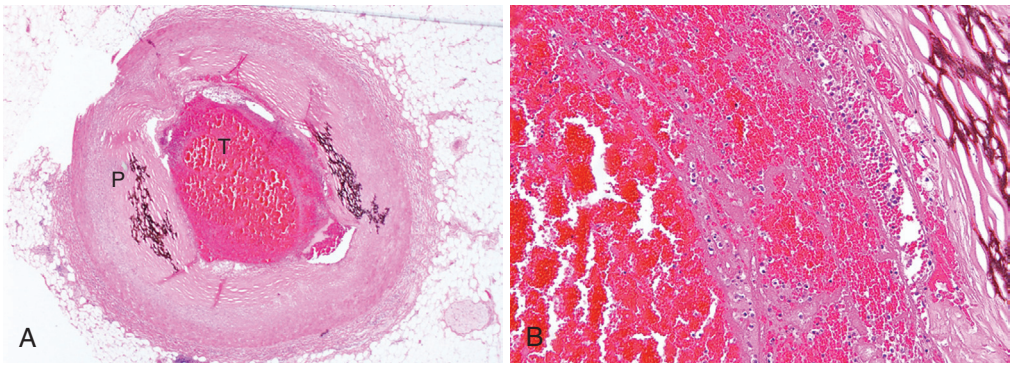


FIGURE 27-1 High-power view of right coronary artery. **A,** Layering of acute thrombus (T). *P,* Plaque. **B,** Red blood cells alternate between layers of fibrin (hematoxylin and eosin, 20×). (Courtesy Shannon Mackey-Bojack MD, Jesse E. Edwards Registry of Cardiovascular Disease Collection, Nasseff Heart Center, United Hospitals, University of Minnesota School of Medicine, St. Paul, MN.)

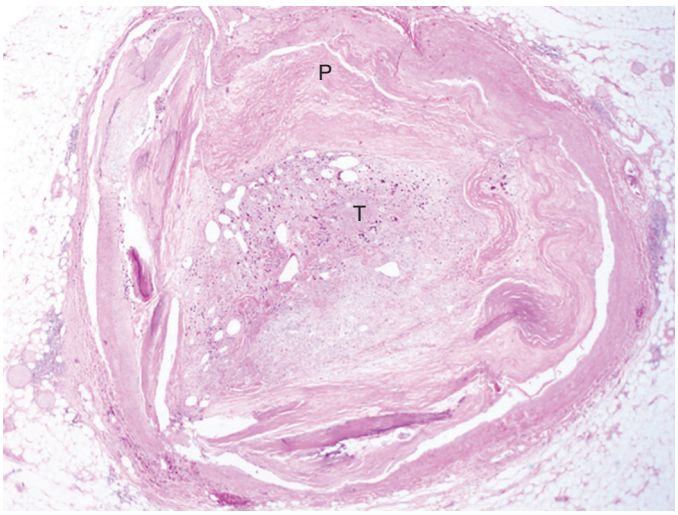


FIGURE 27-2 Cross section of right coronary artery occluded by calcified, complicated atherosclerotic plaque (P) and organized thrombus (T; hematoxylin and eosin, 2×). (Courtesy Shannon Mackey-Bojack MD, Jesse E. Edwards Registry of Cardiovascular Disease Collection, Nasseff Heart Center, United Hospitals, University of Minnesota School of Medicine, St. Paul, MN.)

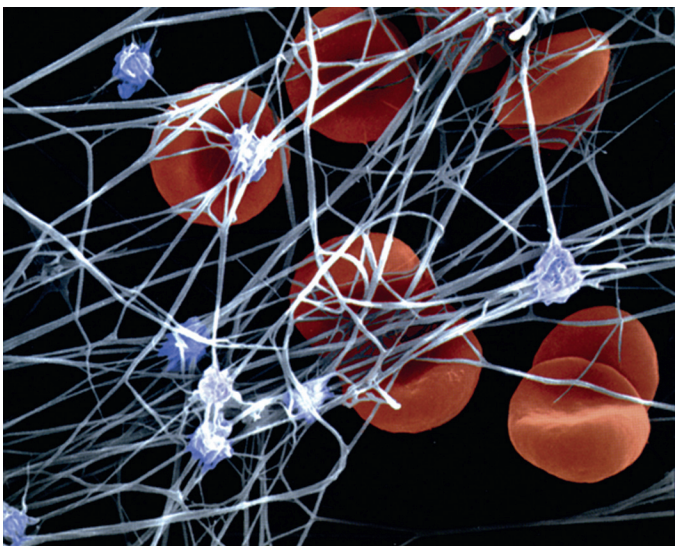


FIGURE 27-3 Scanning electron microscopy of a thrombus. Note the criss-crossing thick and thin fibrin fibers, which provide a scaffolding system for the thrombus structure. Platelets (*violet color*) and red blood cells are attached to the fibrin net. (Courtesy Marc Carr Jr, MD PhD, and Hemodyne Inc., Richmond, VA.)

From a clinical management perspective, coronary risk factors such as hypercholesterolemia, smoking, and male sex adversely influence plaque morphology in patients with ACSs and are associated with a higher frequency of thrombus. Once the thrombus is formed in the culprit lesion, its size is associated with larger infarct size and worse left ventricular (LV) function. The thrombus size also relates to PCI-related complications such as distal embolization, as suggested in a pathologic analysis of aspirated embolized debris; this demonstrated that the larger the thrombus volume at a culprit lesion, the larger the dimensions of the debris collected inside the filter.[24] The dimensions of the debris predicted arteriolar occlusion.

DETECTION OF THROMBUS-CONTAINING LESIONS

Various imaging modalities are available for diagnosis of intracoronary thrombus. Numerous studies have demonstrated the poor sensitivity of angiography, although specificity approaches 100% when multiple angiographic views are obtained for verification and strict definitions are used. Nevertheless, angiography remains the practical gold standard for recognition of thrombus and demonstrates the classic findings of reduced contrast density; staining; haziness; irregular lesion contour; filling defect; or a smooth, convex meniscus at the site of a total thrombotic occlusion.

When thrombus is suspected but not apparent angiographically, the more sensitive techniques for thrombus detection may be utilized, including angioscopy[25] and IVUS (Fig. 27-5).[26] OCT[27] is a more recent imaging technique for accurate detection of plaque and thrombus (Fig. 27-6) and is rapidly gaining popularity because of its user-friendly features and remarkable imaging quality.[28,29]

THROMBUS GRADING

Grading systems are essential for adequate assessment of thrombus burden to assist management decisions prior to and during interventions.[30] The established, most commonly used thrombus grading classification was introduced by the TIMI Study Group.[31] This method is based on visual angiographic assessment of the thrombus size using a score that ranges from grade 0 to grade 5 (Fig. 27-7; Table 27-2). An

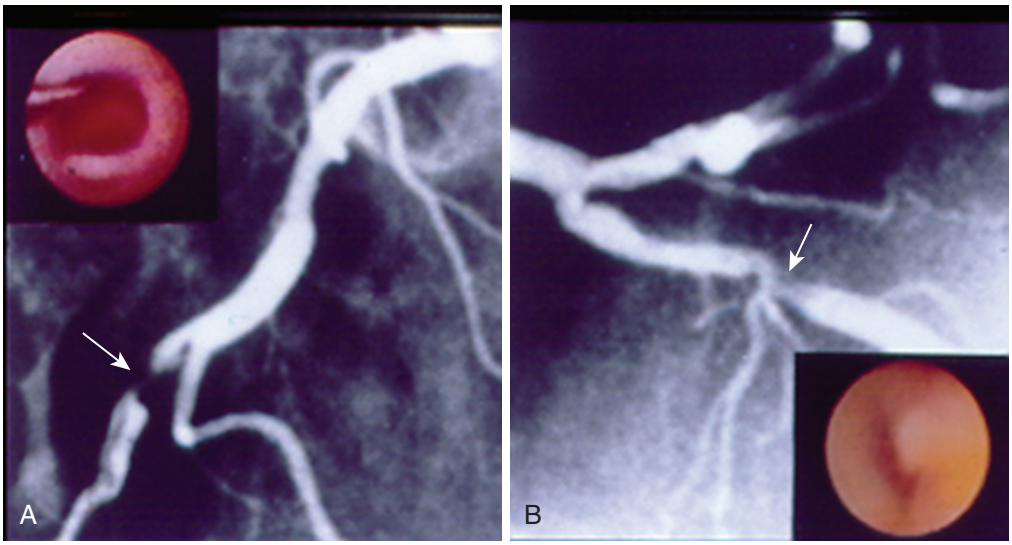


FIGURE 27-4 **A,** Angiogram of right coronary artery demonstrates a 1-cm filling defect with a trace amount of contrast crossing the tight atherosclerotic obstruction (*arrow*). Corresponding angioscopy demonstrates a bulging red thrombus. **B,** Angiogram demonstrates a hazy eccentric lesion in the obtuse marginal branch (*arrow*). Angioscopy reveals a white thrombus emerging from a yellow plaque. (Courtesy George Abela MD, Division of Cardiology, Michigan State University, East Lansing, MI. From Abela GS et al: *Am J Cardiol* 83:94-97, 1999.)

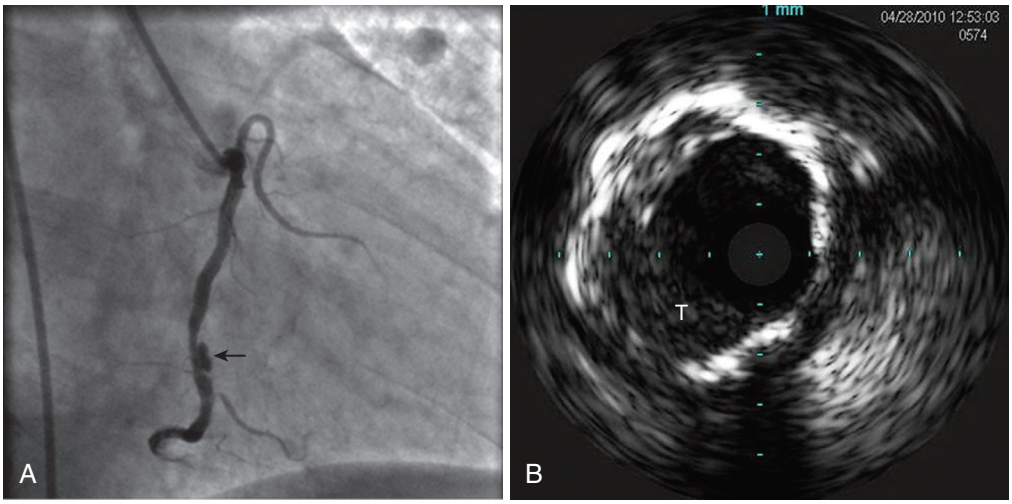


FIGURE 27-5 **A,** Ultrasound of thrombus. **B,** Corresponding right coronary artery angiogram. *T,* Thrombus. (Courtesy Michael Foster MD, South Carolina Heart Center, Columbia, SC.)

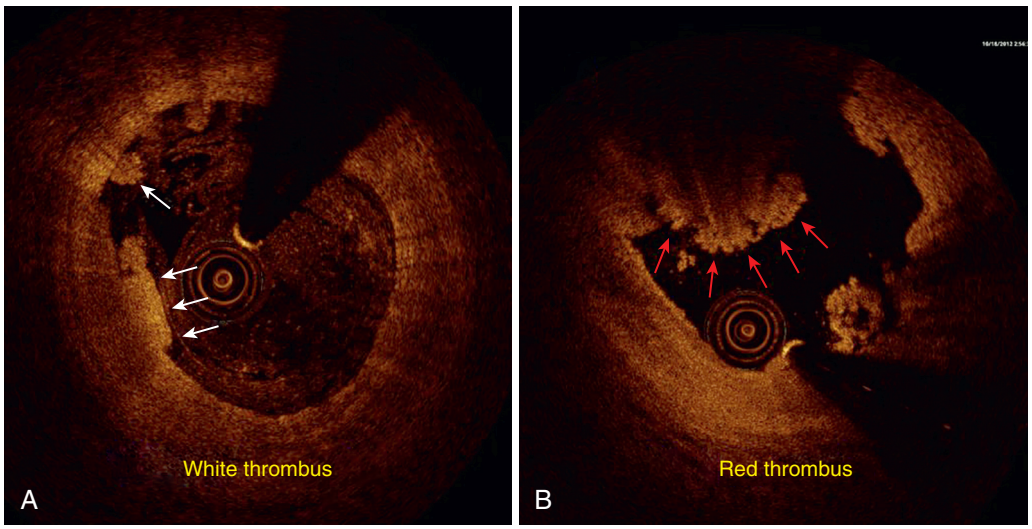


FIGURE 27-6 Optical coherence tomography demonstrates white thrombus (**A**) and red thrombus (**B**). (Courtesy Peter O'Kane MD, cardiac intervention unit, department of cardiology, Dorset Heart Center, Royal Bournemouth Hospital, Bournemouth, UK.)

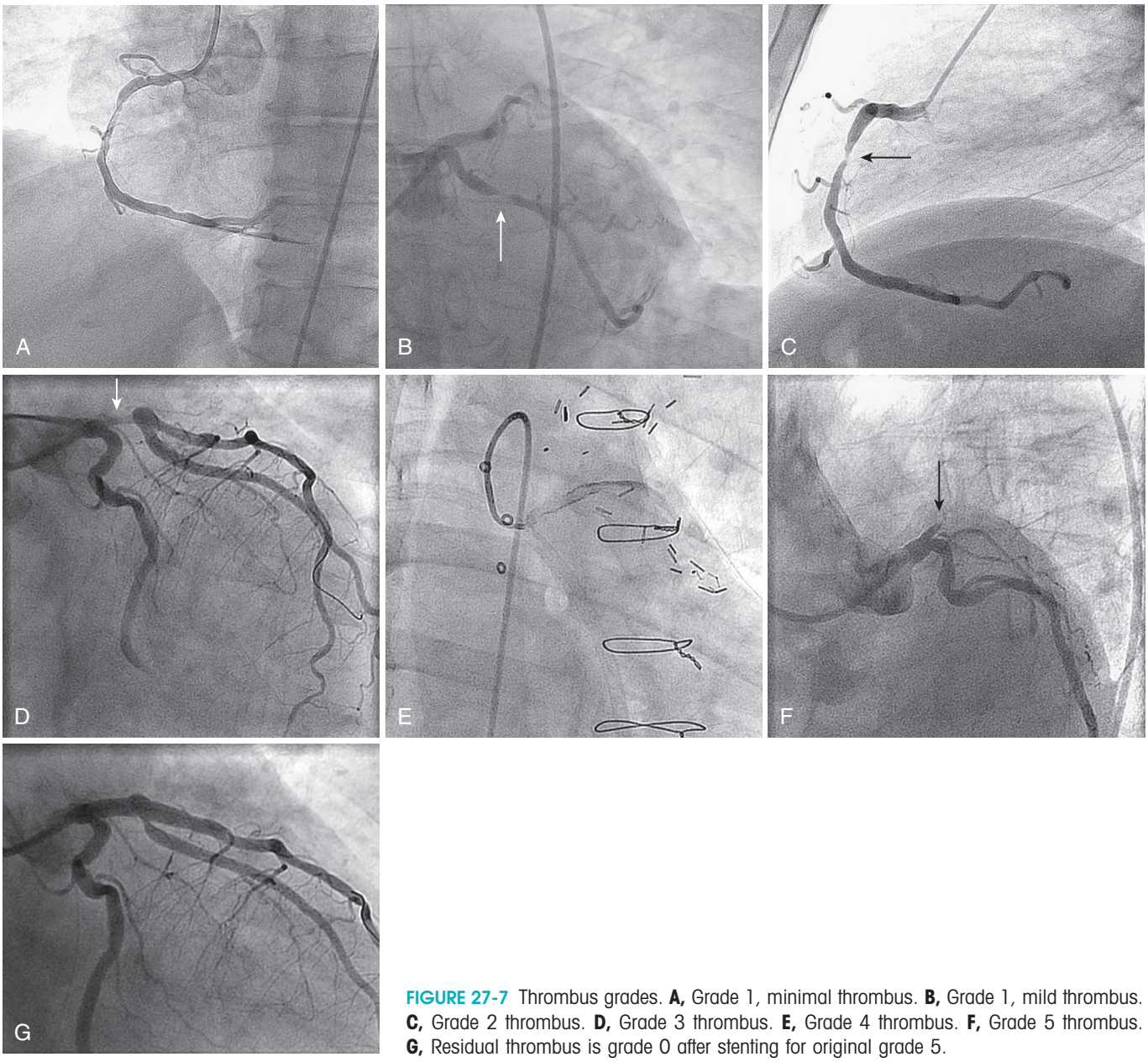


FIGURE 27-7 Thrombus grades. **A,** Grade 1, minimal thrombus. **B,** Grade 1, mild thrombus. **C,** Grade 2 thrombus. **D,** Grade 3 thrombus. **E,** Grade 4 thrombus. **F,** Grade 5 thrombus. **G,** Residual thrombus is grade 0 after stenting for original grade 5.

TABLE 27-2 Thrombus Grading Scores

Definition*	
Grade 0	No angiographic characteristics of thrombus
Grade 1	*Possible thrombus:* Angiographic features include decreased density of contrast; haziness; irregular lesion contour; or a smooth, convex meniscus at the site of total occlusion suggestive, but not diagnostic, of thrombus
Grade 2	*Definite thrombus:* Present in multiple angiographic views; marked irregular lesion contour with a significant filling defect; greatest dimension less than half the vessel diameter
Grade 3	Definite thrombus in multiple views with greatest dimension more than half but less than twice the vessel diameter
Grade 4	Definite large thrombus with greatest dimension more than twice the vessel diameter
Grade 5	Complete thrombotic occlusion of the vessel: a convex margin that stains with contrast and persists for several cardiac cycles
Grade 5 Reclassification**	
Intervention-based: The occlusion is crossed with a guidewire or small balloon; once antegrade flow is restored, the culprit thrombus undergoes restratification	
Small thrombus: Grades 1 through 3	
Large thrombus: Grade 4	
Thrombus Grading by a Two-Category Scale***	
Low thrombus grade corresponds to TIMI thrombus grades 1 through 3	
High thrombus grade corresponds to TIMI thrombus grades 4 and 5	

*From Gibson CM, de Lemos JA, Murphy SA, et al: Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction: a TIMI 14 substudy. *Circulation* 103:2550-2554, 2001.
**From Sianos G, Papafaklis MI, Daemen J, et al: Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. *J Am Coll Cardiol* 50:572-583, 2007.
***From Niccoli G, Spaziani C, Marino M, et al: Effect of chronic aspirin therapy on angiographic thrombotic burden in patients admitted for a first ST-elevation myocardial infarction. *Am J Cardiol* 105:587-591, 2010.

important modification to this scoring system was recently introduced by the Thoraxcenter investigators,[5] who reclassified the highest grade—that is, grade 5, which consists of TIMI grade 0 flow and a strong angiographic suspicion of a large thrombus. When this grade is encountered, either a guidewire or a 1.5-mm balloon (inflated or uninflated) is applied for recanalization of the suspected thrombus (Fig. 27-8). As soon as antegrade flow is restored, the exposed apparent thrombotic content undergoes restratification into either a small thrombus burden (grades 1 through 3) or a large thrombus burden (grade 4), and treatment ensues accordingly. Niccoli and colleagues[32] recently introduced a minimalistic thrombus categorization whereby a low grade is assigned to the aforementioned TIMI grades of 1 through 3, and a high thrombus grade corresponds to grades 4 through 5. For a more accurate, quantitative thrombus measurement, Aleong and colleagues[33] innovated a technique that combines edge detection and videodensitometry-based quantitative coronary angiography (QCA); in their early experience with patients who exhibited a large IC clot, this modality appeared to accurately quantify the thrombus volume. The advantages and limitations of these thrombus grading classifications are described in Table 27-3.

Factors that specifically account for formation of a high-grade thrombus are depicted in Table 27-4. Among those, the relationship among hyperglycemia, increased white blood cell count, and findings of a high thrombus grade merits clinical attention.[32] These factors also impact the lack of ST-segment resolution and are associated with worse PCI outcome.[33] A plausible direct relationship between high thrombus content and large vessel size has been known for a long time.[34] A recent study investigating predictors of thrombus grade in patients undergoing PCI identified that absence of periinfarction angina and a proximal culprit lesion are associated with higher thrombus burden [35]

TABLE 27-3 Advantages and Limitations of Contemporary Thrombus-Grading Classifications

Advantages
1. Convenient assessment during diagnostic angiography and interventions
2. Constitutes a logical grading scale applied globally
3. High interobserver and intraobserver agreement
4. Correlates well with clinical outcomes
5. Readily available means of comparison with previous angiograms
Limitations
1. Reliance solely on visual assessment of the thrombus
2. Underestimation of thrombus presence and size in comparison with angioscopy and intracoronary ultrasound
3. Applicability mainly for native coronary arteries
4. Underestimation of the extent of thrombus in saphenous vein grafts
5. Cannot differentiate between types of thrombus
6. Inability to detect the thrombotic content of chronic total occlusions
7. Do not quantitate or qualify the underlying plaque burden

TABLE 27-4 Factors That Favor Formation of a High-Grade Thrombus in Atherosclerotic Lesions

Myocardial Infarction Related
1. Absence of preinfarction angina
2. Late presentation (>12 hours) after onset of acute MI
3. Established Q-wave MI with continuous chest pain and ischemia
4. Cardiogenic shock
Lesion Related
1. Acute plaque rupture, complex morphology, and proximal culprit lesion
Vessel Related
1. Slow or stagnant antegrade coronary or SVG flow
2. Large anatomic size increases thrombus formation and accumulation in native coronary vessels and SVG
3. Morphology: ectasia, aneurysm, old SVG
4. Failed thrombolytics
Percutaneous Coronary Intervention Related
1. Triggering of the plaque and thrombus with a guidewire, balloon, or stent: the so-called angry clot phenomenon
2. Inadequate anticoagulation during intervention
3. Poor stent apposition to the vessel wall
4. Lack of or premature or abrupt cessation of thienopyridines
5. Hypercoagulability
6. Heparin-induced thrombocytopenia and thrombosis (HITT)
7. Vasculitis
8. Increased white blood count
9. Hyperglycemia
10. Cocaine

MI, Myocardial infarction; *SVG,* saphenous vein graft.

Intriguingly, despite the convenience of the above classifications, a significant number of studies of PCI in ischemic coronary syndromes do not measure, grade, or report the presence of the thrombus burden.[36] This unfortunate omission occurs despite the growing recognition of the structural complexity of thrombus[37] and its significant impact on PCI outcome.[38-40]

LIMITATIONS OF STANDARD PERCUTANEOUS CORONARY INTERVENTION IN THROMBUS-CONTAINING LESIONS

In the absence of an apparent thrombus, or when only a small thrombus (grade 1 or 2) is detected, the recommended PCI strategy includes standard pharmacotherapy, balloon angioplasty, and stenting.[41] Aspiration catheters can be useful, as well, in this situation. However, management of a significant (grade 3) or heavy thrombus burden (grades 4 and 5) is considerably more challenging.[42] In this scenario,

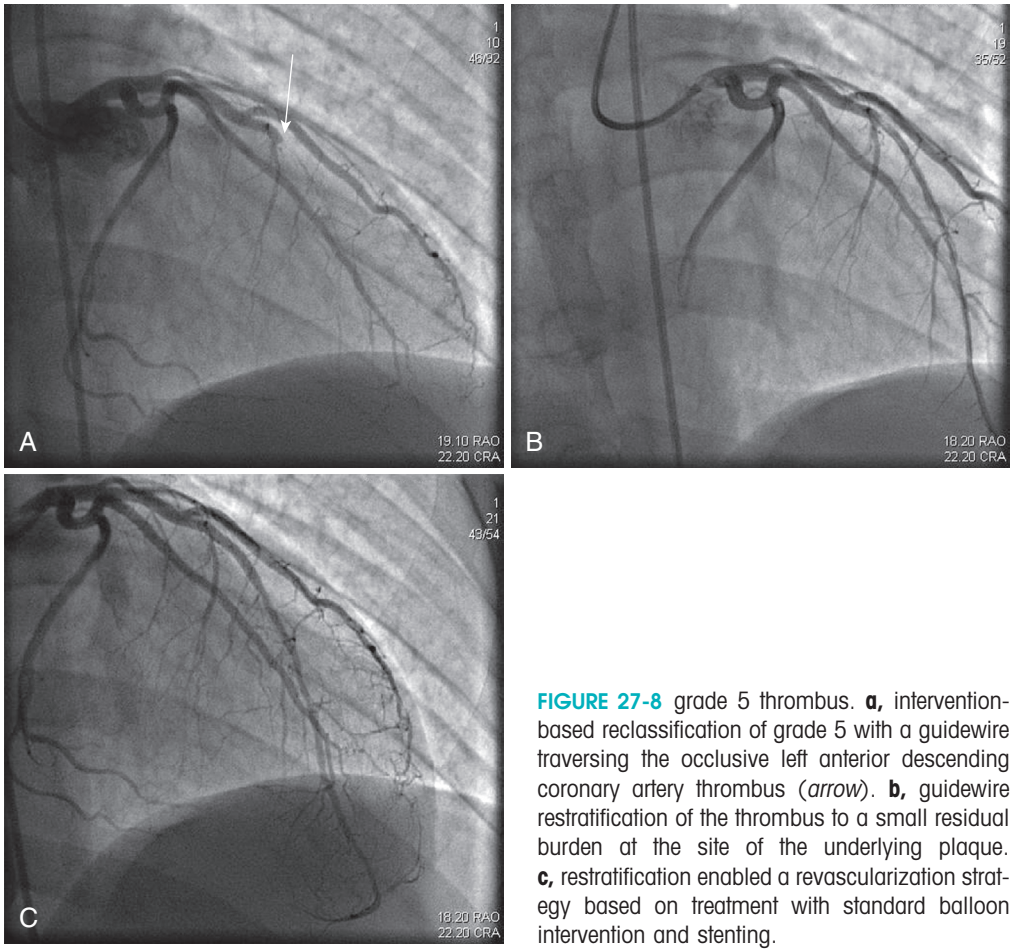


FIGURE 27-8 grade 5 thrombus. **a,** intervention-based reclassification of grade 5 with a guidewire traversing the occlusive left anterior descending coronary artery thrombus (*arrow*). **b,** guidewire restratification of the thrombus to a small residual burden at the site of the underlying plaque. **c,** restratification enabled a revascularization strategy based on treatment with standard balloon intervention and stenting.

dislodgment of friable thrombotic material by balloon and stent deployment is an issue of significant concern. Embolization of fragmented thrombotic particles obstructs flow within distal arterial segments, side branches, and myocardial microvessels. Overall, distal embolization occurs in the range of 6% to 15% of standard PCIs for all lesions types in ACSs and is associated with up to a sevenfold increase in the rate of periprocedural MI. In most instances, resultant severe ischemia, microinfarctions, inflammatory response, and contractile dysfunction reduce coronary reserve and cause deleterious effects on recovery and salvage.[43] These complications are especially encountered among patients who undergo primary PCI for AMI.[4,5] This was convincingly shown by the Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) investigators,[4] who studied the sequelae of angiographically visible distal embolization after PCI in 883 ST-elevation myocardial infarction (STEMI) patients receiving triple-antiplatelet therapy. Those who sustained angiographically evident embolization had significantly worse outcomes than patients without, as expressed by lower myocardial blush grade, impaired ST-segment resolution, and higher level of myocardial enzyme leakage.[4] At 1-year follow-up, reinfarction occurred in 8.9% versus 3.0% of patients without embolization ($P = .018$). Notably, the size of the aspirated thrombus was larger in patients with evidence of angiographic embolization versus those without ($P = .002$), and it more often contained erythrocytes (50% vs. 15.7%, $P < .001$, respectively). When compared with revascularization of thrombus-free lesions, embolization also significantly increases the need for emergency bypass surgery and the procedure-related death rate.[44]

The considerably limited yield of standard PCI in thrombus-containing lesions is further elucidated by the phenomenon termed the "illusion of reperfusion."[45] Essentially, it describes a marked discrepancy between primary PCI–gained TIMI grade 3 flow versus the disappointing, suboptimal degree of myocardial salvage. Notably, the desired grade 3 myocardial blush score is gained in only 28% to 35% of patients in whom standard PCI induces a TIMI grade 3 epicardial flow.[46] The main cause of this marked discrepancy is the prevalent IC thrombus and related distal embolization, microvessel obstruction, no-reflow phenomenon, and myocardial necrosis.[47] Clearly, patients who develop procedure-related no-reflow phenomenon sustain a larger infarct size, significantly worsened LV function, and a greater risk of adverse cardiac events and death.[48,49] Thus the thrombus's deleterious impact as a source of hazardous material that promotes adverse coronary events and suboptimal outcome should be anticipated and dealt with promptly before, during, and after PCI.[39,50] Accordingly, Table 27-5 delineates the indications for a dedicated thrombus-removal strategy.

PHARMACOTHERAPY FOR THROMBUS-CONTAINING LESIONS

The mainstay pharmacologic therapy for management of thrombus-containing lesions includes aspirin, heparin, GP IIb/IIIa platelet receptor antagonists, thienopyridines (clopidogrel, prasugrel, ticlopidine), and direct thrombin inhibitors. A beneficial decrease of thrombus burden can be achieved even before intervention to improve PCI results and reduce the risk of distal thrombotic embolization. Specifically, chronic aspirin therapy has been shown to decrease thrombus burden before stent deployment,[31] heparin is used to reduce fibrin formation and abolish platelet contractile forces,[51] and the IIb/IIIa receptor antagonists dramatically reduce platelet aggregate size and increase the fibrin accessibility of the platelet-rich clot to thrombolytics.[52] However, these agents are less effective in an already formed, active, and unstable thrombus,[53] especially when a high thrombus

TABLE 27-5 Indications for a Targeted Thrombus Strategy

Pathology
Atherosclerosis with associated thrombus Thrombotic embolus in a coronary artery or SVG Intracoronary thrombus accumulation secondary to hypercoagulability
Clinical
Unstable and stable angina, STEMI, or NSTEMI associated with: 1. Need to reduce thrombus burden in clot-laden lesions 2. Need to reduce thrombus impairment to forward flow 3. Need to reduce threat of thrombotic embolization 4. Need to reduce risk of no-reflow phenomenon
Targets
Native coronary arteries, old SVGs, CTOs, and stents

CTO, Chronic total occlusion; *NSTEMI,* non–ST-elevation myocardial infarction; *STEMI,* ST-elevation myocardial infarction; *SVG,* saphenous vein graft.

TABLE 27-6 Usefulness of Thrombectomy Devices

Benefits
1. Shortening the door-to-thrombus clearance time 2. Direct contact with the thrombus for targeted extraction 3. Allows selective infusion of thrombolytics, platelet aggregation inhibitors, and vasodilators through the device 4. Removal of thrombus-induced prothrombotic coagulants and promoters of vasoconstriction and platelet aggregation 5. Reduction of distal embolization and no-reflow phenomenon 6. Restoration or antegrade flow, improved myocardial blush score, and lowering of cTFC 7. Enables accurate assessment of underlying plaque morphology and stenosis 8. Facilitates stenting 9. Improves post-MI 6-month and 1-year MACE and survival rates
Limitations
1. May prolong PCI duration 2. Higher dependency on operator technique 3. May not achieve complete thrombus removal 4. Can cause distal embolization due to device manipulation 5. Do not completely eliminate no-reflow phenomenon 6. Do not reduce the need for adjunct stenting 7. Increased cost

cTFC, Corrected TIMI frame count; *MACE,* major adverse coronary event; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention.

grade is evident. For example, significant limitations of these useful pharmacologic therapies are quite apparent during the revascularization of old saphenous vein grafts (SVGs), which contain a large thrombus burden.[54] Suboptimal PCI results in these thrombotic vessels are manifested by inadequate ST-resolution at 60 minutes in patients with AMI, limited prevention of distal embolization, and an insufficient degree of revascularization. Thus in ACS patients with lesions that contain a significant clot burden, attempts to improve PCI outcomes should incorporate a mechanical removal strategy.[55]

APPROACH TO MECHANICAL THROMBUS REMOVAL

Role of Adjunct Thrombectomy

Following the publication of several landmark studies,[5,56] a rekindled interest in mechanical thrombus extraction arose—especially for STEMI management—and these devices are currently considered the mainstay of therapy.[57] Contemporary mechanical thrombus removal or dissolution devices can be categorized into four main types according to their activation mode: (1) manual aspiration catheters, (2) power-sourced thrombectomy, (3) ultrasound-induced sonication, and (4) embolic protection. The potential benefits and limitations of mechanical thrombectomy devices are described in Table 27-6.

A different classification defines thrombus extraction modalities as either "simple" aspiration-based or "complex" mechanically based modalities.[58] This categorization is supported by a recent meta-analysis[59] of 17 randomized trials on thrombus removal versus standard PCI in 3909 patients, which found that thrombus removal was associated with a significantly greater likelihood of TIMI grade 3 flow, myocardial blush grade 3, and ST-segment resolution. The investigators concluded that thrombus-removal devices appear to improve markers of myocardial perfusion in patients undergoing primary PCI with no difference in overall 30-day mortality but with an increased likelihood of stroke. The clinical benefits of thrombectomy appeared to be influenced by the device type, with a trend toward survival benefit with manual aspiration catheters and worsening outcomes with mechanical devices. Nevertheless, facing the large variability of thrombus content and size among patients with ACSs, well-trained operators can match the device choice to the morphologic characteristics of the target thrombus burden and achieve excellent results with each of these tools. The last point was recently reemphasized by a large Dutch study[5] of 812 consecutive patients treated with drug-eluting stents for STEMI. The investigators examined the impact of underlying thrombus size on procedural outcome and demonstrated the direct, proportional effect of the thrombus's initial and final burden on mortality and its role as an independent predictor of postprocedure MACEs and stent thrombosis (Fig. 27-9). The TAPAS study investigators[56] found that thrombus aspiration is applicable in a large majority of patients with STEMI, affording better reperfusion and clinical outcomes than PCI without a mechanical thrombus-removal strategy. These findings confirm previous observations from smaller trials and provide credence to the notion that manual aspiration protects the microcirculation during primary PCI. However, it is unclear whether these findings are attributed to immediate reduction in thrombus burden, facilitation of direct stenting, or a combination of the two mechanisms.[60]

Aspiration Catheters

Manual thrombus aspiration of the infarct-related vessel with dedicated catheters has gained intense interest over the course of the last decade as a useful technology for rapid reduction of thrombus burden, prevention of thrombus embolization, preservation of microvascular integrity, and reduction of the infarct size.[61] This technology is by far the most utilized in patients with thrombotic lesions. Data that attest to the merits and limitations of the thrombus-removal strategy with aspiration catheters are presented in (Table 27-7).

Most aspiration-based catheters are available in 4- to 6-Fr sizes and contain an extraction lumen and aspiration syringes. They are user friendly because of their low crossing profile, hydrophilic coating, flexibility, and tapered distal tip. Among commercially available aspiration catheters are the Export (Medtronic, Minneapolis, MN), Pronto extraction catheter (Vascular Solutions, Minneapolis, MN), Diver CE (Invatec, Roncadelle, Italy), Xtract (Volcano, Rancho Cordova, CA), QuickCat (Kensey Nash, Exton, PA), and Fetch (Possis, Minneapolis, MN). Several prospective trials that involve these catheters—including the Dethrombosis to Enhance Acute Reperfusion in Myocardial Infarction (DEAR-MI) trial[62] and the Randomized Evaluation of the Effect of Mechanical Reduction of Distal Embolization by Thrombus Aspiration in Primary and Rescue Angioplasty (REMEDIA)[63]—demonstrated increased myocardial blush grade of 2 to 3 and adequate ST-segment resolution of greater than 70% in a substantial number of patients who received this treatment versus those who underwent standard PCI. In addition, the manual thrombus-aspiration modality improved myocardial tissue-level perfusion, as well as LV functional recovery and modeling.[64]

It is unclear whether one aspiration catheter provides a significant advantage over others. In the prospective single-center STEMI study, Randomized Evaluation of Thrombus Aspiration by Two Thrombectomy Devices in Acute Myocardial Infarction (RETAMI),[65] the investigators found that the use of a certain aspiration catheter before stenting removed more thrombus burden and provided a greater

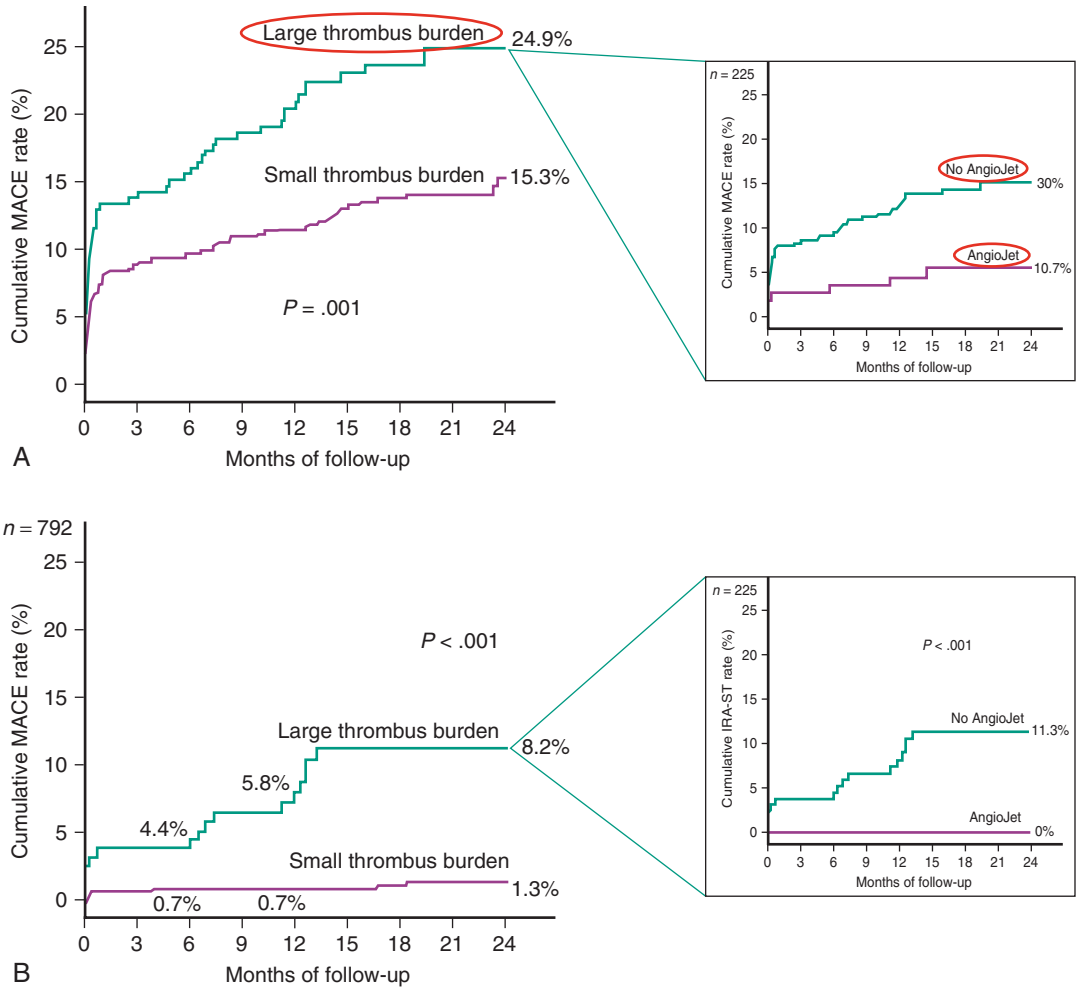


FIGURE 27-9 **A,** Large unresolved thrombus increases major adverse cardiac events (MACEs). **B,** Large unresolved thrombus increases stent thrombosis. IRA-ST, Infarct-related artery stent thrombosis. (Adapted from Sianos G, Papafaklis MI, Daemen J, et al: Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. *J Am Coll Cardiol* 50:572-583, 2007.)

postintervention epicardial flow and microvascular perfusion than a catheter made by another manufacturer. However, such conclusions strongly depend on operator preference and other factors, such as cost. In a study similar to the REMEDIA trial, investigators observed a significant decrease in procedure-related elevation of cardiac enzymes, in comparison to patients who did not receive aspiration, as well as only 3% no-reflow versus 15%, respectively.[66] Notably, aspiration catheters do not increase procedural time; rather they offer a safe, straightforward approach for thrombus removal. Follow-up over 6 months demonstrated a significantly decreased occurrence of LV dilatation versus that of patients who underwent standard PCI. Meta-analysis of randomized studies on catheter thrombus aspiration shows a significant benefit of reducing mortality compared with standard PCI alone, 2.7% versus 4.4% ($P = .05$), respectively.[67] However, it should be noted that several studies failed to find any advantage to the routine use of aspiration catheters in STEMI patients and observed that this approach does not increase myocardial salvage and in fact may *increase* final infarct size.[68]

A cautionary observation was recently suggested by the multicenter, prospective, randomized, controlled, open-label Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) registry, which compared manual thrombus aspiration followed by PCI against PCI only in patients with STEMI. Patients were enrolled from the national Swedish Coronary Angiography and Angioplasty Registry (SCAAR), and end points were evaluated through national registries. The primary end point was all-cause mortality at 30 days, and 7244 patients who presented within 24 hours of onset of symptoms were recruited. The TASTE investigators reported no reduction of all-cause 30-day mortality in the study patients (2.8% in the aspiration catheter group vs. 3.0% in the PCI-only group).[69] The TASTE study design, inclusion criteria leading to selection bias, and the relatively low statistical power of analysis encountered considerable criticism. Thus several questions remain unanswered regarding the findings of this study, including the need for analysis of the long-term follow-up results.

Indeed, certain limitations of aspiration catheters should be recognized,[70] such as the difficult delivery along tortuous vessels, reduced capability to aspirate at the distal coronary segments, and the risk of dissection/perforation in cases where the guidewire is not located within the true lumen. The low negative aspiration pressure and the small evacuation holes also limit the yield of these catheters in the presence of a large-volume thrombus. Commonly, the application of aspiration catheters results in inadequate clot extraction that leaves at least 30% to 50% residual thrombus volume.[68] The risk of catheter-induced distal embolization, especially during a hurried maneuver, and the need for antegrade and retrograde crossing of a large thrombus should be taken into account when removal will be undertaken with aspiration catheters. It is important to remember that even sequential use of thrombus-aspiration catheters and distal protection filters can result in insufficient thrombus removal.[67,71,72]

TABLE 27-7 Outcomes of a Dedicated Thrombus-Removal Strategy Using Aspiration Catheters

1. Thrombus removal is improved.[74]
2. Visual thrombotic aspirate can be obtained in most patients without definite angiographic thrombus; the extent of underlying thrombus does not influence the PCI result.[140]
3. Infarct size is reduced and myocardial viability is preserved.[141]
4. Myocardial edema, hemorrhage, microvascular obstruction, and left ventricular remodeling are reduced.[142]
5. The reduction in thrombus burden has a positive impact on myocardial reperfusion and late clinical outcome.[39]
6. One-year mortality is reduced, and a survival benefit is provided.[143]
7. Recurrent MI and stroke are reduced.[78]
8. The rate of stent restenosis is reduced.[144]
9. Rate of PCI-related MACEs is lower, late lumen loss is reduced, and rate of stent restenosis is reduced in diabetics.[145]
10. The adverse effects of delay in time to intervention is limited in patients who present 6 hours to 12 hours after STEMI onset.[146]
11. The need for balloon angioplasty and stenting in select STEMI patients is obviated.[147]
12. All-cause 30-day mortality in STEMI patients is not reduced.[69]
13. Aspiration thrombectomy in early PCI for NSTEMI in thrombus-containing lesions does not reduce the extent of no-reflow phenomenon compared with standard PCI.[73]

MACE, Major adverse coronary event; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention *NSTEMI,* non–ST-elevation myocardial infarction; *STEMI,* ST-elevation myocardial infarction.

Because thrombus aspiration is most frequently used for STEMI, a valid question arises as to the role of aspiration thrombectomy in patients with non–ST-elevation myocardial infarction (NSTEMI). The Thrombus Aspiration in Thrombus-Containing Culprit Lesions in Non–ST-Elevation Myocardial Infarction (TATORT) NSTEMI study was a prospective, controlled, multicenter, randomized trial that compared adjunctive aspiration thrombus removal to conventional PCI in patients with thrombus-containing lesions. The trial randomized 460 patients in a 1:1 fashion to aspiration thrombectomy and standard PCI.[73] The primary end point was the extent of microvascular obstruction assessed by cardiac magnetic resonance within 4 days after randomization. Clinical end points that included death, myocardial reinfarction, target-vessel revascularization, and new congestive heart failure (CHF) were analyzed at 6 months. Microvascular obstruction was not different between the aspiration thrombectomy and standard PCI groups (1.7% LV vs. 1.6% LV, respectively, $P = .65$). Similarly, no significant differences were observed in infarct size, myocardial salvage index, or angiographic parameters such as blush grade or TIMI flow grade. Clinical follow up at 6 months also revealed no differences in the combined clinical end point between the thrombectomy and the standard PCI groups ($P = .85$). Accordingly, the investigators concluded that aspiration thrombectomy in patients with NSTEMI who undergo early PCI in thrombus-containing lesions does not reduce the extent of no-reflow phenomenon compared with standard PCI without thrombectomy.

Power-Sourced Thrombectomy Devices

The mainstay representatives of this group of mechanical tools include the rheolytic thrombectomy, excimer laser, and X-Sizer (eV3, Plymouth, MN). The question of whether power-based mechanical thrombectomy offers any advantage over aspiration catheters is pertinent to practical management. However, only a limited number of prospective studies with direct comparison between these two modalities have been conducted. Parodi and colleagues[74] included 80 AMI patients in a prospective study to compare rheolytic thrombectomy to a manual thrombus aspiration catheter. They used OCT to assess residual thrombus after removal by these devices and found that all but one patient had residual thrombus after rheolytic thrombectomy or aspiration catheter. The number of OCT quadrants that contained thrombus in the manual-aspiration arm was higher than in the rheolytic arm, but the difference did not reach statistical significance. Large residual thrombus was more frequently identified in the manual-aspiration arm ($P = .039$), and all markers of reperfusion were better in the rheolytic-thrombectomy arm. At 6 months, the percentage of malapposed stent struts in the manual-aspiration arm was higher than in the rheolytic arm ($2.7 \pm 4.5\%$ and $0.81 \pm 1.6\%$, respectively; $P = .02$). The investigators concluded that both technologies result in incomplete removal of thrombus in patients with AMI, although rheolytic thrombectomy seemed more effective in thrombus removal and myocardial reperfusion.

Overall, there is a strong clinical impression that the larger the target thrombus volume, the higher the extracting yield of a power-based mechanical thrombectomy device.[75-77] This is supported by a recent meta-analysis[78] of 24 randomized trials (including 21 with indirect comparison and three with direct comparison of these thrombus-removal methods) that involved 4927 STEMI patients. The authors concluded that the meta-analysis lends support to the benefits of mechanical thrombectomy but only when used in patients with high thrombus burden. Some controversy surrounds this issue, and some authors argue that a comparison between manual aspiration and power-based mechanical thrombectomy is unethical in patients with lesions that contain large thrombus burden because these patients should be treated specifically with mechanical, power-sourced thrombectomy devices.[79]

The X-Sizer thrombectomy system is mainly used in Europe[80] and consists of a helical cutter enclosed within a protective housing attached to a dual-bore catheter shaft that contains a guidewire and vacuum/extraction lumens. Activation of the handheld controller simultaneously rotates the helical cutter at 2100 rpm, which entraps and macerates soft atherosclerotic plaque and thrombus and channels it to a vacuum collection bottle. The device operates 1.5-, 2.0-, and 2.3-mm diameter cutters and is compatible with 0.014-inch guidewires. Napodano and colleagues[80] studied 92 AMI patients and demonstrated that direct PCI for AMI with X-Sizer thrombectomy followed by stenting significantly improves myocardial reperfusion as assessed by myocardial blush score and ST-segment resolution. The large, prospective X-Sizer in Acute Myocardial Infarction Patients for Negligible Embolization (X-AMINE) multicenter study that followed demonstrated a device success rate of 87% and adequate thrombus removal in 95% of the lesions.[81]

The AngioJet rheolytic thrombectomy system (Possis/Medrad, Minneapolis, MN) is a U.S. Food and Drug Administration (FDA) approved device for thrombus-containing lesions in coronary and peripheral interventions. The principle of activation is based on creation of saline jets inside the catheter that travel backward at high speed to create a negative pressure zone (Venturi effect). Side windows along the catheter's tip optimize fluid flow and draw thrombus into the catheter for fragmentation and removal (Fig. 27-10). A new AngioJet console, the ULTRA, was recently introduced and features automated, rapid setup and support for a wide range of catheters. Multiple rapid-exchange 4- or 5-Fr flexible catheters are available for various target vessels, including native coronary arteries, old SVGs, and peripheral arteries. Proper thrombectomy technique that incorporates slow advancement of the catheter essentially eliminates the need for a temporary pacemaker; however, some operators recommend it in patients who require revascularization of a major vessel or in cases with limited myocardial reserve. The AngioJet's ability to treat large thrombus burden in STEMI patients and to provide more effective myocardial perfusion than that obtained with standard balloon and stenting has been well documented (Fig. 27-11).[82,83] The Thoraxcenter group elegantly demonstrated that AngioJet thrombectomy is a significant independent predictor of reduced risk for stent thrombosis and MACE specifically when applied for removal of large thrombus burden in STEMI patients.[5]

In the Femoral Artery Stenting Trial (FAST), AngioJet was used in 116 AMI patients with extensive thrombus load, which led to significant improvements in perfusion compared with a control group with similar thrombus burden who received standard PCI.[84] The in-hospital

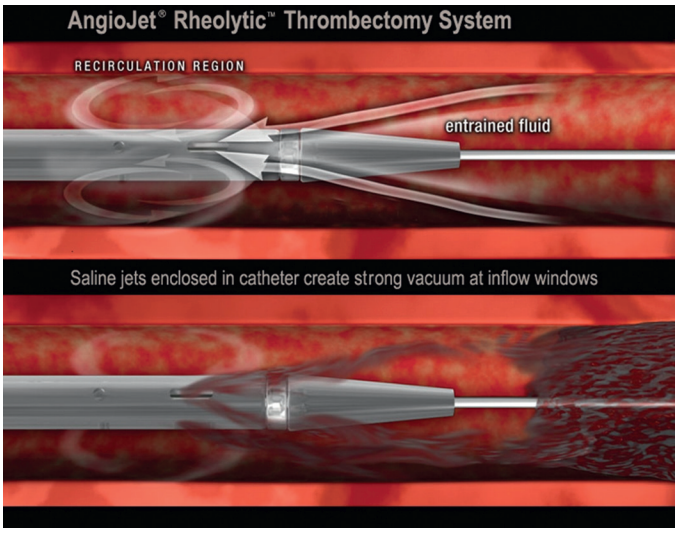


FIGURE 27-10 AngioJet rheolytic thrombectomy system.

major adverse coronary event (MACE) rate for the AngioJet was relatively low at 8%. Further evidence of the excellent safety profile of the AngioJet has been repeatedly reported.[85,86]

Nevertheless, this tool, together with the entire concept of thrombus extraction, sustained a major setback a few years ago when negative results from the multicenter AngioJet Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction (AIMI) study were published.[87] In retrospect, this study was poorly designed because the presence of thrombus in the target lesion was not required for enrollment, and operators were required to utilize a technique mandating passive advancement to the distal end of the target vessel, which allowed only retrograde thrombectomy. In order to address questions raised by and about the AIMI study, a prospective, multicenter AngioJet Rheolytic Thrombectomy Before Direct Infarct Artery Stenting in Patients Undergoing Primary PCI for Acute Myocardial Infarction (JETSTENT) study was launched to compare the effect of the AngioJet versus direct stenting on myocardial reperfusion, infarct size, and clinical outcomes in STEMI patients.[88] The study exclusively focused on AMI patients with angiographically visible thrombus, using only slow, single-pass antegrade thrombectomy and a narrower temporal definition of early ST-segment resolution (>50% within 30 min). This study enrolled 501 STEMI patients with visible thrombus (grades 1 through 4) or with a totally occluded infarct-related vessel (thrombus grade 5 with subsequent restratification). At baseline both groups had a thrombus grade of 3 to 5 in 99% and TIMI grade 0 flow in 83% of the patients. A platelet receptor antagonist was

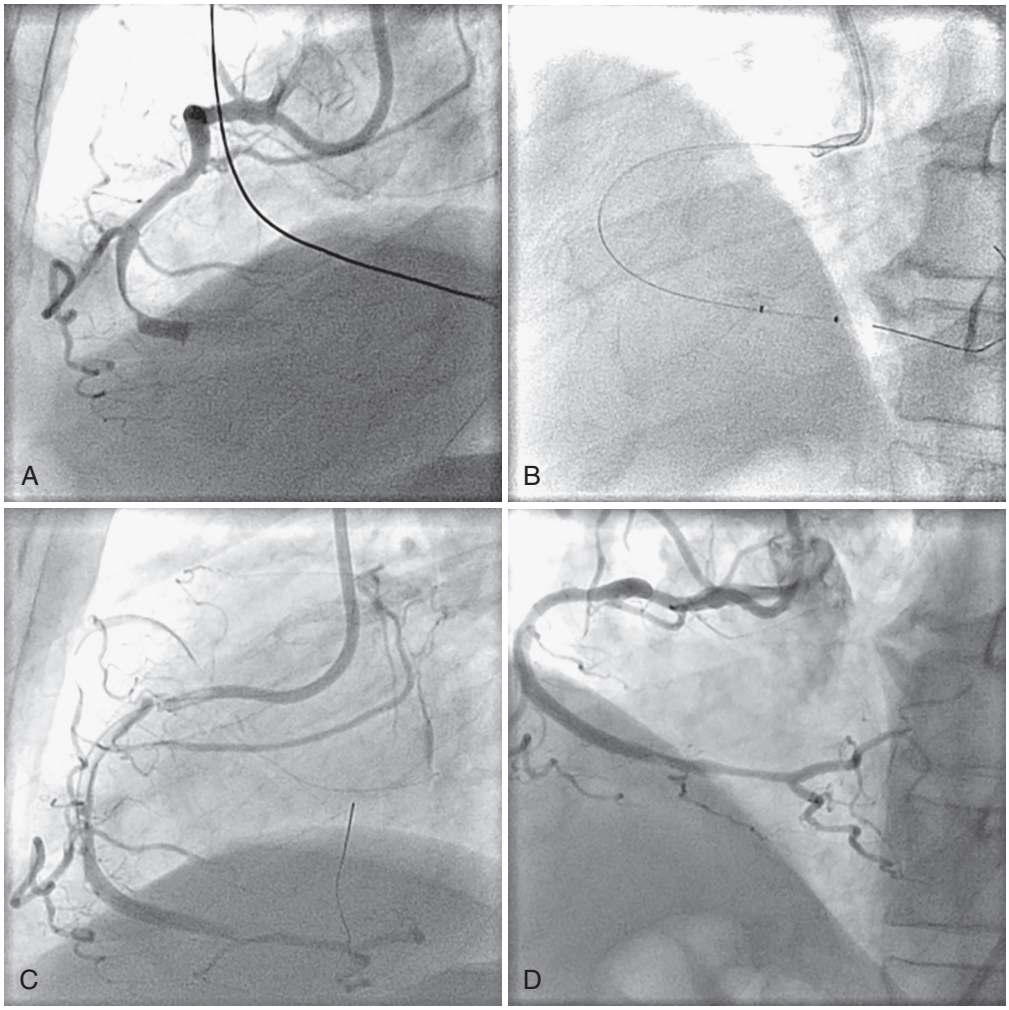


FIGURE 27-11 Rheolytic thrombectomy in a patient with ST-elevation myocardial infarction. **A,** Initial angiographic view: thrombus grade 5. **B,** AngioJet catheter crossing the target thrombotic occlusion. **C,** After AngioJet. **D,** Final results.

used in 97% and 98%, respectively, and a 93% procedural success rate was achieved in both groups. The results demonstrated improved myocardial reperfusion with the AngioJet as determined by higher rates of early ST-segment resolution (86% vs. 79%, respectively, $P = .04$). A significant difference in MACE rates was observed between the groups at 1 month (3.1% AngioJet vs. 6.9% direct stenting, $P = .05$) and at 6 months (12% AngioJet vs. 21% direct stenting, $P = .01$). No difference was found between the two approaches regarding myocardial blush score and corrected TIMI frame count. Multivariable regression analysis showed that randomization to rheolytic thrombectomy was a predictor of ST-segment resolution (odds ratio [OR] 1.7; 95% confidence interval [CI], 1.03 to 2.8; $P < .039$) and 6-month MACE rate (hazard ratio [HR] 0.5; 95% CI, 0.31 to 0.82; $P = .06$). Figures 27-12 and 27-13 demonstrate the application of two other mechanical thrombectomy devices in heavy thrombotic settings, the X-Sizer from eV3 and the ThromCat (Spectranetics, Colorado Springs, CO), respectively.

Lasers are mainly used for debulking of lesions deemed unsuitable for standard PCI and can be applied for revascularization of thrombus-containing lesions.[89] The pulsed-wave ultraviolet wavelength excimer laser (Spectranetics, Colorado Springs, CO) has been successfully applied in patients with ACSs, including AMI (Fig. 27-14).[90] The excimer laser light interacts favorably with several components of the occluding thrombus. Laser-generated acoustic shock waves dissolve fibrin fibers[91] and suppress platelet aggregation (Fig. 27-15).[92] The thrombus dissolution capability of this laser was further examined by the Excimer Laser Angioplasty in Acute Myocardial Infarction (CARMEL) multicenter study.[76] The trial enrolled 151 "real world" AMI patients with continuous chest pain and ischemia in the presence of either STEMI or NSTEMI, including those with late presentation, cardiogenic shock (13%), failed thrombolytic therapy (11%), or contraindications for this therapy (17%). The target vessel was a coronary artery in 79% and an old bypass graft in 21%. As opposed to many studies, the entire cohort underwent quantitative and statistical analyses by independent core laboratories. The results proved that despite the presence of compromised hemodynamics and a heavy thrombus burden in as many as 65% of the patients, laser success was achieved in 95%, angiographic success in 97%, and procedural success in 91%. It is worth noting that thrombus was not identified as a predictor of PCI failure. A baseline TIMI grade 0 flow of 1.2 (±1.1) increased to 2.8 (± 0.5) with the laser energy and was followed by final TIMI flow of 3.0 (± 0.2; $P < .001$ vs. baseline) with adjunct stenting. Distal embolization occurred in only 2%, no-reflow phenomenon occurred in 3%, device-induced small dissection was observed in 4%, and a small perforation occurred in 0.6%. The total MACE rate was relatively low at 13%. The most important finding attested to the fact that maximal removal effect was directly proportional to the baseline thrombus burden; that is, the larger the initial thrombus burden at the target lesion, the more effective and the higher the gain for the laser-induced dissolution (Fig. 27-16).

Further subgroup analysis of this trial recognized a specific laser gain among late-presentation patients who exhibited a heavy thrombus burden and unstable hemodynamic parameters.[93] Thus although not a randomized comparison, this study provided the first quantitative evidence of the considerable benefit of a dedicated mechanical thrombectomy device in thrombus-removal strategy and, in particular, in AMI. The expanding role of excimer laser technology in revascularization of thrombus-containing lesions has been refined in the last decade with the growing recognition of the laser's unique ability to create favorable coronary lumen morphology, which in turn facilitates stent deployment and long-term results.[94]

Ultrasound-induced thrombus dissolution can be offered as adjunctive therapy aimed at increasing the efficacy of common thrombolytic therapies.[95] Ultrasound-producing devices are defined by their different acoustic intensity and frequency, ranging from low (20 to 400 KHz) to high (0.5 to 3 GHz). The two main approaches to sonication therapy rely on an external device to deliver transcutaneous therapeutic ultrasound energy[96] and on the invasive intravessel catheter, which delivers sonication directly to the targeted thrombus. Further randomized studies will be required in order to investigate both the promise and the safety issues that relate to the external mode of delivery and to examine whether it provides improved enhancement of pharmacologic thrombolytic agents and superior thrombus dissolution in comparison with the more invasive, direct intracoronary delivery method.

EMBOLIC PROTECTION DEVICES

These tools are used to prevent the propagation of atheromatous or thrombotic debris downstream. These devices can be classified into three categories: (1) filter-based devices, (2) proximal occlusion devices, and (3) distal flow occlusion devices.[97] The use of embolic protection devices (EPDs) does not require any special preparation of the patient other than the standard anticoagulation therapy for percutaneous intervention. These devices are user friendly; however, a clear limitation relates to the need to cross the very same clot, which requires protection with a somewhat bulky protection device, and the need for an adequate length of distal landing zone. Overall, the EPDs are useful adjuncts in primary PCI for ACS and have been shown to efficaciously reduce the rate of periprocedural infarction.[98] The EPDs have a class I indication for SVG interventions because of the prevalence of thrombus-containing lesions.[99] However, studying the value of distal protection during rescue PCI, the Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD)[100]

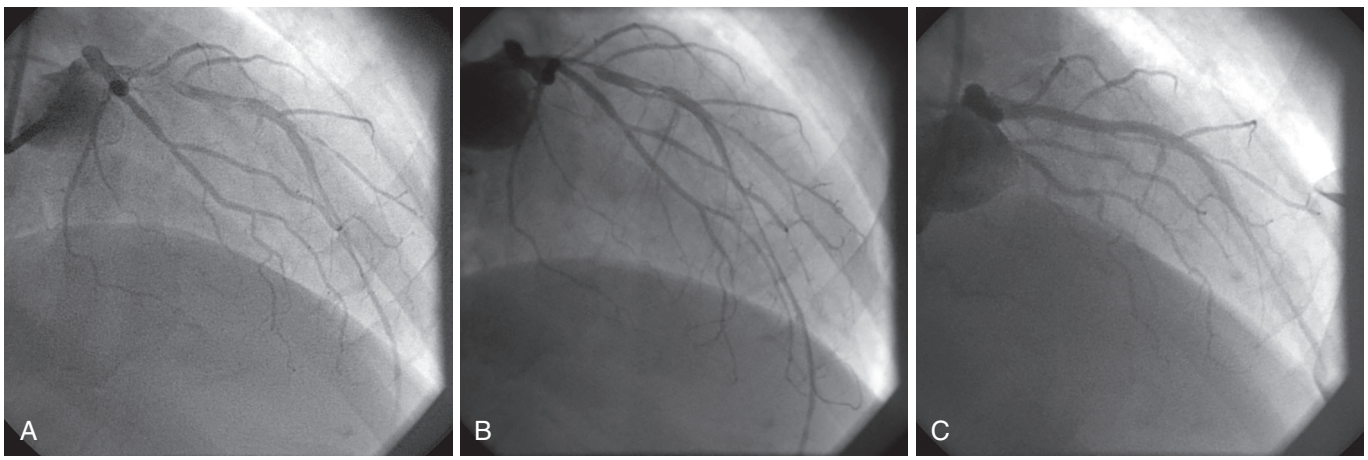


FIGURE 27-12 **A,** Initial angiogram prior to X-Sizer thrombectomy in a patient with ST-elevation myocardial infarction and a heavy thrombus load in the left anterior descending coronary artery. **B,** Thrombus cleaning by the X-Sizer leads to adequate exposure of the underlying diseased plaques. **C,** Final percutaneous coronary intervention results.

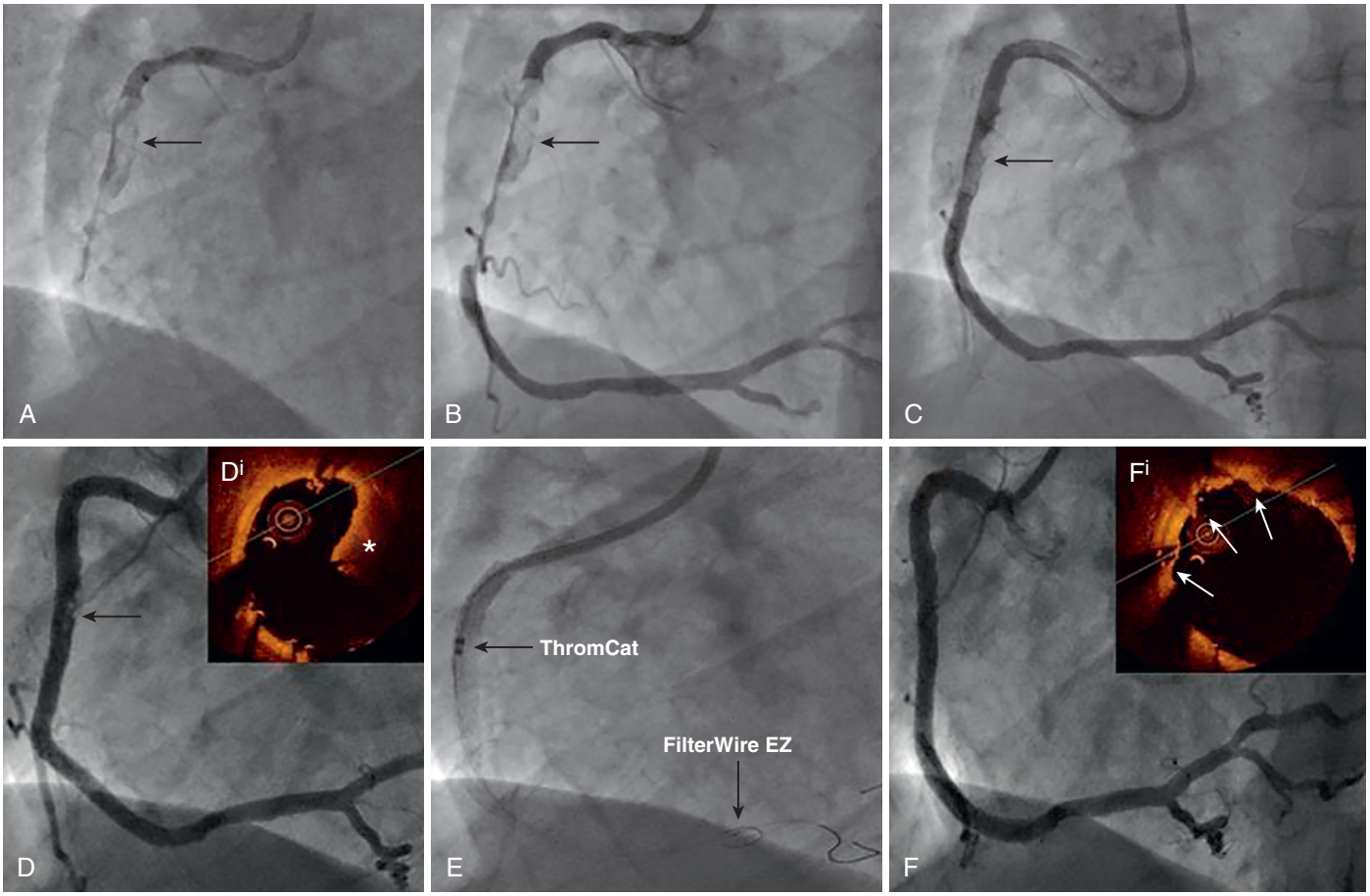


FIGURE 27-13 Application of the ThromCat device, which uses a high-speed rotational helix to macerate and extract thrombus. This thrombectomy tool can be synergistically applied with a filter protection device. *Di,* The treated site as demonstrated by optical coherence tomography technique; asterisk indicates residual thrombosis; *Fi,* final view of treated site (*arrows*) as observed through optical coherence tomography. (From Rawlins J, Sambu N, O'Kane P: Strategies for the management of massive intra-coronary thrombus in acute myocardial infarction. *Heart* 99:510, 2013.)

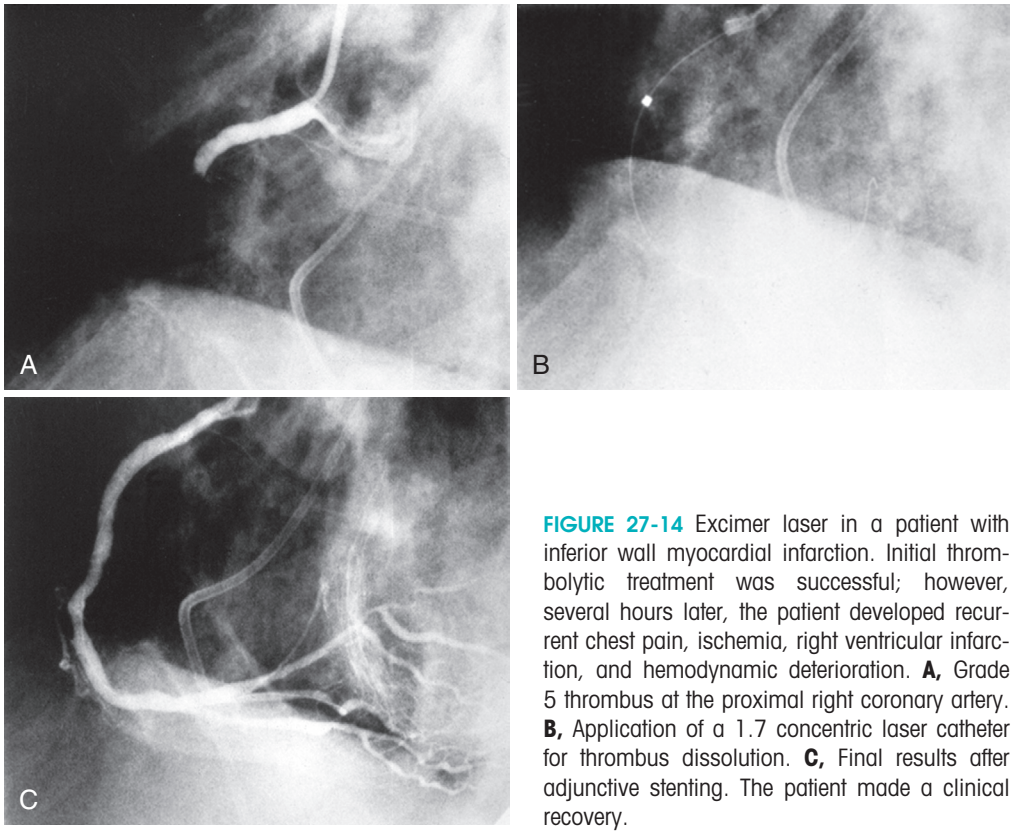


FIGURE 27-14 Excimer laser in a patient with inferior wall myocardial infarction. Initial thrombolytic treatment was successful; however, several hours later, the patient developed recurrent chest pain, ischemia, right ventricular infarction, and hemodynamic deterioration. **A,** Grade 5 thrombus at the proximal right coronary artery. **B,** Application of a 1.7 concentric laser catheter for thrombus dissolution. **C,** Final results after adjunctive stenting. The patient made a clinical recovery.

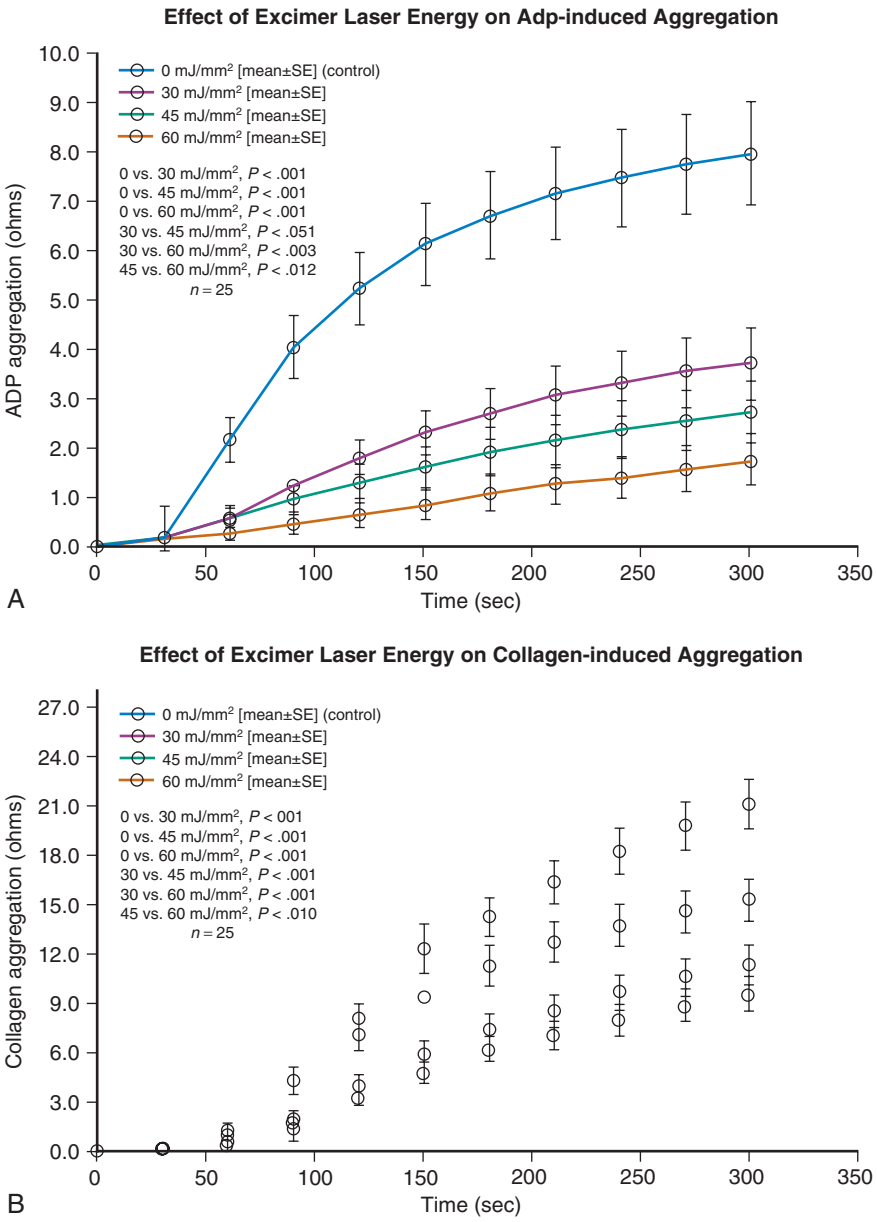


FIGURE 27-15 **A** and **B,** The in vitro effect of ultraviolet wavelength excimer laser on platelet aggregation. *ADP,* Adenosine diphosphate; *SE,* standard error. (Based on Topaz O, Minisi AJ, Bernardo NL, et al: Alterations of platelet aggregation kinetics with ultraviolet laser emission: the "stunned platelet phenomenon." *Thromb Haemost* 86:1087-1093, 2001.)

investigators found that patients with AMI undergoing rescue PCI compared with primary PCI have similar myocardial perfusion, infarct size, and clinical outcomes, concluding that distal protection apparently does not offer any detectable benefit in this patient population. In fact, there is a concern that the routine use of filter protection for PCI of STEMI may increase the incidence of stent thrombosis and the clinically driven target-lesion and target-vessel revascularization.[101] A selective, rather than routine, strategy of protection device utilization should be applied, limited to those patients with the highest risk of clinically relevant embolization.[102]

Stents for Dedicated Thrombus Management

Direct stenting during PCI of thrombus-containing lesions with either bare-metal or drug-eluting stents is a commonly used strategy.[103] Nonetheless, despite the popularity and perceived success of direct stenting, distal embolization and no-reflow phenomenon do occur, mainly because of the mobilization of fragmented clot.[83,104] Two novel stents have been developed to directly treat an underlying thrombus. The first, a thrombus-capturing stent, is represented by the MGuard stent (InspireMD, Tel-Aviv, Israel), which offers a trapping stent mechanism for the dedicated management of IC thrombus and reduction of embolization. This stent is made of a unique stainless steel bare-metal stent (BMS) covered with an ultrathin, micron-level (150 by 180 μ) flexible mesh net fabricated by circular knitting (Fig. 27-17). During stent deployment, the net stretches and slides over the expanding stent struts, creating custom-designed pores parallel to the vessel wall. Once deployed, the MGuard stent seals the thrombus and accompanying plaque and captures potential embolic debris between the fiber net and the arterial wall (Figs. 27-18 and 27-19).[105] The aim of this unique stent is to prevent thrombotic distal embolization and, consequently, to improve the microcirculation. The early experience with this stent included 100 STEMI patients who enrolled in a prospective multicenter study, all with angiographic evidence of thrombus in the infarct-related artery. The stent achieved an impressive 90% myocardial blush grade of 3 and 90% of complete (>70%) ST-segment resolution.[106] The investigators concluded that the MGuard stent offers a safe and feasible option for PCI in STEMI patients and provides a very high perfusion grade and significant electrocardiographic (ECG) improvement. Recently, Romaguera and associates[107] set out to assess specifically the usefulness of this stent in STEMI patients in whom a high thrombus burden persists despite aggressive manual aspiration.

FIGURE 27-16 Maximal device gain and thrombus dissolution are obtained in the extensive thrombus group. *DS,* Diameter stenosis; *MLD,* minimal luminal diameter; *QCA,* quantitative coronary angiography; *TIMI,* thrombolysis in myocardial infarction. (Adapted from Topaz O, Ebersole D, Das T: Excimer laser angioplasty in acute myocardial infarction [the CARMEL multicenter study]. *Am J Cardiol* 93:694-701, 2004.)

QCA per TIMI Thrombus

GRADE	0 No thrombus	1 Small thrombus	2 Medium thrombus	3 Large thrombus	4 Extensive thrombus
Patients (*n*)	11	14	28	45	63
MLD: Baseline (mm)	.87 ± .69	.72 ± .43	.65 ± .45	.59 ± .49	.37 ± .49
Post laser	1.74 ± .46	1.48 ± .49	1.51 ± .51	1.50 ± .41	1.62 ± .62
Laser acute gain	.90 ± .63	.76 ± .52*	.84 ± .60	.94 ± .48	1.21 ± .72*
Final	2.97 ± .60	2.54 ± .55	2.47 ± .62	2.62 ± .55	2.76 ± .62
%DS: Baseline	74% ± 21%	76% ± 16%	77% ± 16%	82% ± 16%	89% ± 15%
Post laser	47% ± 13%	51% ± 11%	52% ± 15%	51% ± 13%	53% ± 17%
Laser acute reduction	27% ± 18%	25% ± 15%	25% ± 19%	31% ± 16%	36% ± 20%
Final	16% ± 17%	15% ± 13%	22% ± 14%	16% ± 17%	22% ± 16%

*$P = .03$

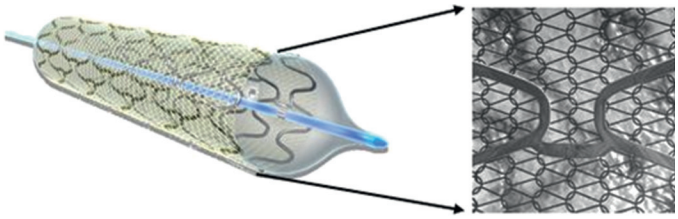


FIGURE 27-17 MGuard thrombus-capturing stent system.

They prospectively enrolled 56 patients with residual angiographic TIMI thrombus grade 4 or 5 after targeted manual catheter aspiration. After MGuard stent implantation, more than 85% of the cases had thrombus grade 0, and final TIMI grade 3 flow was gained in 82%, normal myocardial blush in 55%, and complete ST-segment resolution in 59%. Occlusion of a side branch occurred in 2 cases (3.6%), embolization in 5 cases (8.9%), and transient no-reflow phenomenon in 4 cases (7.1%). The MACE rate at 9 months was 3.6%, including one definite stent thrombosis and one target-vessel revascularization. The investigators concluded that this stent may be useful for preventing distal embolization in STEMI patients and high thrombus burden after failed manual catheter aspiration.

A different approach to thrombus eradication with stents involves the concept of exclusion/displacement. Gunn and colleagues[108] introduced the novel use of pericardium-covered stent graft to treat massive thrombus in the setting of ACS. The Aneugraft stent graft (ITGI Medical, Or Akiva, Israel) consists of a conventional, balloon-expandable, 316L stainless steel stent sutured externally at either end with a single layer of blemish-free equine pericardium 105 μ thick. The initial experience with 10 lesions demonstrated immediate elimination of the large filling defect and restoration or maintenance of TIMI grade 3 blood flow. Only one of these unique stents thrombosed (in a patient who could take only aspirin). At present it appears that this intriguing stent technology is suitable for select patients in whom conventional thrombus-removal technology is not available or failed.[109]

Power Thrombectomy

This reperfusion strategy is mainly aimed at treatment of lesions and vessels laden with very heavy thrombus burden associated with slow antegrade flow. It combines power-sourced mechanical thrombectomy with selective injection of thrombolytic agents into the target vessels and offers the benefit of direct interaction of thrombolytic pharmacotherapy with the underlying clot, a decreased risk of systemic lytic effects, and precise maceration of the thrombus load by the mechanical device.[110,111] The thrombolytic agents can be selectively administered during the intervention through a dedicated perfusion balloon such as the ClearWay device (Atrium Medical, Hudson, NH; Fig. 27-20).

UNIQUE THROMBUS-CONTAINING TARGETS AND RELATED REVASCULARIZATION TECHNIQUES

Bypass Grafts

Myocardial ischemia that occurs early after CABG is typically caused by graft thrombosis resulting from surgery-related mechanical issues, whereas late ischemic events are caused by progression of soft, friable, atheromatous plaques in the grafts.[112,113] Collagen-rich (firm) or collagen-poor (soft) thrombus superimposition, an integral component of this process (Fig. 27-21), is found in as many as 80% of old bypass grafts.[114] The thrombotic content is often much greater in vein grafts than in native arteries because of the greater caliber of vein grafts and the lack of side branches, conditions that promote blood stagnation and coagulation.

The Thrombocyte Activity Reassessment and Genotyping (TARGET) investigators[53] clearly demonstrated that in the current strategy of routine stenting and GP IIb/IIIa inhibitors, thrombus is still the angiographic characteristic most closely associated with adverse outcome of PCI in SVGs. Thus revascularization of degenerated, friable, old SVGs is fraught with technical difficulties and risks.[115] Among those vessels, a unique group can be encountered that consists of totally occluded grafts that continue to account for ongoing ischemia at their distal perfusion territory. Commonly, the corresponding grafted native coronary artery is occluded by severe atherosclerosis and thrombus, which originally migrated from the diseased vein graft.[116] In most cases, percutaneous revascularization of these grafts, whether occluded for a short or long period, provides the only viable treatment option, albeit a technically highly demanding one.[117] Indeed, operators have been traditionally advised to resist the challenge of opening such occluded old grafts because of the remarkable technical difficulties and concerns for procedure-induced complications.[118] However, in our experience, a technique known as *SVG sculpturing* can be used to facilitate revascularization of totally occluded grafts through maximal

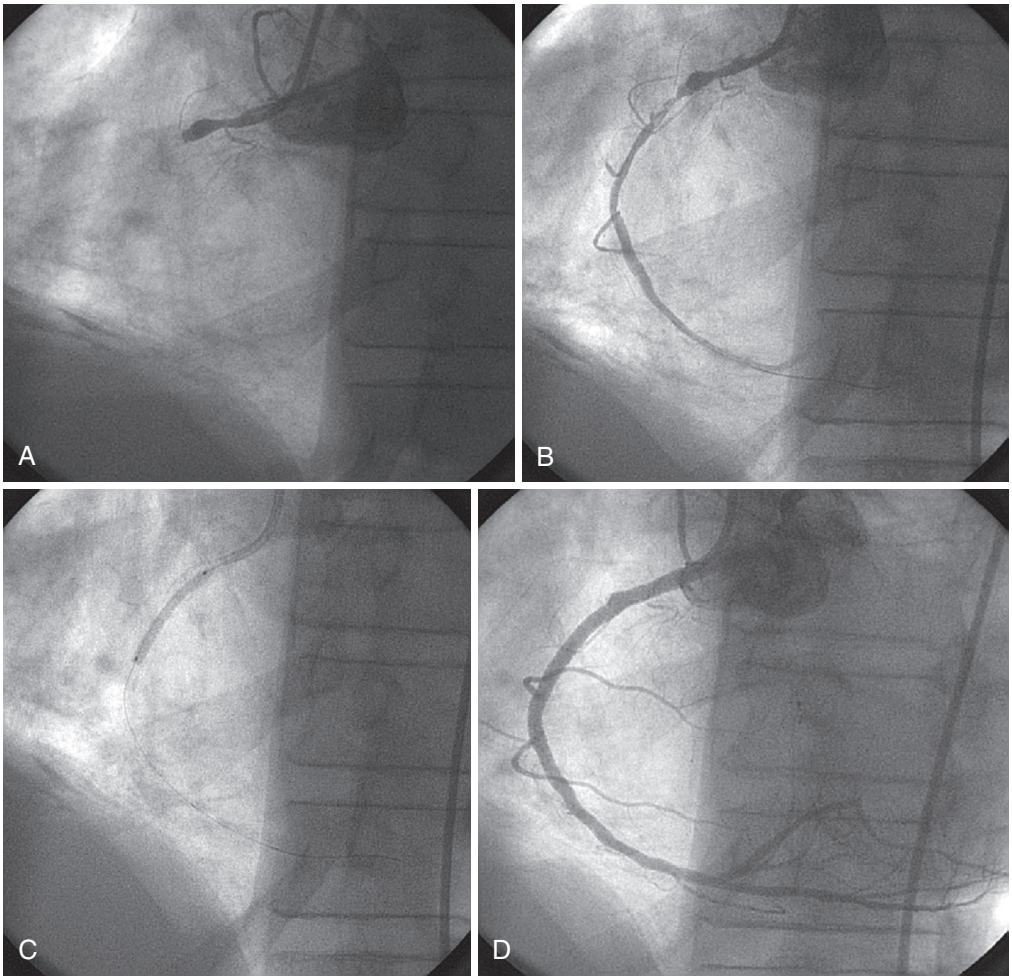


FIGURE 27-18 An 81-year-old patient with inferior ST-elevation myocardial infarction. **A,** Grade 5 thrombus occludes the right coronary artery (RCA). **B,** After aspiration and balloon dilation, antegrade flow is restored, but grade 2 thrombus is present. **C,** Deployment of a 3.0/24-mm MGuard thrombus-capturing stent. **D,** Final results demonstrate complete patency of the RCA with TIMI grade 3 blush. ST-segment resolved. (Courtesy Ran Kornowski MD, Rabin Medical Center, Israel.)

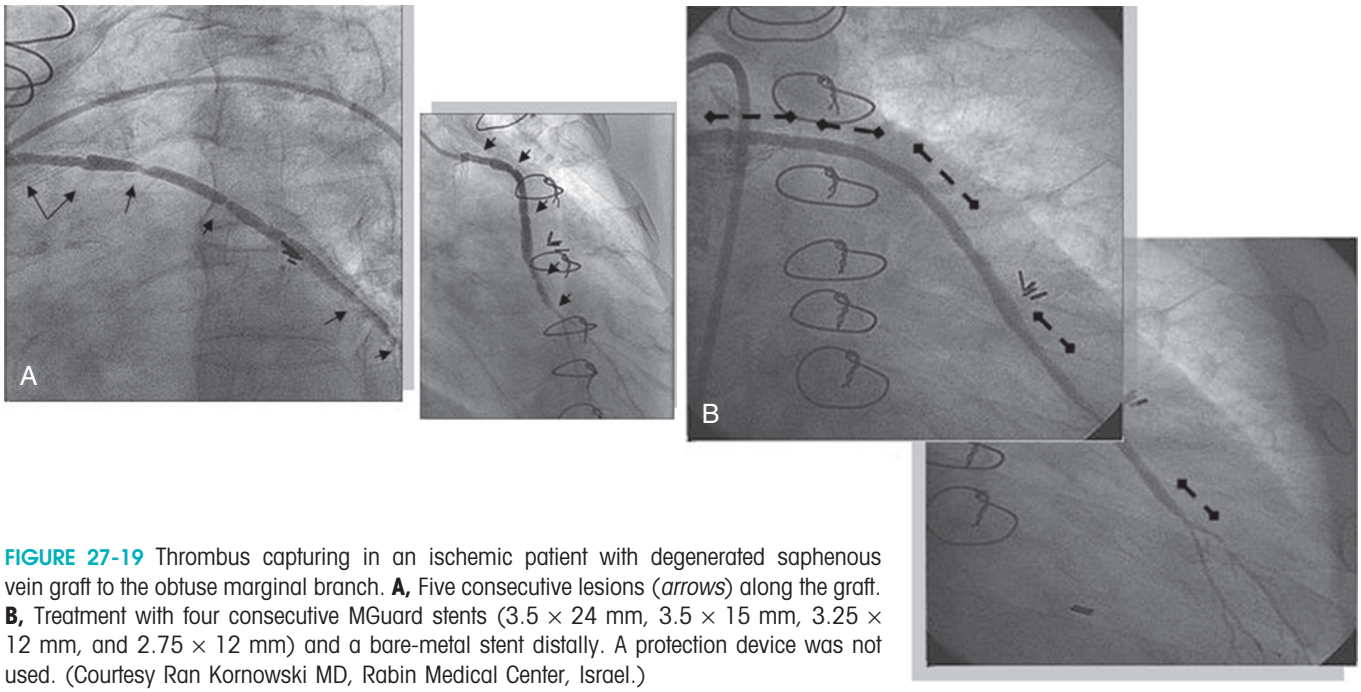


FIGURE 27-19 Thrombus capturing in an ischemic patient with degenerated saphenous vein graft to the obtuse marginal branch. **A,** Five consecutive lesions (*arrows*) along the graft. **B,** Treatment with four consecutive MGuard stents (3.5 × 24 mm, 3.5 × 15 mm, 3.25 × 12 mm, and 2.75 × 12 mm) and a bare-metal stent distally. A protection device was not used. (Courtesy Ran Kornowski MD, Rabin Medical Center, Israel.)

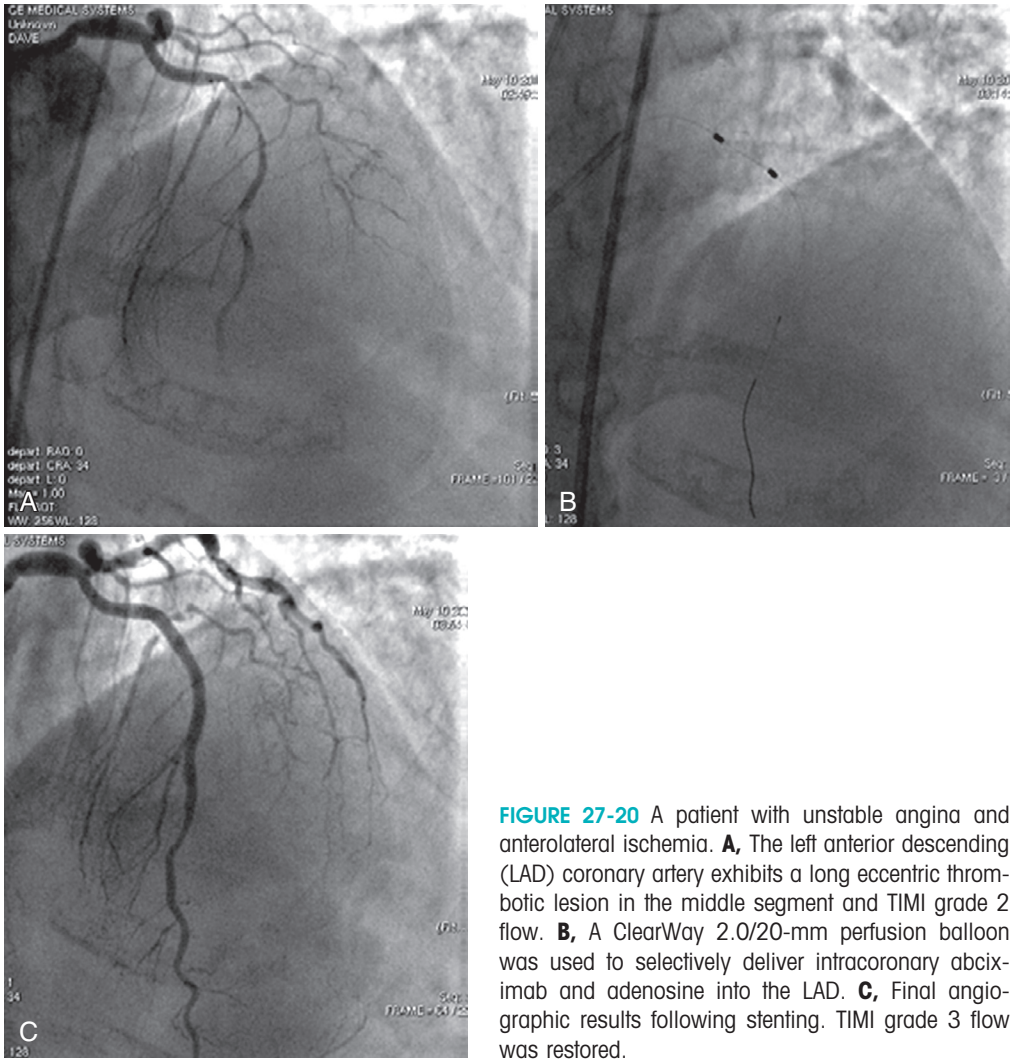


FIGURE 27-20 A patient with unstable angina and anterolateral ischemia. **A,** The left anterior descending (LAD) coronary artery exhibits a long eccentric thrombotic lesion in the middle segment and TIMI grade 2 flow. **B,** A ClearWay 2.0/20-mm perfusion balloon was used to selectively deliver intracoronary abciximab and adenosine into the LAD. **C,** Final angiographic results following stenting. TIMI grade 3 flow was restored.

FIGURE 27-21 Cross-sectional histopathology of a 95% to 99% stenosis of a saphenous vein graft. The lumen is narrowed mainly by organized thrombus (T), which consists of loose fibrous tissue with small recanalized vascular channels (ELVG 4×). During percutaneous coronary intervention, such channels enable guidewire crossing, which should be followed by thrombus removal before plaque modification by balloon intervention and stenting. (Courtesy Shannon Mackey-Bojack MD, Jesse E. Edwards Registry of Cardiovascular Disease Collection, Nasseff Heart Center, United Hospitals, University of Minnesota School of Medicine, St. Paul, MN.)

TABLE 27-8 Saphenous Vein Graft Sculpturing: A Percutaneous Coronary Intervention Technique for Revascularization of Chronic Total Occlusions

1. Engage the SVG with a supporting guiding catheter and carefully advance a penetrating guidewire onto the CTO.
2. Enhance guidewire penetration with a support catheter.
3. Once the CTO has been crossed, allow the guidewire to reach the distal graft or enter the native vessel beyond the anastomosis; exchange with a maximal support guidewire.
4. Apply a mechanical thrombectomy device along the graft in a slow antegrade and retrograde fashion.
5. When restored antegrade flow is angiographically apparent, assess residual thrombus burden and the exposed underlying lesions.
6. In the case of significant residual thrombus, selectively inject into the graft 10 to 20 mg tPA and allow 10 to 15 minutes for interaction with the thrombus.
7. Repeat thrombectomy for further reduction of the clot burden.
8. Dilate/stent the underlying graft stenoses as indicated.
9. A protection device can be added at the discretion of the operator.
10. Adjunctive pharmacotherapy can be added at the discretion of the operator; agents may include aspirin, heparin, glycoprotein (GP) IIb/IIIa platelet receptor blocker, direct thrombin inhibitor, thienopyridines, nitroglycerin, adenosine, or thrombolytic agents.

CTO, Chronic total occlusion; *SVG,* saphenous vein graft; *tPA,* tissue plasminogen activator.

removal of their thrombus content and subsequent stenting, as described in Table 27-8.

The initial step of this strategy involves careful guidewire entry and recanalization of the occluded graft, followed by targeted removal of the voluminous occlusive thrombus with mechanical thrombectomy. A critical component of this approach incorporates selective intragraft administration of a thrombolytic agent. This usually is followed by final passage with the thrombectomy device for extraction of the postlytic residual thrombotic material. After maximal mechanical removal of the thrombus, final vessel patency is ensured with stenting of the underlying stenosis (Fig. 27-22). Nevertheless, the SVG sculpturing technique is not a panacea, and device-related failure is a reality; complications can occur, and therefore it is still very controversial because of the complex pathology of the target vessels (Fig. 27-23). Other operators recommend a synergistic use of balloon-based distal embolization protection with rheolytic thrombectomy in this challenging context.[119]

Chronic Total Occlusions

Considered one of the last frontiers in interventional cardiology, chronic total occlusions (CTOs) remain the most powerful predictor for referral for coronary bypass surgery.[120] The benefits of PCI for this complex lesion include symptom relief, improved LV function, and a potential survival benefit when compared with failed CTO intervention. Technically, CTO is considered a highly demanding revascularization target.[121] In addition to fibrotic tissue, calcifications, and atherosclerotic material, CTOs frequently contain organized thrombi of various ages. Histopathology demonstrates an original arterial lumen that has been narrowed by atherosclerosis and contains an organized thrombus that consists of a vascular plexus through which either no flow or only very restricted flow is possible (Fig. 27-24). Commonly, a recanalization of such organized thrombus by microchannels occurs and results in limited antegrade flow beyond the plaque.[122] Indeed, whereas the angiographic hallmark of a CTO is a 100% stenosis without any dye propagation distally, approximately 50% of these lesions are, in fact, less than 99% stenosed.[123] The morphologic constituents account for the marked technical difficulty in crossing CTOs but also provide a potential PCI approach. Operators should aim to traverse the thrombus through the aforementioned vascular microchannels and remove the thrombus bulk before attempting to dilate or stent the lesion.[124] Thus careful guidewire maneuvering into these microchannels, either by the antegrade or retrograde approach, can lead to successful crossing and subsequent plaque treatment. Nevertheless, efforts to cross a CTO can be hampered by evoking an underlying thrombus to a great extent, culminating in rapid formation and accumulation of a large volume "angry clot" (Fig. 27-25), which then threatens the entire PCI outcome. Therefore following guidewire recanalization and distal positioning, further decrease of the burden of the occlusive thrombus with a mechanical removal device is warranted. Then, as most of the obstructive thrombotic component is extracted, contrast injections can precisely assess the residual plaque, and subsequent balloon dilation and stenting can be facilitated.

Corroborating the benefit of focus on the thrombotic component of CTO is recent evidence from the National Heart, Lung, and Blood Institute registry, whereby multivariable regression analysis demonstrated that the presence of thrombus is a strong predictor of success in CTO revascularization (adjusted OR 0.31; 95% CI, 0.15 to 0.61; $P = .0008$). This intriguing finding attests to the fact that thrombus removal clears the way for subsequent successful stenting.[125]

Left Main Disease

Percutaneous revascularization of left main disease is a topic of great global interest.[126] Thrombus frequently accompanies left main lesions and exerts a major impact on clinical and procedure-related risks and complications. Acute thrombosis of an underlying left main plaque carries grave consequences, and in cases of acute total occlusion, an emergency PCI constitutes the only realistic revascularization option (Fig. 27-26).

Prasad and colleagues[127] reported a series of 28 patients with unprotected thrombotic left main lesions who underwent standard PCI, and only a modest angiographic success rate of 83% ($N = 24$) was achieved, accompanied by a cumulative in-hospital mortality of 36%. These outcomes raise a valid concern: that the thrombus-containing stenoses were not treated by a dedicated thrombus-removal approach. For such high-risk interventional scenarios, and in order to reduce the risk of distal embolization, our experience denotes a need to first focus on a thrombus-removal strategy, preferably with a mechanical thrombectomy device. The merits of this approach are adequate clot clearance, proper exposure and assessment of the associated underlying atherosclerotic plaque, and facilitated stent delivery and deployment, and the results show a high success rate.[128] For selected, symptomatic patients who present with a CTO of the left main artery,[129] a PCI can become a viable management option with either an antegrade or retrograde recanalization through one of the distinct angiographic collateral channels connecting the right coronary artery with the left coronary vessels.[130]

Stent Thrombosis

Early, late, and very late stent thrombosis is an ominous clinical development that has a significant impact on clinical outcomes (Fig. 27-27).[131] Stent thrombosis is often multifactorial.[132] One of the major causes is post-PCI residual thrombus, which either gradually accumulates over a period of time or rapidly aggregates to form a fully occlusive thrombus. Stent thrombosis can be manifested by serious complications such as nonfatal and fatal AMI[133,134] and marked

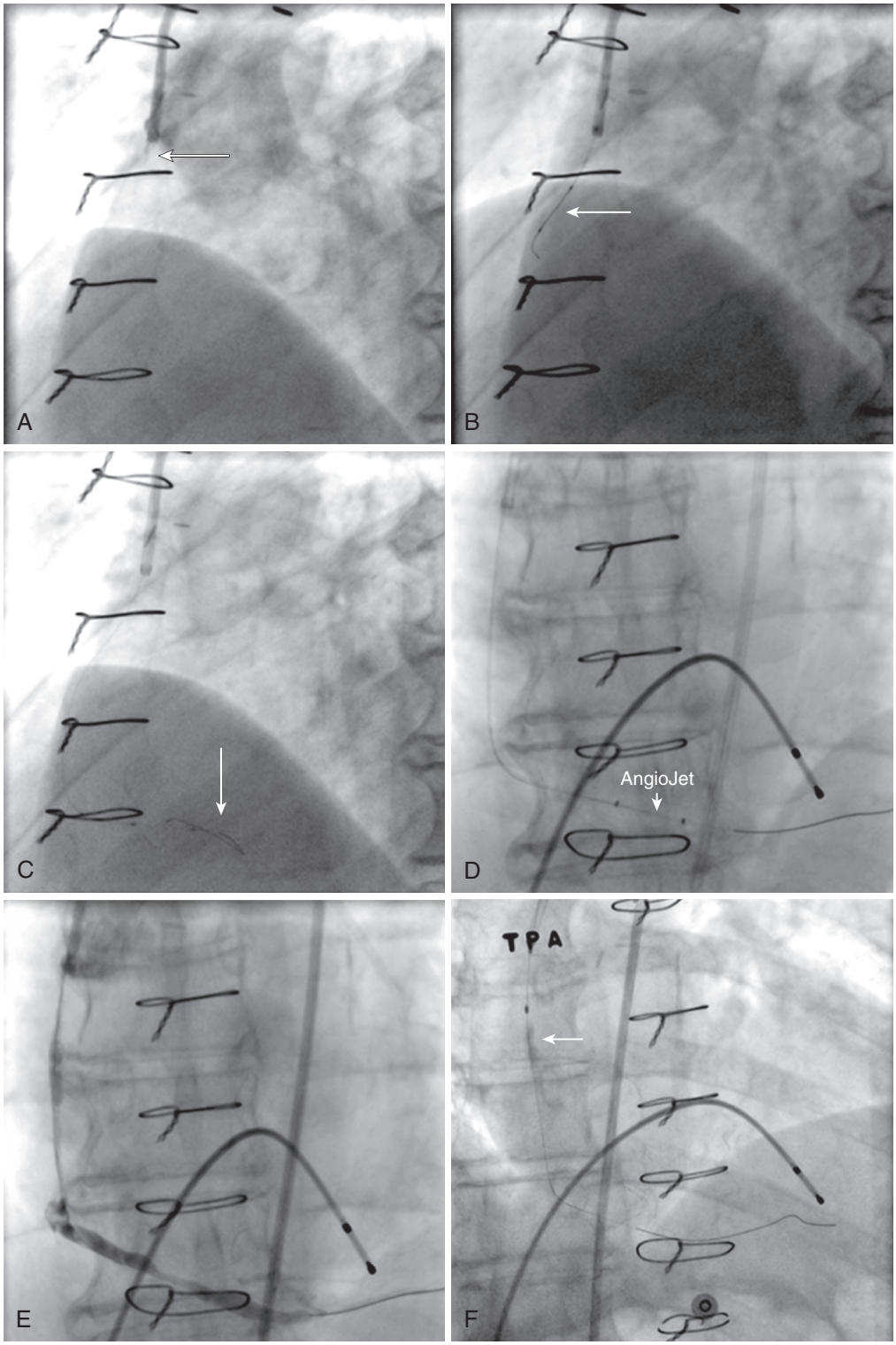


FIGURE 27-22 Saphenous vein graft (SVG) sculpturing technique for a totally occluded SVG. Following two coronary artery bypass grafting surgeries, the patient presented after several weeks of unstable angina. Significant inferolateral ischemia was noted. He developed a third-degree atrioventricular (AV) block, hypotension, and worsening chronic renal failure. A year earlier, both the right coronary artery and its SVG demonstrated complete occlusion. **A,** An 8-Fr multipurpose guide with sideholes positioned firmly at the ostium of the occluded SVG (*arrow*). **B,** Advancement of a Whisper guidewire (Abbott Vascular, Temecula, CA) into the proximal portion of the graft meets resistance and then is enhanced with a supporting catheter (QuickCross; Spectranetics, Colorado Springs, CO). **C,** Guidewire reaching the distal anastomosis site (*arrow*). It was exchanged for a Platinum Plus supporting guidewire (Boston Scientific, Natick, MA). **D,** A rheolytic thrombectomy catheter (*arrow*) is activated slowly in an antegrade and retrograde fashion along the occluded graft, retrieving a large volume of thrombotic content. **E,** Angiogram of SVG recanalization after initial thrombectomy. **F,** Selective administration of 20-mg tissue plasminogen activator (TPA) into the graft through a ClearWay perfusion catheter (*arrow*).

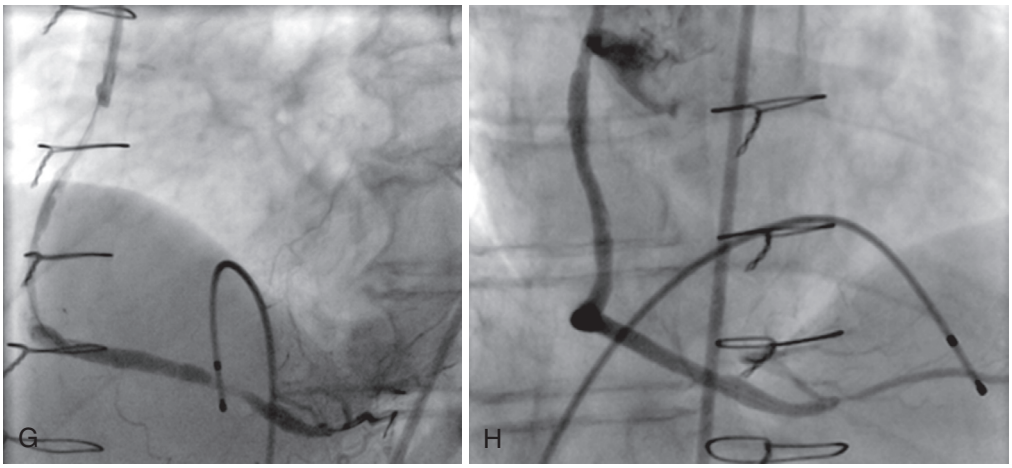


FIGURE 27-22, cont'd **G,** Angiogram after 20 minutes dwell time. **H,** Final angiogram after stenting of the graft body and the distal anastomosis site. (Note dye reflux from the sideholes of the guiding catheter). TIMI grade 3 flow was restored, accompanied by alleviation of chest pain and ischemia, hemodynamic stability, and return to a rhythm baseline of first-degree AV block. Renal function improved from a creatinine value of 3.1 to a baseline of 2.0.

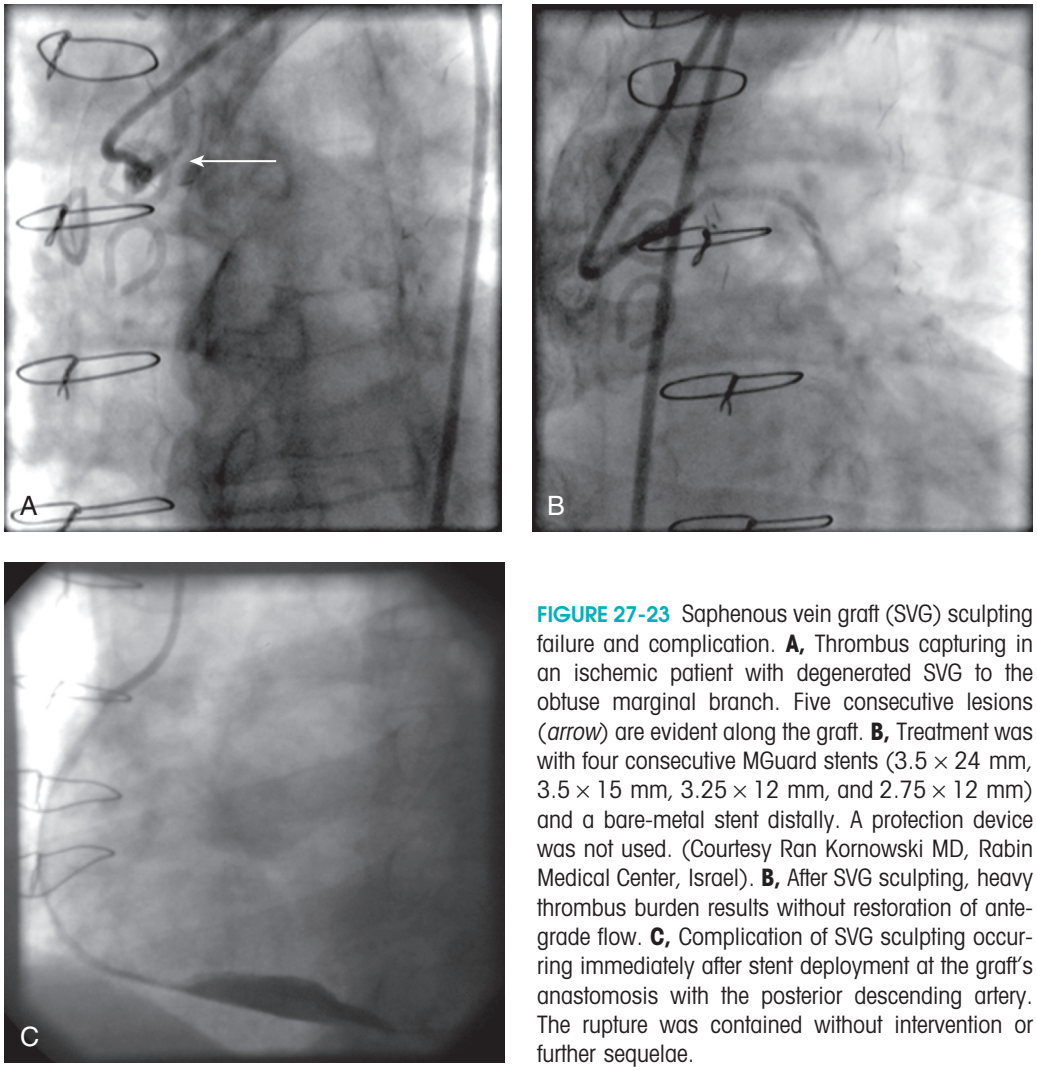


FIGURE 27-23 Saphenous vein graft (SVG) sculpting failure and complication. **A,** Thrombus capturing in an ischemic patient with degenerated SVG to the obtuse marginal branch. Five consecutive lesions (*arrow*) are evident along the graft. **B,** Treatment was with four consecutive MGuard stents (3.5 × 24 mm, 3.5 × 15 mm, 3.25 × 12 mm, and 2.75 × 12 mm) and a bare-metal stent distally. A protection device was not used. (Courtesy Ran Kornowski MD, Rabin Medical Center, Israel). **B,** After SVG sculpting, heavy thrombus burden results without restoration of antegrade flow. **C,** Complication of SVG sculpting occurring immediately after stent deployment at the graft's anastomosis with the posterior descending artery. The rupture was contained without intervention or further sequelae.

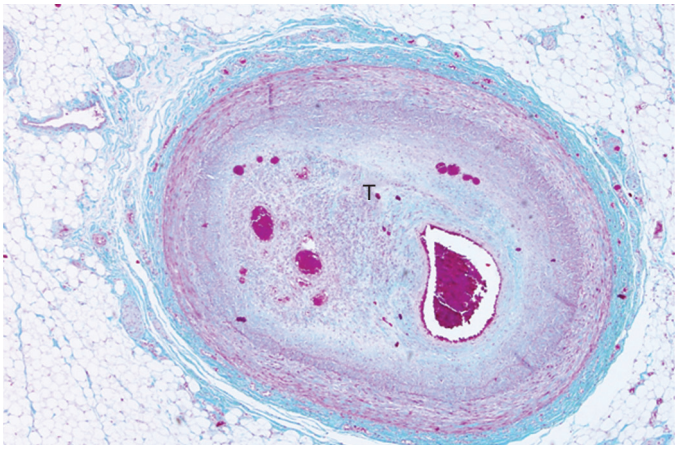


FIGURE 27-24 Histopathology of a cross section of the right coronary artery occluded by an organizing thrombus (T) consisting of loose, fibrous tissue with realized vascular channels (hematoxylin and eosin ×10). (Courtesy Shannon Mackey-Bojack MD, Jesse E. Edwards Registry of Cardiovascular Disease Collection, Nasseff Heart Center, United Hospitals, University of Minnesota School of Medicine, St. Paul, MN.)

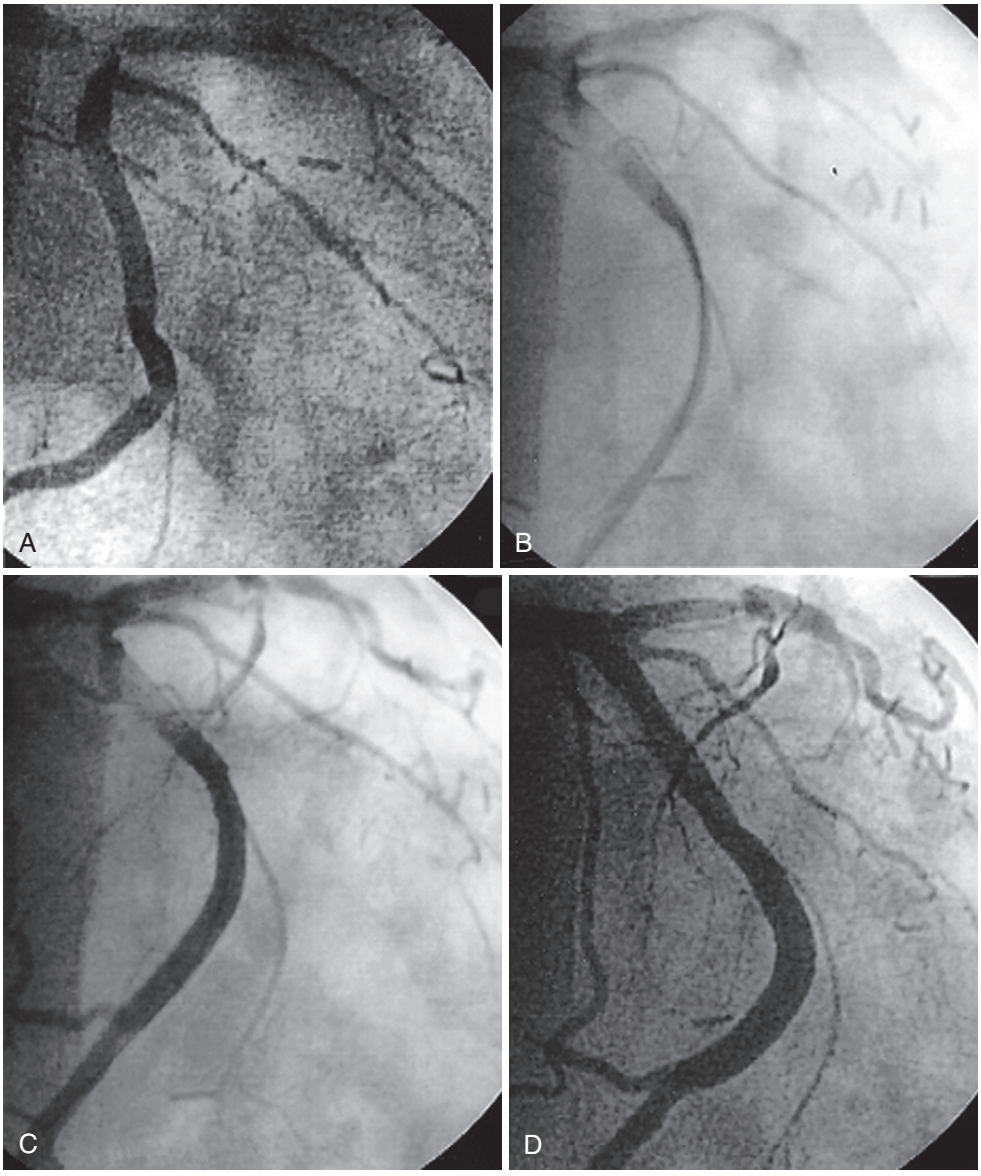


FIGURE 27-25 The so-called angry clot phenomenon: a patient after coronary artery bypass grafting (CABG) who presented with unstable angina, severe ischemia, and hemodynamic compromise. A left internal mammary artery graft to a diffusely diseased left anterior descending artery was patent. **A,** The left main exhibits critical stenosis with grade 2 thrombus. **B,** Percutaneous coronary intervention of the left main lesion: the patient received a IIb/IIIa platelet receptor antagonist, heparin, aspirin, and clopidogrel. However, as soon as the guidewire crossed the left main stenosis and was positioned at the distal circumflex artery, rapid and aggressive thrombus accumulation occurred along the entire vessel and resulted in marked narrowing and slow flow. Increased chest pain, ischemia, and hypotension ensued that required immediate thrombus dissolution. This was achieved with a 0.9-mm rapid exchange X-80 excimer laser catheter (Spectranetics, Colorado Springs, CO), which was activated at maximal flow (80 mJ/mm^2/80 Hz). Angiography after laser debulking and thrombolysis demonstrated restoration of flow, with reversal of the clot accumulation and mild residual clot remaining at the proximal vessel. **D,** Final results after stenting of the left main were accompanied by a clinical recovery.

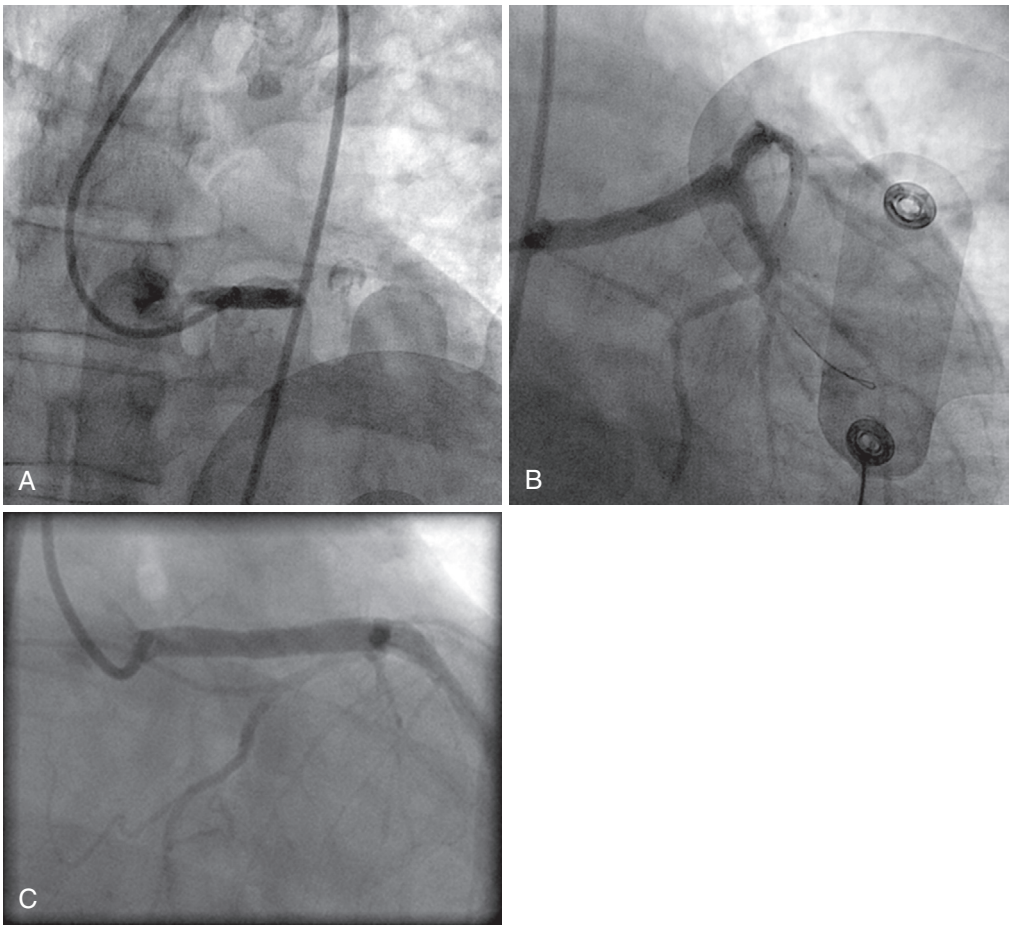


FIGURE 27-26 Acute left main thrombosis. This 48-year-old patient collapsed suddenly in a public place. Following cardiopulmonary resuscitation (CPR), anterior wall ST-elevation myocardial infarction was diagnosed. A stormy course during transfer to the medical center included repeated episodes of intense chest pain, hypotension, increased ischemia, and ventricular tachycardia, which culminated in full arrest upon entry to the cardiac catheterization suite. At 45 minutes, full code was required that included intubation, defibrillation ×17, amiodarone, and epinephrine prior to relative stabilization and catheterization. **A,** Total occlusion of the left main artery. **B,** A 0.014-inch ATW guidewire (Cordis/Johnson & Johnson, Bridgewater, NJ) recanalized the occlusion, followed by Export aspiration catheterization, which extracted clot. **C,** The target left main lesion was dilated and successfully stented with a 5.0/16-mm Liberté stent (Boston Medical, Natick, MA), yielding a diameter of 5.7 mm. TIMI grade 3 flow was restored; however, refractory arrhythmias ensued that required additional CPR, antiarrhythmics, defibrillation ×24, and intraaortic balloon pump insertion. Following stabilization, the patient received therapeutic hypothermia for 2 days. Repeat cardiac catheterization and intravascular ultrasound on day 7 demonstrated patency of the stent and adequate coronary flow. The patient was discharged without angina or congestive heart failure with a left ventricular ejection fraction of 30%, anterolateral hypokinesis, and no neurologic deficit. (Courtesy William R. Hathaway MD and William D. Kuehl MD, Mission Memorial Heart Center, Asheville, NC.)

hemodynamic instability. Expedient thrombus management is the key to a favorable outcome, especially for patients who present with STEMI.[129] Primary PCI, including additional stenting with or without thrombectomy, is effective in restoring vessel patency, but reocclusion and restenosis are frequent.[135] The often raised practical question as to which device is best for management of stent thrombosis can be addressed according to the amount of occlusive thrombus and associated clinical findings.[136,137] Whereas a small to medium thrombus load in a stable patient can be managed with combination therapy of pharmacologic agents (especially GP IIb/IIIa inhibitors) and an aspiration catheter, a large burden—especially in the presence of hemodynamic instability and ongoing ischemia—calls for enhanced removal by a power-based mechanical thrombectomy device. Nevertheless, even successful PCI for stent thrombosis is associated with a larger infarct and poorer outcome than in patients with de novo STEMI.[136]

Multiple Thrombi in a Single Vessel

Several thrombotic occlusions may appear simultaneously in the initial angiogram of patients with ACSs (Fig. 27-28). These thrombi may be mobile or rigid, and each may exhibit a different morphology, size, and mobility The etiology in most instances relates to the progression of the atherosclerotic process; however, at times this unusual occurrence may represent hypercoagulation, the so-called angry clot phenomenon, or breaking of the original thrombus into independent particles. In consideration of PCI, in most instances the use of thrombin inhibitors or platelet receptor antagonists in synergy with a power-sourced mechanical thrombectomy device yields adequate thrombus removal. A filter protection device can be applied as well, provided it does not interrupt the occluding thrombi during the initial placement manipulations.

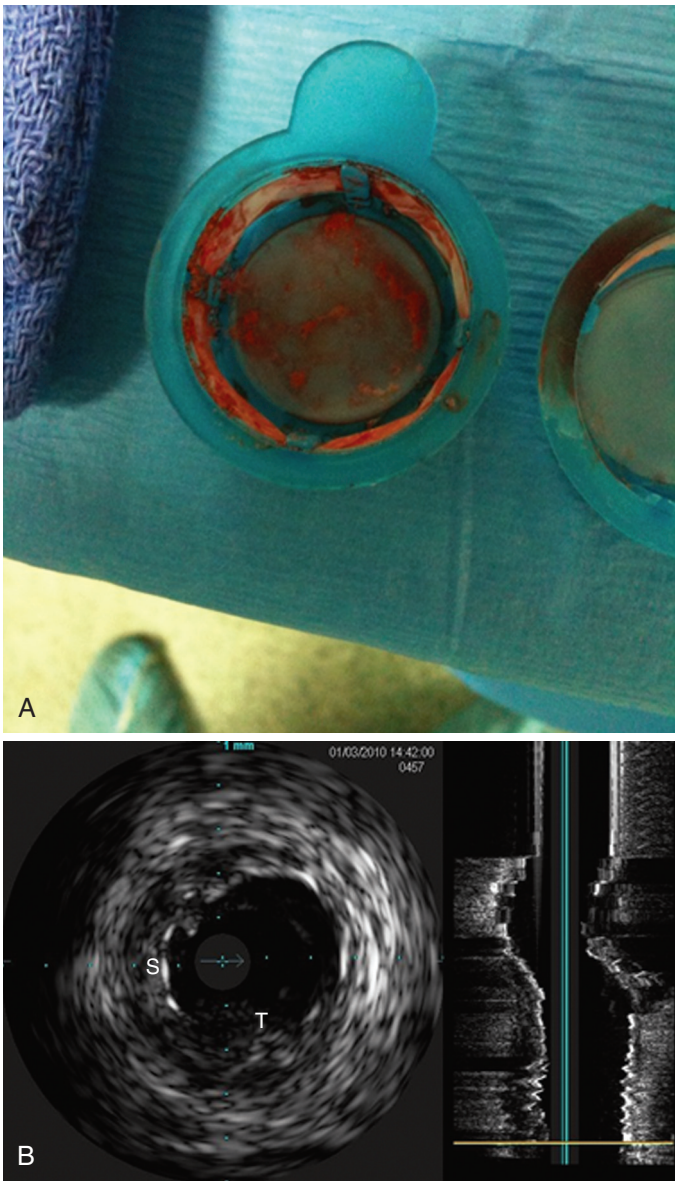


FIGURE 27-27 **A,** Extracted thrombus. **B,** Ultrasound of stent (S) and thrombosis (T). (Courtesy James Margolis MD, Miami Beach, FL.)

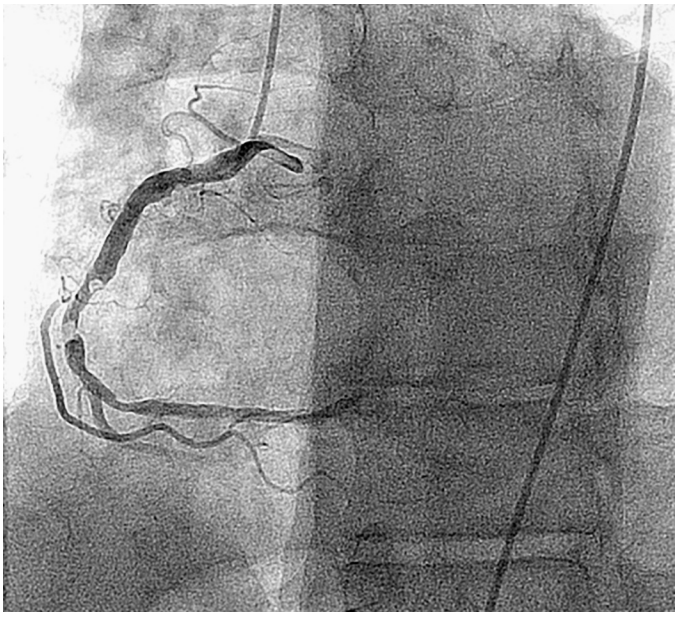


FIGURE 27-28 Multiple thrombi with different morphology presenting in a patient with acute coronary syndrome and severe inferior-lateral ischemia.

Multivessel Coronary Thrombosis

This is an uncommon occurrence that presents a very significant management challenge. Patients with simultaneous multivessel thrombosis frequently present with ACS, mostly with either STEMI or NSTEMI, accompanied by severe hemodynamic compromise. The multivessel thrombosis can affect coronary arteries (Fig. 27-29) and old bypass grafts alike (Fig. 27-30). The pathophysiologic process that accounts for this situation begins when plaque ruptures and resultant acute thrombosis of a single artery leads to development of cardiogenic shock. This in turn further decreases coronary perfusion pressure, and consequently multivessel thrombus is formed on other preexisting lesions.[138] Another mechanism of multivessel coronary thrombosis involves thrombotic embolization and occlusion of multiple coronary vessels from a left chamber cardiac tumor.[139]

The optimal treatment approach to multivessel coronary thrombosis is unknown, but it varies considerably from PCI to urgent bypass surgery. When the most critical culprit thrombotic lesion can be identified with certainty, selective treatment with an aspiration catheter, aggressive pharmacotherapy, and subsequent stenting can be beneficial. However, in a case of PCI failure or in patients with continuous global ischemia due to thrombus-laden lesions in the other coronary arteries (especially during hemodynamic deterioration), urgent coronary bypass surgery is the preferred management option.

SUMMARY

Thrombus plays a major role in the pathophysiology of ACSs. Understanding the structural components of the thrombus and proper assessment of its burden are essential steps for tailoring appropriate strategies for revascularization. Although useful American College of Cardiology/American Heart Association guidelines for management of patients with ACSs are readily available, developing precise algorithms for PCI management of thrombus-containing lesions is a difficult task because of the complex characteristics of coronary thrombus, the presence of underlying associated atherosclerotic plaque, and the anatomic characteristics of the host vessels. Angiographic interpretation of thrombus burden and experience with removal technologies widely differ; therefore current approaches to these challenging targets diverge considerably. Enhanced capabilities of thrombus-defining diagnostic tools, development of new dedicated pharmacotherapy, increased accuracy of thrombus classifications, and further availability of specific technologies are warranted. This prospect will undoubtedly lead to a significant improvement in the outcomes of interventions for acute coronary syndromes.

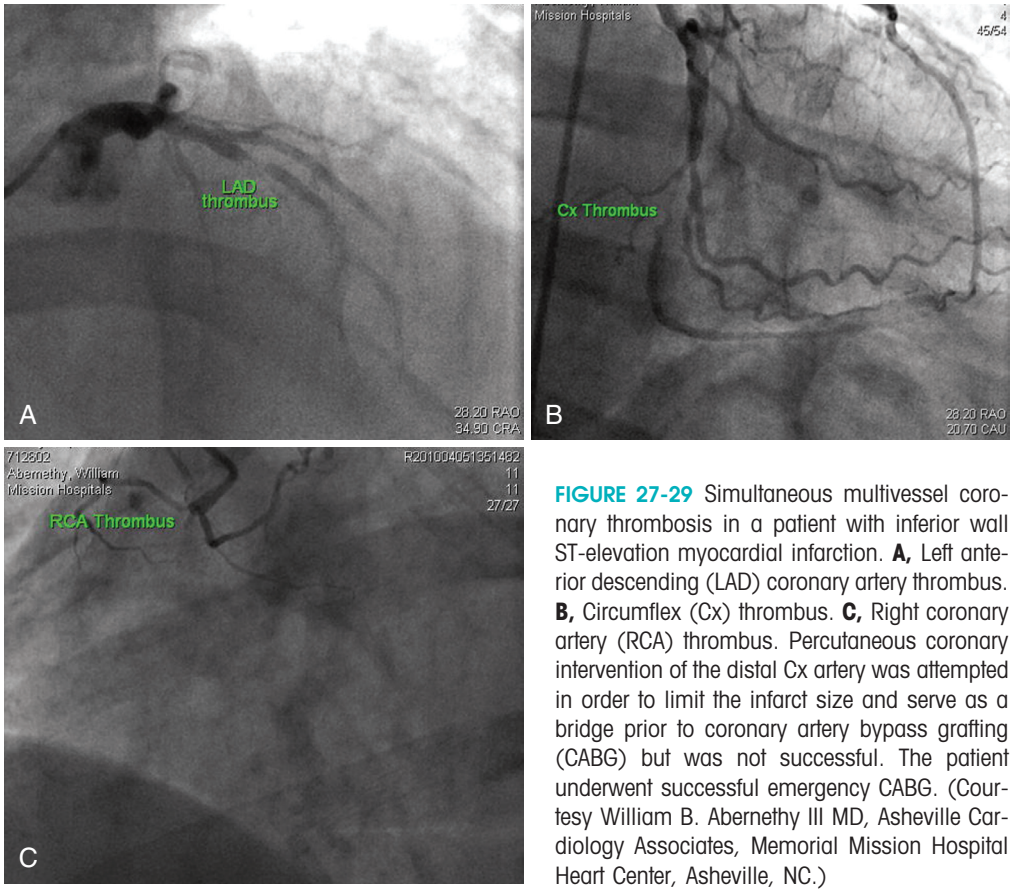


FIGURE 27-29 Simultaneous multivessel coronary thrombosis in a patient with inferior wall ST-elevation myocardial infarction. **A,** Left anterior descending (LAD) coronary artery thrombus. **B,** Circumflex (Cx) thrombus. **C,** Right coronary artery (RCA) thrombus. Percutaneous coronary intervention of the distal Cx artery was attempted in order to limit the infarct size and serve as a bridge prior to coronary artery bypass grafting (CABG) but was not successful. The patient underwent successful emergency CABG. (Courtesy William B. Abernethy III MD, Asheville Cardiology Associates, Memorial Mission Hospital Heart Center, Asheville, NC.)

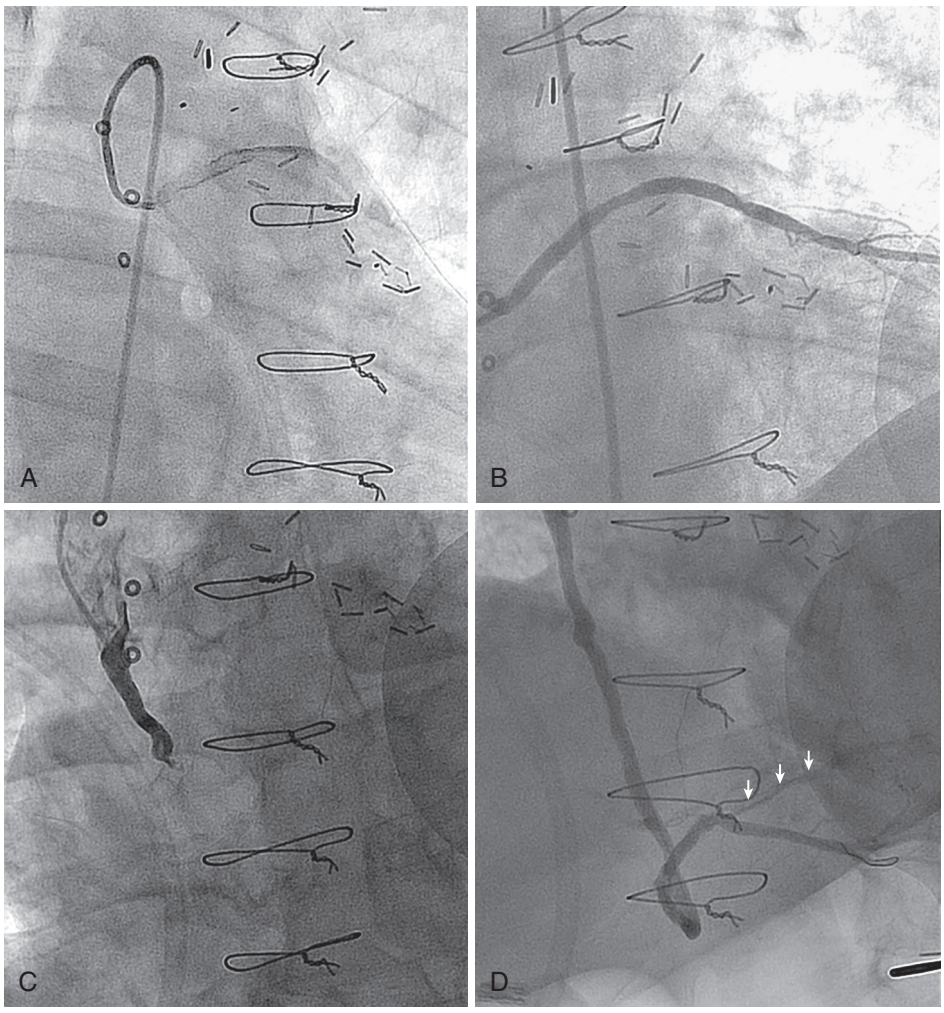


FIGURE 27-30 Simultaneous multivessel thrombosis in the bypass grafts of a patient with anterior and inferior non–ST-elevation myocardial infarction. **A,** Grade 4 thrombus burden in the saphenous vein graft (SVG) to the left anterior descending coronary artery. **B,** Final revascularization results after aspiration catheter and stenting. **C,** Grade 5 thrombotic occlusion of the SVG to the posterior descending artery. **D,** Final revascularization results after aspiration catheter and stenting. (Courtesy William B. Abernethy III MD, Asheville Cardiology Associates, Mission Memorial Hospital Heart Center, Asheville, NC.)

REFERENCES

1. Vankitachalam L, Kip KE, Selzer F, et al: Twenty-year evolution of percutaneous coronary intervention and its impact on clinical outcomes: a report from the National Heart, Lung, and Blood Institute-sponsored, multicenter 1985-1986 PTCA and 1997-2006 dynamic registries. *Circ Cardiovasc Interv* 2:6–13, 2009.
2. Singh M, Berger PB, Ting HH, et al: Influence of coronary thrombus on outcome of percutaneous coronary angioplasty in the current era. *Am J Cardiol* 88:1091–1096, 2001.
3. White CJ, Ramee SR, Collins TJ, et al: Coronary thrombi increase PTCA risk: angioscopy as a clinical tool. *Circulation* 93:253–258, 1996.
4. Fokkema ML, Vlaar PJ, Svilaas T, et al: Incidence and clinical consequences of distal embolization on the coronary angiogram after percutaneous coronary intervention for ST-elevation myocardial infarction. *Eur Heart J* 30(8):908–915, 2009.
5. Sianos G, Papafaklis MI, Daemen J, et al: Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. *J Am Coll Cardiol* 50(7):573–583, 2007.
6. Freeman MR, Williams AE, Chisholm RJ, Armstrong PW: Intracoronary thrombus and complex morphology in unstable angina: relation to timing of angiography and in-hospital cardiac events. *Circulation* 80:17–23, 1989.
7. Napodano M, Dariol G, Al Mamary AH, et al: Thrombus burden and myocardial damage during primary percutaneous coronary intervention. *Am J Cardiol* 113:1449–1456, 2014.
8. Topaz O: Revascularization of thrombus-laden lesions in AMI: the burden on the interventionalist. *J Invasive Cardiol* 19:324–325, 2007.
9. Yunoki K, Naruko T, Sugioka K, et al: Thrombus aspiration therapy and coronary thrombus components in patients with acute ST-elevation myocardial infarction. *J Atheroscler Thromb* 20:524–537, 2013.
10. Virmani R, Burke AP, Farb A, et al: Pathology of the unstable plaque. *Prog Cardiovasc Dis* 44:349–356, 2002.
11. Abela GS, Aziz K, Vedre A, et al: Effect of cholesterol crystals on plaques and intima in arteries of patients with acute coronary and cerebrovascular syndromes. *Am J Cardiol* 103:959–968, 2009.
12. Sami S, Willerson JT: Contemporary treatment of unstable angina and non-ST-segment elevation myocardial infarction. *Tex Heart Inst J* 37(2):141–148, 2010.
13. Schwartz SM, Galis SG, Rosenfeld ME, Falk E: Plaque rupture in humans and mice. *Arterioscler Thromb Vasc Biol* 27:705–713, 2007.
14. Whittaker P, Przyklenk K: Fibrin architecture in clots: a quantitative polarized light microscopy analysis. *Blood Cells Mol Dis* 42:51–56, 2009.
15. Carr ME, Carr SL: Fibrin structure and concentration alter clot elastic modulus but do not alter platelet mediated force development. *Blood Coagul Fibrinolysis* 6:79–86, 1995.
16. Kereiakes DJ, Michelson AD: Platelet activation and progression to complications. *Rev Cardiovasc Med* 7:75–81, 2006.
17. Krishnaswami A, Carr ME, Jesse RL, et al: Patients with coronary artery disease who present with chest pain have significantly elevated platelet contractile force and clot elastic modulus. *Thromb Haemost* 88:739–744, 2002.
18. Abela GS, Eisenberg JD, Mittleman MA, et al: Detecting and differentiating white from red coronary thrombus by angiography in angina pectoris and in acute myocardial infarction. *Am J Cardiol* 83:94–97, 1999.
19. Beygui F, Collet JP, Nagaswami C, et al: Architecture of intracoronary thrombi in ST-elevation acute myocardial infarction: time makes the difference. *Circulation* 113:e21–e23, 2006.
20. Johnstone E, Friedl SE, Maheshwari A, et al: Distinguishing characteristics of erythrocyte-rich and platelet-rich thrombus by intravascular ultrasound catheter system. *J Thromb Thrombolysis* 24:233–239, 2007.
21. Vlaar PJ, Svilaas T, Vogelzang M, et al: A comparison of two thrombus aspiration devices with histopathological analysis of retrieved material in patients presenting with ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv* 1:265–267, 2008.
22. Topaz O: On the hostile massive thrombus and the means to eradicate it. *Catheter Cardiovasc Interv* 65:280–281, 2005.
23. Zhao HY, Han HB, Li D, et al: Pathological analysis of aspirated materials from the culprit lesion in patients with acute myocardial infarction. *Zhonghua Xin Xue Guan Bing Za Zhi* 37(9):785–789, 2009.
24. Limbruno U, De Carlo M, Pistolesi S, et al: Distal embolization during primary angioplasty: histopathologic features and predictability. *Am Heart J* 150:102–108, 2005.
25. Teirstein PS, Schatz RA, Wong SC, Rocha-Singh KJ: Coronary stenting with angioscopic guidance. *Am J Cardiol* 75:344–347, 1995.
26. Bonello L, De Labriolle A, Lemesle G, et al: Intravascular ultrasound-guided percutaneous coronary interventions in contemporary practice. *Arch Cardiovasc Dis* 102:143–151, 2009.
27. Kubo T, Imanishi T, Kashiwagi M: Multiple coronary lesion instability in patients with acute myocardial infarction as determined by optical coherence tomography. *Am J Cardiol* 105(3):318–322, 2010.
28. Hiram G, Bezerra HG, Marco A, et al: Intracoronary optical coherence tomography: a comprehensive review. *JACC Cardiovasc Interv* 2:1035–1046, 2009.
29. Rawlins J, Shah N, O'Kane P: Adjunct interventional techniques for the treatment of intra-coronary thrombus. *Heart* 99:216–222, 2013.
30. Topaz O, Topaz A, Owen K: Thrombus grading for coronary interventions: the role of contemporary classifications. *Interv Cardiol* 3(6):705–712, 2011.
31. Gibson CM, de Lemos JA, Murphy SA, et al: Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction: a TIMI 14 substudy. *Circulation* 103:2550–2554, 2001.
32. Niccoli G, Spaziani C, Marino M, et al: Effect of chronic aspirin therapy on angiographic thrombotic burden in patients admitted for a first ST-elevation myocardial infarction. *Am J Cardiol* 105(5):587–591, 2010.
33. Aleong G, Vaqueriza D, Del Valle R, et al: Dual quantitative coronary angiography: a novel approach to quantify intracoronary thrombotic burden. *EuroIntervention* 4:475–480, 2008.
34. CLARITY-TIMI-28 Investigators: Association of blood glucose with angiographic and clinical outcomes among patients with ST-segment elevation myocardial infarction. *Am J Cardiol* 101:303–307, 2008.
35. Ahmed TA, Sorgdrager BJ, Cannegieter SC, et al: Pre-infarction angina predicts thrombus burden in patients admitted for ST-segment elevation myocardial infarction. *EuroIntervention* 7:1396–1405, 2012.
36. Topaz O, Topaz A, Polkampally PR: Thrombectomy in acute myocardial infarction. *Intervent Cardiol* 4:86–91, 2009.
37. Furie B, Furie BC: Mechanisms of thrombus formation. *N Engl J Med* 359:938–949, 2008.
38. Listro F, Grotti S, Angioli P, et al: Impact of thrombus aspiration on myocardial tissue reperfusion and left ventricular functional recovery and remodeling after primary angioplasty. *Circ Cardiovasc Interv* 2:376–383, 2009.
39. Vlaar PJ, Svilaas T, van der Horst IC, et al: Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS); a 1-year follow-up study. *Lancet* 371:1915–1920, 2008.
40. Napodano M, Dariol G, Al Mamary AL: Thrombus burden and myocardial damage during primary percutaneous coronary intervention. *Am J Cardiol* 113:1449–1456, 2013.
41. Kunadian V, Zorkun C, Williams SP, et al: Intracoronary pharmacotherapy in the management of coronary microvascular dysfunction. *J Thromb Thrombolysis* 26:234–242, 2008.
42. Eeckhout E, Kern MJ: The coronary no-reflow: a review of mechanisms and therapies. *Eur Heart J* 22:729–739, 2001.
43. Heusch G, Kleinbongard P, Bose D, et al: Coronary microembolization: from bedside to bench and back to bedside. *Circulation* 120(18):1822–1836, 2009.
44. Ohtani T, Ueda Y, Shimizu M, et al: Association between cardiac troponin T elevation and angioscopic morphology of culprit lesion in patients with non-ST segment elevation acute coronary syndrome. *Am Heart J* 150:227–233, 2005.
45. Lincoff AM, Topol EJ: Illusion of reperfusion: Does anyone achieve optimal reperfusion during acute myocardial infarction? *Circulation* 88:1361–1374, 1993.
46. Kaya MG, Arsian F, Abaci A, et al: Myocardial blush grade: a predictor for major adverse cardiac events after primary PTCA with stent implantation for acute myocardial infarction. *Acta Cardiol* 62:445–451, 2007.
47. Napodano M, Peluso D, Perazzolo MM, et al: Time-dependent detrimental effects of distal embolization on myocardium and microvasculature during primary percutaneous coronary intervention. *JACC Cardiovasc Interv* 5:1170–1177, 2012.
48. Brosh D, Assali AR, Mager A, et al: Effect of no-reflow during primary percutaneous coronary intervention for acute myocardial infarction on six-month mortality. *Am J Cardiol* 99:442–445, 2007.
49. Niccoli G, Burzotta F, Galiuto L, et al: Coronary no-reflow in humans. *J Am Coll Cardiol* 54:281–292, 2009.
50. Topaz O: Focus on the infarct-related artery: a thrombus runs through it. *Catheter Cardiovasc Interv* 57:340–341, 2002.
51. Carr ME, Carr SL, Greilich PE: Heparin ablates force development during platelet mediated clot retraction. *Thromb Haemost* 75(4):674–678, 1996.
52. Collet JP, Montalescot G, Lesty C, et al: Effects of abciximab on the architecture of platelet-rich clots in patients with acute myocardial infarction undergoing primary coronary intervention. *Circulation* 103:2328–2331, 2001.
53. Silva JA: Percutaneous coronary intervention of thrombotic lesions: still challenging! *Catheter Cardiovasc Interv* 56:8–9, 2002.
54. Kalyanasundaram A, Blankenship JC, Berger P, et al: Thrombus predicts ischemic complications during percutaneous coronary intervention in saphenous vein grafts: results from TARGET trial. *Catheter Cardiovasc Interv* 69:623–629, 2007.
55. Topaz O: Ischemic coronary syndromes and SVG interventions: Do 2b/3a inhibitors miss the target? *Catheter Cardiovasc Interv* 69:630–631, 2007.
56. Svilaas T, Vlaar PJ, van der Horst IC, et al: Thrombus aspiration during primary percutaneous intervention. *N Eng J Med* 358:557–567, 2008.
57. Topaz O: Thrombectomy during primary PCI for STEMI: call of the thrombus, Editorial. *Catheter Cardiovasc Interv* 80:1181–1182, 2012.
58. Mamas MA, Fraser D, Fath-Ordoubadi F: The role of thrombectomy and distal protection devices during percutaneous coronary interventions. *EuroIntervention* 4:115–123, 2008.
59. Tamahane UU, Chetcuti SJ, Hameed I, et al: Safety and efficacy of thrombectomy in patients undergoing primary percutaneous coronary intervention for acute ST elevation MI: a meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord* 10:10–20, 2010.
60. Srinivasan M, Rihal C, Holmes DR, et al: Adjunctive thrombectomy and distal protection in primary percutaneous coronary intervention. *Circulation* 119:1311–1319, 2009.
61. Sardella G, Mancone M, Bucciarelli-Ducci C, et al: Thrombus aspiration during primary percutaneous coronary intervention improves myocardial reperfusion and reduces infarct size: the EXPIRA (thrombectomy with export catheter in infarct-related artery during primary percutaneous coronary intervention) prospective, randomized trial. *J Am Coll Cardiol* 53:309–315, 2009.
62. Silva-Orrego P, Colombo P, Bigi R, et al: Thrombus aspiration before primary angioplasty improves myocardial perfusion in acute myocardial infarction: the DEAR-MI study. *J Am Coll Cardiol* 48:1552–1559, 2006.
63. Burzotta F, Trani C, Romangnoli E, et al: Manual thrombus-aspiration improves myocardial reperfusion: the randomized evaluation of the effect of mechanical reduction of distal embolization by thrombus aspiration in primary and rescue angioplasty (REMEDIA) trial. *J Am Coll Cardiol* 46:371–376, 2005.
64. Liistro F, Grotti S, Angioli P, et al: Impact of thrombus aspiration on myocardial tissue reperfusion and left ventricular functional recovery and remodeling after primary angioplasty. *Circ Cardiovasc Interv* 2:376–383, 2009.
65. Sardella G, Mancone M, Nguyen BL, et al: The effect of thrombectomy on myocardial blush in primary angioplasty: the randomized evaluation of thrombus aspiration by two thrombectomy devices in acute myocardial infarction RETAMI trial. *Catheter Cardiovasc Interv* 71:84–91, 2008.
66. De Luca L, Sardella G, Davidson CJ, et al: Impact of intracoronary aspiration thrombectomy during primary angioplasty on left ventricular remodeling in patients with anterior ST-elevation myocardial infarction. *Heart* 92:951–957, 2006.
67. Bavry AA, Kumbhani DJ, Bhatt DL: Role of adjunctive thrombectomy and embolic protection devices in acute myocardial infarction: a comprehensive meta-analysis of randomized trials. *Eur Heart J* 29:2989–3001, 2008.
68. Kaltof A, Bottcher M, Nielsen SS, et al: Routine thrombectomy in percutaneous coronary intervention for acute ST-segment elevation myocardial infarction. *Circulation* 114:40–47, 2006.
69. Fröbert O, Lagerqvist B, Olivecrona GK, et al: Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 369:1587–1597, 2013.
70. Topaz O: The anomalous infarct-related artery: importance of angiographic detection for successful revascularization. *Catheter Cardiovasc Interv* 76:973–974, 2010.
71. Brilakis ES, Banerjee S, Lombardi WL: Retrograde recanalization of native coronary artery chronic occlusions via acutely occluded vein grafts. *Catheter Cardiovasc Interv* 75:109–113, 2010.
72. Burzotta F, Trani C, Romagnoli E, et al: Feasibility of sequential thrombus aspiration and filter distal protection in the management of very high thrombus burden lesions. *J Invasive Cardiol* 19:317–323, 2007.
73. de Waha S, Desch S, Scheller B, et al: Thrombus Aspiration in ThrOmbus containing culpRiT lesions in Non-ST-Elevation Myocardial Infarction: study protocol for randomized controlled trial. *Trials* 14:110–122, 2013.
74. Parodi G, Valenti R, Migliorini A, et al: Comparison of manual thrombus aspiration with rheolytic thrombectomy in acute myocardial infarction. *Circ Cardiovasc Interv* 6:224–230, 2013.
75. Matar F, Anderson D, Rossi P, et al: Benefits of rheolytic thrombectomy in patients with ST-elevation myocardial infarction and high thrombus burden: findings from the Cardioquest interventional database. *Cardiovasc Revasc Med* 9:113–114, 2008.
76. Topaz O, Ebersole D, Das T: Excimer laser angioplasty in acute myocardial infarction (the CARMEL multicenter study). *Am J Cardiol* 93:694–701, 2004.
77. Antoniucci D, Valenti R, Migliorini A: Thrombectomy during PCI for acute myocardial infarction: Are the randomized controlled trial data relevant to the patients who really need this technique? *Catheter Cardiovasc Interv* 71:863–869, 2008.
78. Navarese EP, Terantini G, Musumeci G, et al: Manual vs mechanical thrombectomy during PCI for STEMI: a comprehensive direct and adjusted indirect meta-analysis of randomized trials. *Am J Cardiovasc Dis* 3:146–157, 2013.
79. Beran G, Lang I, Schreiber W, et al: Intracoronary thrombectomy with the X-Sizer catheter system improves epicardial flow and accelerates ST-segment resolution in patients with acute coronary syndrome: a prospective, randomized controlled study. *Circulation* 105:2355–2360, 2002.
80. Napodano M, Pasquetto G, Sacca S, et al: Intracoronary thrombectomy improves myocardial reperfusion in patients undergoing direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 42:1395–1402, 2003.

81. Lefevre T, Garcia E, Reimers B, et al: X-Sizer for thrombectomy in acute myocardial infarction improves ST-segment resolution. *J Am Coll Cardiol* 46:246–252, 2005.
82. Sianos G, Papafaklis MI, Vaina S, et al: Rheolytic thrombectomy in patients with ST-elevation myocardial infarction and large thrombus burden: the Thoraxcenter experience. *J Invasive Cardiol* 18:3C–7C, 2006.
83. Antoniucci D, Valenti R, Migliorini A, et al: Comparison of rheolytic thrombectomy before direct infarct artery stenting versus direct stenting alone in patients undergoing percutaneous coronary intervention for acute myocardial infarction. *Am J Cardiol* 93:1033–1035, 2004.
84. Margheri M, Falai M, Vittore G, et al: Safety and efficacy of the AngioJet in patients with acute myocardial infarction: results from the Florence Appraisal Study of Rheolytic Thrombectomy (FAST). *J Invasive Cardiol* 18:481–486, 2006.
85. Chinnaiyan K, Grines CL, O'Neill WW, et al: Safety of AngioJet thrombectomy in acute ST-segment elevation myocardial infarction: a large, single-center experience. *J Invasive Cardiol* 18:17C–21C, 2006.
86. Sherev DA, Shavelle DM, Abdelkarim M, et al: AngioJet rheolytic thrombectomy during rescue PCI for failed thrombolysis: a single-center experience. *J Invasive Cardiol* 18:12C–16C, 2006.
87. Ali A, Cox D, Dieb N, et al: Rheolytic thrombectomy with percutaneous coronary intervention for infarct size reduction in acute myocardial infarction: 30-day results from a multicenter randomization study. *J Am Coll Cardiol* 48:244–250, 2006.
88. JETSTENT Trial Investigators: Comparison of AngioJet rheolytic thrombectomy before direct infarct artery stenting with direct stenting alone in patients with acute myocardial infarction: the JETSTENT trial. *J Am Coll Cardiol* 56:1298–1306, 2010.
89. Topaz O: Laser. In Topol EJ, editor: *Textbook of interventional cardiology*, ed 4, Philadelphia, 2003, Saunders, pp 675–703.
90. Topaz O, Bernardo NL, Shah R, et al: Effectiveness of excimer laser coronary angioplasty in acute myocardial infarction or in unstable angina pectoris. *Am J Cardiol* 87:849–855, 2001.
91. Topaz O, Minisi AJ, Morris C, et al: Photoacoustic fibrinolysis: pulsed wave mid infrared laser-clot interaction. *J Thromb Thrombolysis* 3:209–214, 1996.
92. Topaz O, Minisi AJ, Bernardo NL, et al: Alterations of platelet aggregation kinetics with ultraviolet laser emission: the "stunned platelet Phenomenon". *Thromb Haemost* 86:1087–1093, 2001.
93. Topaz O, Ebersole D, Dahm JB, et al: Excimer laser in myocardial infarction: a comparison between STEMI patients with established Q-wave versus patients with non-STEMI (non-Q). *Lasers Med Sci* 23:1–10, 2008.
94. Rawlins J, Talwar S, Green M, et al: Optical coherence tomography following percutaneous coronary intervention with excimer laser coronary atherectomy. *Cardiovasc Revasc Med* 15:29–34, 2014.
95. Shen X, Chandra N, Holmberg M, et al: Therapeutic ultrasound-enhanced thrombolysis in patients with acute myocardial infarction. *Angiology* 6(3):253–258, 2010.
96. Cohen MG, Tuero E, Blugermann J, et al: Transcutaneous ultrasound facilitated coronary thrombolysis during acute myocardial infarction. *Am J Cardiol* 92(4):454–457, 2003.
97. Jovin IS, Topaz A, Polkampally PR, Topaz O: Embolic protection devices, rotational atherectomy, and mechanical thrombectomy devices. In Mukherjee D, Bavry A, editors: *Interventional cardiology*, New York, 2011, Oxford University Press, pp 153–164.
98. Bates ER: Aspirating and filtering atherothrombotic debris during percutaneous coronary intervention. *JACC Cardiovasc Interv* 1:265–267, 2008.
99. Baim DS, Wahr D, George B, et al: Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. *Circulation* 105: 1285–1290, 2002.
100. Dangas G, Stone GW, Weinberg MD, et al: Contemporary outcomes of rescue PCI for AMI: comparison with primary angioplasty and the role of distal protection devices (EMERALD trial). *Am Heart J* 156(6):1090–1096, 2008.
101. Kaltoft A, Kelbaek H, Klovgaard L, et al: Increased rate of stent thrombosis and target lesion revascularization after filter protection in primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: 15 months follow-up of the DEDICATION (Drug Eluting and Distal Protection in ST Elevation Myocardial Infarction) trial. *J Am Coll Cardiol* 55(9): 867–871, 2010.
102. Limbruno U, De Caterina R: EMERALD, AIMI, and PROMISE: Is there still a potential for embolic protection in primary PCI? *Eur Heart J* 27:1139–1145, 2006.
103. Timurkaynak T, Ozdemir M, Cengel A, et al: Direct stenting in angiographically apparent thrombus-containing lesions. *J Invasive Cardiol* 13:742–747, 2001.
104. Alfonso F, Rodriguez P, Phillips P, et al: Clinical and angiographic implications of coronary stenting in thrombus-containing lesions. *J Am Coll Cardiol* 29:725–733, 1997.
105. Assa-Vaknin H, Assali A, Kornowski R: Preliminary experiences using the MGuard stent platform in saphenous vein graft lesions. *Catheter Cardiovasc Interv* 74:1055–1057, 2009.
106. Piscione F, Danzi GB, Cassese S, et al: Multicenter experience with MGuard net protection stent in ST-elevation myocardial infarction: safety, feasibility and impact on myocardial reperfusion. *Catheter Cardiovasc Interv* 75:715–721, 2010.
107. Romaguera R, Gomez-Hospital JA, Sanchez-Elvira G, et al: MGuard mesh-covered stent for treatment of ST-segment elevation myocardial infarction with high thrombus burden despite manual aspiration. *J Interv Cardiol* 26:1–7, 2013.
108. Gunn J, Siotia A, Malkin CJ, et al: Novel use of pericardium-covered stent graft to treat bulky coronary artery thrombus. *Catheter Cardiovasc Interv* 80:59–64, 2012.
109. Topaz O: Novel thrombus displacement technology for STEMI revascularization, Editorial. *Catheter Cardiovasc Interv* 80:65–66, 2012.
110. Topaz O, Perin EC, Jesse RL, et al: Power thrombectomy in acute coronary syndromes. *Angiology* 54:457–468, 2003.
111. Atar S, Rosenschein U: Perspectives on the role of ultrasonic devices in thrombolysis. *J Thromb Thrombolysis* 17(2):107–114, 2004.
112. Parang P, Arora A: Coronary vein graft disease: pathogenesis and prevention. *Can J Cardiol* 25:e57–e62, 2009.
113. Yong A, Groenestein P, Brieger D, et al: Late thrombotic occlusion of a left internal mammary artery graft causing ST-elevation myocardial infarction. *Int J Cardiol* 142:e42–e44, 2010.
114. Hata M, Takayama T, Sezai A, et al: Efficacy of aggressive lipid controlling therapy for preventing saphenous vein graft disease. *Ann Thorac Surg* 88:1440–1444, 2009.
115. Veldkamp RF, Valk SD, van Domburg RT, et al: Mortality and repeat interventions up until 20 years after aorto-coronary bypass surgery with saphenous vein grafts: a follow-up of 1041 patients. *Eur Heart J* 21:747–753, 2000.
116. Holmes DR, Jr, Berger PB: Percutaneous revascularization of occluded vein grafts: Is it still a temptation to be resisted? *Circulation* 99(1):26–29, 1999.
117. Perin EC, Leite-Sarmento R, Silva GV, et al: "Wireless" laser recanalization of chronic total coronary occlusions. *J Invasive Cardiol* 13:401–405, 2001.
118. Londero HF: Totally occluded saphenous vein graft recanalization: a dangerous option, Editorial. *Catheter Cardiovasc Interv* 60:218–220, 2003.
119. Gaitonde RS, Sharma N, von der Lohe E, et al: Combined distal embolization protection and rheolytic thrombectomy to facilitate percutaneous revascularization of totally occluded saphenous vein grafts. *Catheter Cardiovasc Interv* 60:212–217, 2003.
120. Grantham JA, Marso SP, Spertus J, et al: Chronic total occlusion angioplasty in the United States. *JACC Cardiovasc Interv* 2(6):479–486, 2009.
121. George S, Cockburn J, Clayton TC, et al: Long-term follow-up of elective chronic total coronary occlusion angioplasty: analysis from the U.K. central cardiac audit database. *J Am Coll Cardiol* 64:235–243, 2014.
122. Edwards JE: Atherosclerotic lesions: their distribution and histopathology. In Budinger TF, editor: *Noninvasive techniques for assessment of atherosclerosis in peripheral, carotid and coronary arteries*, New York, 1982, Raven Press, pp 1–13.
123. Srivatsa SS, Edwards WD, Boos CM, et al: Histologic correlates of angiographic chronic total coronary artery occlusions: influence of occlusion duration on neovascular channel patterns and intimal plaque composition. *J Am Coll Cardiol* 29:955–963, 1997.
124. Topaz O: Revascularization of the impenetrable CTO: in support of the enhanced antegrade approach. *Catheter Cardiovasc Interv* 73:276–277, 2009.
125. Abbott JD, Vlachos HA, Sawhney N, et al: Recent trends in the percutaneous treatment of chronic total coronary occlusions. *Am J Cardiol* 97:1691–1696, 2006.
126. Morice MC, Serruys PW, Kappetein AP, et al: Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. *Circulation* 10: 2388–2394, 2014.
127. Prasad SB, Whitbourn R, Maliapan Y, et al: Primary percutaneous coronary intervention for acute myocardial infarction caused by unprotected left main stem thrombosis. *Catheter Cardiovasc Interv* 73:301–307, 2009.
128. Topaz O, Polkampally PR, Mohanty PK, et al: Excimer laser debulking for percutaneous coronary intervention in left main coronary artery disease. *Lasers Med Sci* 24:955–960, 2009.
129. Topaz O: Total left main coronary artery occlusion: the acute, the chronic and the iatrogenic. *Chest* 101:843–846, 1992.
130. Topaz O, DiSciascio G, Cowley MJ, et al: Complete left main coronary artery occlusion: angiographic evaluation of collateral vessel patterns and assessment of hemodynamic correlates. *Am Heart J* 121:450–456, 1991.
131. ARTS II Investigators: 5-Year clinical outcomes of the ARTS 2 (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. *J Am Coll Cardiol* 55(11):1093–1101, 2010.
132. Costa JR, Jr, Sousa A, Moreira AC, et al: Incidence and predictors of very late (>or=4 years) major cardiac adverse events in the DESIRE (Drug-Eluting Stents in the Real World)-Late registry. *JACC Cardiovasc Interv* 3(1):12–18, 2010.
133. Alexopoulos D, Xanthopoulos I, Davlouros P, et al: Mechanisms of nonfatal acute myocardial infarction late after stent implantation: the relative impact of disease progression, stent restenosis, and stent thrombosis. *Am Heart J* 159(3):439–445, 2010.
134. Garg S, Serruys P: Benefits and safety concerns associated with drug-eluting coronary stents. *Expert Rev Cardiovasc Ther* 8(3): 449–470, 2010.
135. Ergelen M, Gorgulu S, Uyarel H, et al: The outcome of primary percutaneous coronary intervention for stent thrombosis causing ST-elevation myocardial infarction. *Am Heart J* 159(4): 672–676, 2010.
136. Parodi G, Memisha G, Bellandi B, et al: Effectiveness of primary percutaneous coronary interventions for stent thrombosis. *Am J Cardiol* 103(7):913–916, 2009.
137. Topaz O: Late stent thrombosis: Is AngioJet rheolytic thrombectomy the preferred revascularization technique? *Catheter Cardiovasc Interv* 58:18–19, 2003.
138. Turgeman Y, Suleiman K, Atar S: Multivessel acute coronary thrombosis and occlusion—an unusual cause of cardiogenic shock. *J Invasive Cardiol* 19(9):E278–E280, 2007.
139. Konagai N, Cho M, Nakamura K, Shigematsu H: Left atrial myxoma as a cause of acute myocardial infarction. *Tex Heart Inst J* 37(1):125–126, 2010.
140. Balevski I, Sajko MC, Kanic V, Noc M: Catheter aspiration in ST-elevation myocardial infarction and different extent of coronary thrombus. *Am J Cardiol* 107(68):681–684, 2011.
141. Yoshimori A, Schuichiro K, Kitae K, et al: Successful thrombus aspiration during primary percutaneous coronary interventions reduces infarct size and preserves myocardial viability: a cardiac magnetic resonance imaging study. *J Invasive Cardiol* 23:172–176, 2011.
142. Zia M, Ghugre N, Connelly KA, et al: Thrombus aspiration during primary percutaneous coronary intervention is associated with reduced myocardial edema, hemorrhage, microvascular obstruction and left ventricular remodeling. *J Cardiovasc Magn Reson* 14:19–29, 2012.
143. Burzotta F, De Vita M, Gu YL, et al: Clinical impact of thrombectomy in acute ST-elevation myocardial infarction: an individual patient-data pooled analysis of 11 trials. *Eur Heart J* 30: 2193–2203, 2009.
144. Bulum J, Ernst A, Strozzi M: The impact of successful manual thrombus aspiration on in-stent restenosis after primary PCI: angiographic and clinical follow-up. *Coron Artery Dis* 23:487–491, 2012.
145. Shehata M: Angiographic and Clinical Impact of Successful Manual Thrombus Aspiration in Diabetic Patients Undergoing Primary PCI. *Int J Vasc Med* 2014. doi: 10.1155/2014/263926. [Epub 2014 Apr 2].
146. De Vita M, Burzotta F, Porto I, et al: Thrombus aspiration in ST elevation myocardial infarction: comparative efficacy in patients treated early and late after onset of symptoms. *Heart* 96:1287–1290, 2010.
147. Cervinka P, Spaček R, Bystroň M, et al: Optical coherence tomography-guided primary percutaenous coronary intervention in ST-segment elevation myocardial infarction patients: a pilot study. *Can J Cardiol* 30:420–427, 2014.

28 Complications of Percutaneous Coronary Intervention

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KEY POINTS

- Although most complications of percutaneous coronary intervention (PCI) are avoidable, when they do occur, rapid recognition and a corrective response are necessary to mitigate adverse consequences such as myocardial infarction (MI) or death.
- Abrupt closure and intraprocedural stent thrombosis/acute stent thrombosis (<24 hr) are serious complications that can result in MI and death. Treating them requires rapid steps to restore perfusion and carefully evaluate, identify, and treat the cause.
- Coronary perforations are generally due to guidewires, overdilation, and/or atheroablative devices. Sealing the perforation with balloon occlusion is imperative, followed by halting anticoagulation. Should it be necessary, either implantation of a polytetrafluoroethylene (PTFE) stent graft or referral to emergent cardiac surgery remain options if extravasation persists.
- Stents are the most common devices embolized; if possible, retain wire access through the center of the stent. Retrieval involves an array of techniques, including distal balloon inflation, snaring, and wire wrapping. If retrieval is not possible, deployment of the stent in the unintended location may be necessary.
- Emergent referral for cardiac surgery is associated with significant morbidity and mortality due to ongoing MIs and the powerful anticoagulants used during PCI.
- Periprocedural MI is associated with increased morbidity and mortality. Strategies to avoid periprocedural MI include pharmacologic optimization and appropriate use of adjunctive devices such as distal protection filters.
- Coronary no-reflow phenomenon results when the distal microcirculatory bed is overwhelmed with particulate matter, resulting in impaired perfusion. Although this is sometimes reversible with vasodilators, prevention remains the best strategy.
- Air embolism is almost always iatrogenic and preventable through meticulous catheter management.
- Radiocontrast hypersensitivity occurs rarely and is sometimes difficult to recognize. Treatment with steroids and sometimes epiphephrine may be necessary to stablize hemodynamics.
- Bleeding is associated with significant in-hospital and 30-day mortality. Strategies to avoid bleeding include optimization of patient selection for revascularization, pharmacology, and access-site management.

Good judgment comes from experience and experience comes from bad judgment.

—Unknown

Although the best approach to PCI complications is avoidance, unfortunately complications occur and are an important part of the interventional cardiologist's learning. Prompt recognition of complications along with a calm and effective response is essential to successful management. This chapter will explore the most common procedural complications.

ABRUPT CLOSURE

Incidence

The incidence of abrupt closure, often called *acute closure,* during PCI has steadily decreased, from 3% in the balloon angioplasty era to 0.3% in the current era (Fig. 28-1). The trend in decreasing acute closure rates corresponds to the increased utilization of stents and effective antithrombotics that include glycoprotein (GP) IIb/IIIa inhibitors, dual antiplatelet therapy (DAPT), and direct thrombin inhibitors. According to the National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry, lower rates of abrupt closure decreased referrals for emergent coronary artery bypass grafting (CABG) and reduced periprocedural PCI mortality from 1.4% in 1985 to 1986 to 0.7% in 2006 (Fig. 28-2).[1]

Mechanisms

The most common mechanism of acute closure is dissection with injury to the media (Table 28-1, Fig. 28-3, and Video 28-1).[2] Intramural hematoma can develop along with intimal flaps, causing mechanical obstruction. With mechanical obstruction and the exposure of subintimal tissue, thrombus formation is often initiated. Vasoconstriction further complicates this milieu but is rarely a major mechanism of closure.[3]

Whereas the predominant causes of acute closure in the prestent era were dissection (28%), thrombus (20%), or both (7%), the cause is indeterminate in almost 50% of cases.[4,5] Patient factors predictive of abrupt closure include unstable angina, multivessel disease, and female sex.[6,7] When examining the angiographic risk factors of dissection-mediated acute closure, proximal tortuosity was the strongest predictor followed by American College of Cardiology (ACC) lesion grade C (Table 28-2), longer lesion length, and de novo stenosis. Similarly, risks for thrombotic closure include presence of preexisting thrombus, degenerated vein grafts, and recent MI.[7] Air embolism and no-reflow phenomenon are also part of the differential diagnosis of abrupt closure; these will be discussed elsewhere.

Prognostic Significance

Most data regarding outcomes of patients experiencing abrupt closure are derived from the prestent era. In studies from the balloon angioplasty era, 6% of patients died, 36% suffered nonfatal MI, and 30% were referred for emergency CABG.[4]

Treatment

Abrupt closure results in acute ischemia that may be manifested by dramatic electrocardiographic (ECG) changes, hypotension, hypertension, chest pain, ventricular arrhythmias, and/or bradycardia. The first priorities are to stabilize hemodynamics and relieve ischemia. Vasopressors, inotropes, intraaortic balloon pumping (IABP), or ventricular assist device insertion should be considered for hemodynamic instability. Extreme vagal reactions may also cause bradycardia or hypotension and should be treated with atropine, intravenous (IV) fluid boluses, and vasopressors if necessary. Electrical instability should be recognized immediately and promptly treated with antiarrhythmic medications and/or cardioversion if necessary.[3]

Expeditious efforts to restore antegrade flow, such as repeat angioplasty, must be quickly attempted. Urgent stenting is usually required to stabilize dissections. GP IIb/IIIa antagonists can be helpful if thrombus is responsible for the acute closure. Prospective use of abciximab was compared with placebo in both balloon angioplasty and stenting cohorts in the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial and demonstrated that abciximab decreases rates of abrupt closure and side branch loss.[8] The utility of GP IIb/IIIa inhibitors as a bailout is controversial because the data support upstream use during PCI.[8,9]

In the case of persistent acute closure, the use of intravascular imaging such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT) should be considered to more clearly define the pathology. Intravascular imaging can document the presence and extent of dissections, requiring a long length of stents to restore patency

TABLE 28-1 Classification of Coronary Dissection

Type	Description	Acute Closure (%)
A	Minor radiolucencies within lumen during angiography without dye persistence	0-2
B	Parallel tracks or double lumen separated by radiolucent area during angiography without dye persistence	2-4
C	Extraluminal cap with dye persistence	10
D	Spiral luminal filling defects	30
E	New persistent filling defects	9
F	Non–E types that lead to impaired flow or total occlusion	69

From Klein LW: Coronary complications of percutaneous coronary intervention: a practical approach to the management of abrupt closure. *Catheter Cardiovasc Interv* 64:395-401, 2005.

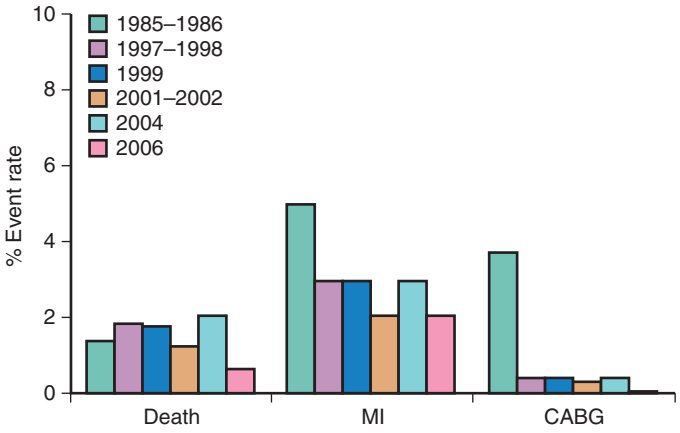


FIGURE 28-1 Improvements in percutaneous coronary intervention (PCI) outcomes—throughout the evolution of PCI, from balloon angioplasty to the drug-eluting stent era—are reflected in the National Heart, Lung and Blood Institute Dynamic Registry. *CABG,* Coronary artery bypass graft; *MI,* myocardial infarction. (From Venkitachalam L, Kip KE, Selzer F, et al: Twenty-year evolution of percutaneous coronary intervention and its impact on clinical outcomes: a report from the National Heart, Lung, and Blood Institute-Sponsored, Multicenter 1985-1986 PTCA and 1997-2006 Dynamic Registries. *Circ Cardiovasc Interv* 2:6-13, 2009.)

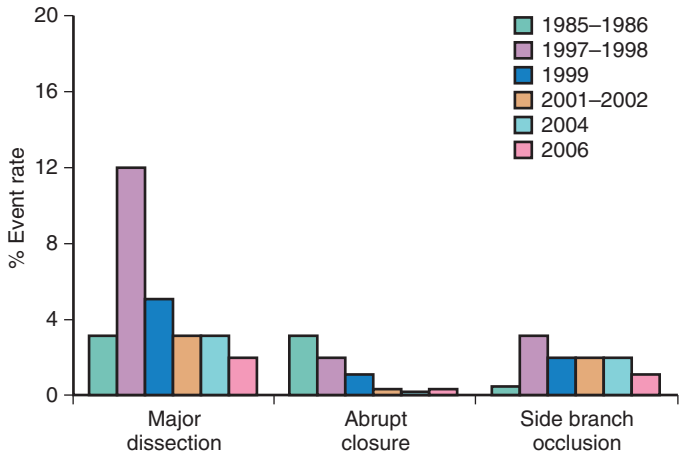


FIGURE 28-2 Progressive decrease in abrupt closure and major dissection with evolution of percutaneous coronary intervention into the current drug-eluting stent era. (Venkitachalam L, Kip KE, Selzer F, et al: Twenty-year evolution of percutaneous coronary intervention and its impact on clinical outcomes: a report from the National Heart, Lung, and Blood Institute-Sponsored, Multicenter 1985-1986 PTCA and 1997-2006 Dynamic Registries. *Circ Cardiovasc Interv* 2:6-13, 2009.)

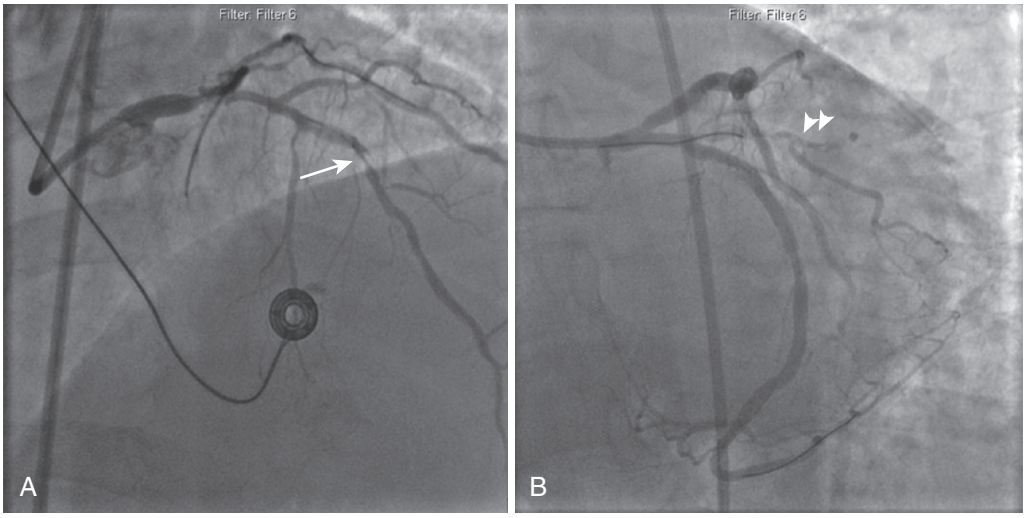


FIGURE 28-3 Coronary dissection. **A,** Non–flow-limiting dissection in the left anterior descending artery (*arrow*). **B,** Flow-limiting spiral dissection of the obtuse marginal branch with incomplete distal filling (*arrowheads*; Video 28-1).

TABLE 28-2 American College of Cardiology/American Heart Association Lesion Classification System

TYPE A
• Discrete (<10 mm length) • Concentric • Readily accessible • Nonangulated segment (<45 degrees) • Smooth contour • Little or no calcification • Less than totally occlusive • Not ostial in location • No major side-branch involvement • Absence of thrombus
TYPE B*
• Tubular (10 to 20 mm length) • Eccentric • Moderate tortuosity of proximal segment • Moderately angulated segment (>45 degrees, <90 degrees) • Irregular contour • Moderate to heavy calcification • Total occlusions less than 3 months old • Ostial in location • Bifurcation lesions requiring double guidewires • Some thrombus present
TYPE C
• Diffuse (>2 cm length) • Excessive tortuosity of proximal segment • Extremely angulated segments (>90 degrees) • Total occlusion more than 3 months old • Inability to protect major side branches • Degenerated vein grafts with friable lesions

*A grade of B1 designates one adverse characteristic; B2 indicates two or more adverse characteristics.

and stabilize a dissection. If the IVUS findings are suspicious for thrombus, aspiration thrombectomy may be valuable, and the addition of a GP IIb/IIIa inhibitor should be considered. Intracoronary (IC) thrombolytic delivery has been used for rescue of abrupt closure but is associated with significant morbidity and is not recommended.[6]

Factors that affect the inflow and outflow should be investigated. The use of multiple angiographic views, IVUS, and selective distal injections may better delineate the anatomy. Guide catheter dissections may cause poor inflow and can easily be overlooked. Pressure dampening, ventricularization, ECG changes, or severe ischemic pain may indicate an ostial guide catheter dissection. Distal wire dissections that occlude outflow may require stenting, even if the distal vessel is small caliber.

In the prestent (balloon angioplasty) era, approximately 40% of cases with acute closure ultimately achieved procedural success.[6] The predominant treatment was repeat balloon dilation with prolonged inflation facilitated by autoperfusion balloon catheters. Historically, the use of stents as bailout devices for abrupt or impending closure dramatically decreased the need for emergent CABG.[10] Although no randomized trial has been performed, the dramatic decrease in urgent and emergent CABG, from 3% to 0.7% in the NHLBI dynamic registry, was clearly associated with the use of stents and more effective anticoagulation, primarily GP IIb/IIIa inhibitors.[1]

Patients with a successful outcome following treatment of abrupt closure require close monitoring in an intensive care setting. If needed, IABP should be continued until the patient is stable. Serial cardiac enzyme assessments, electrocardiograms, and echocardiography to assess the extent of myocardial damage are also recommended (Fig. 28-4 gives an acute vessel closure management algorithm).

Unsuccessful Outcome

If recanalization is unsuccessful, the interventionalist is faced with the choice of referral for emergent CABG or medical management. Medical

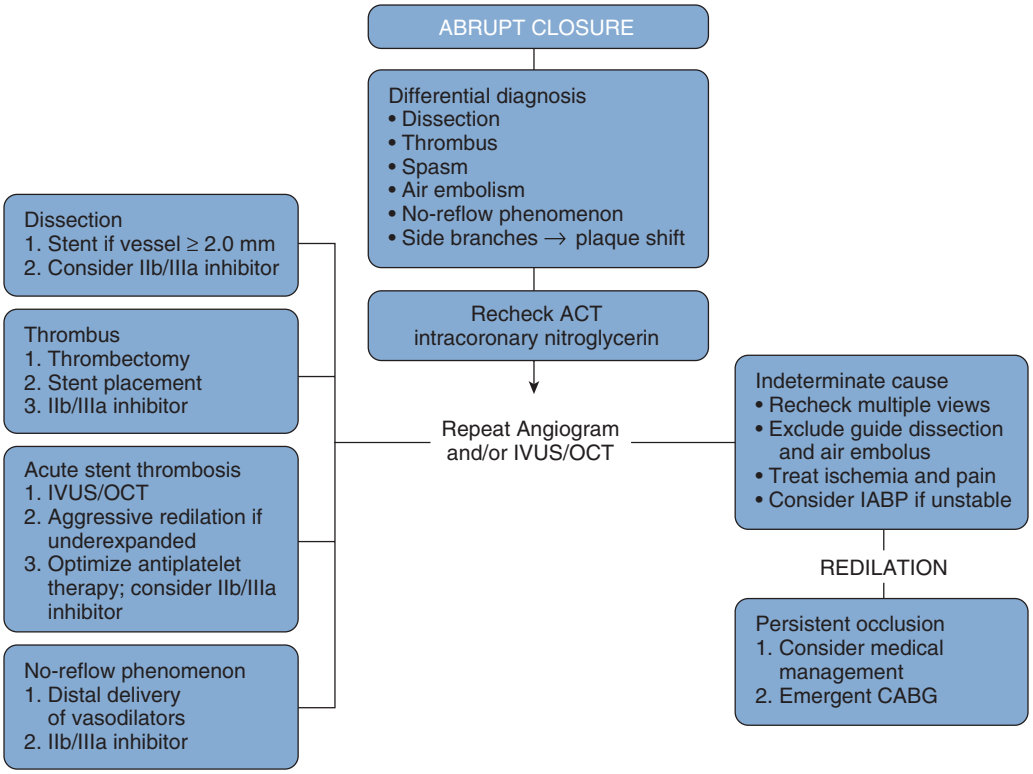


FIGURE 28-4 Suggested algorithm for management of abrupt closure. *ACT,* Activated clotting time; *CABG,* coronary artery bypass graft; *IABP,* intraaortic balloon pumping; *IVUS,* intravascular ultrasound; *OCT,* optical coherence tomography. (Adapted from Klein LW: Coronary complications of percutaneous coronary intervention: a practical approach to the management of abrupt closure. *Catheter Cardiovasc Interv* 64:395-401, 2005.)

management is essentially acceptance that the patient will sustain an MI. The quantity of myocardium subtended by the closed vessel versus the likelihood of a successful surgical result and risks of undergoing emergent surgery are the most important factors when deciding between surgical or medical management of abrupt closure. Care must be taken to distinguish refractory closure from no-reflow phenomenon because CABG is ineffective in a no-reflow situation.

Stent Thrombosis

Intraprocedural and acute stent thrombosis are both forms of abrupt closure. Stents serve to improve patency after dilating stenotic lesions, and they stabilize dissections; however, metal is inherently thrombogenic, and early experience with stents showed thrombosis rates as high as 8% to 16% if implanted for rescuing abrupt closure.[11,12] Early stent thrombosis (<30 days) rates for elective PCI in stable coronary artery disease (CAD) patients ranges from 0.3% to 0.5%, but stenting for acute coronary syndromes (ACSs) demonstrated early stent thrombosis rates as high as 3.4% and 1.4% for ST-elevation myocardial infarction (STEMI) and non–ST-elevation myocardial infarction (NSTEMI), respectively, indicating the impact of a thrombogenic milieu.[13-16] Intraprocedural stent thrombosis (IPST) and acute stent thrombosis are rare events that occur in 0.8% to 1.2% and 0.1% to 0.9% of cases, respectively.[17-20] For purposes of this chapter, we will focus on intraprocedural and acute stent thrombosis (<24 hours from implantation).

Factors that lead to stent thrombosis include a combination of patient comorbidities, suboptimal pharmacology, and procedural variables related to stent implantation, plaque disruption, and vessel injury. Multivariate analysis from the Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention (CHAMPION-PHOENIX) identified NSTEMI and STEMI at presentation (NSTEMI odds ratio [OR] 1.87, $P = .04$; STEMI OR 2.07, $P = .004$), angiographic thrombus prior to PCI (OR 1.79, $P = .01$), and total stent length (OR 1.03/mm, $P < .0001$) as independent predictors of IPST.[18] Post-hoc analysis of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial revealed insulin-dependent diabetes (OR 3.48), renal insufficiency (OR 2.09), Duke jeopardy score (OR 1.15), final stent minimal luminal diameter (OR 0.32), preprocedural thienopyridine administration (OR 0.30), baseline hemoglobin (OR 1.28), and extent of CAD (OR 1.01) as independent factors associated with early stent thrombosis.[13] In an IVUS substudy of stent thrombosis from the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, small cross-sectional area (<5 mm^2), malapposition, plaque protrusion, edge dissection, and residual stenosis played significant roles in predicting early stent thrombosis.[21] All cases of stent thrombosis had at least one abnormality, and 50% of patients had two or more IVUS abnormalities.[21] Ex-vivo histologic analysis of fatal stent thrombosis cases corroborated plaque prolapse and incomplete apposition as contributors of stent thrombosis; however, medial tears were found in 27% of analyzed segments, suggesting that deep vessel wall injuries play a significant role in stent thrombosis.[22] Finally, complex PCI—particularly stenting using the crush technique—carries a higher rate of IPST (0.5% to 1.3%).[23]

Mortality of stent thrombosis (ST) in general ranges from 26% to 45% overall when looking at all-comers.[24] Those who present with STEMI are found to have less successful reperfusion compared with their STEMI counterparts who do not have stent thrombosis (ST 80.4% vs. non-ST 96.9%; $P < .0001$).[25] Along with less successful reperfusion, those with STEMI in the context of ST have greater rates of in-hospital mortality (ST STEMI 17.4% vs. non-ST STEMI 7.1%; $P = .03$) and greater rates of composite major adverse cardiovascular and cerebrovascular events (MACCEs; ST STEMI 25.6% vs. non-ST STEMI 9.2%; $P = .003$).[25] Similarly, IPST has a 30-day mortality rate of 10.1% and carries an adjusted odds ratio of 12.3 of death compared with non-IPST cases. Additionally, IPST predicts a higher rate of 30-day post-PCI stent thrombosis (5.6%; adjusted OR 7.6).[18]

When confronted with acute or intraprocedural stent thrombosis, the interventionalist must be very prompt at restoring perfusion to minimize myocardial damage, and the approach to treatment should include both pharmacologic and mechanical optimization. Certainly if IC thrombus develops, prompt aspiration thrombectomy or angioplasty should be performed immediately to restore patency. Therapeutic anticoagulation should be confirmed, and more potent antiplatelet therapy should be considered; both IV cangrelor and GP inhibition both were associated with less IPST, which indicates the importance of potent platelet inhibition.[18,26] Bailout GP inhibitor, or possibly loading with either prasugrel or ticagrelor, to rapidly reach maximal steady state platelet inhibition may be helpful. If heparin-induced thrombocytopenia (HITT) is suspected, switching the patient to a direct-thrombin inhibitor such as bivalirudin should be considered. Certainly, intravascular imaging with either IVUS or optical coherence tomography (OCT) should be used to determine stent apposition, expansion, and presence of edge dissections. Optimization of stent deployment with appropriate postdilation and treatment of edge dissections with additional stents are imperative to prevent repeat stent thrombosis.[27] Additional stent implantation should be done judiciously because each millimeter of stent increases the probability of IPST.[18]

CORONARY PERFORATION

Incidence

Coronary perforation is a serious complication with an incidence that ranges from 0.19% to 1.5% of cases (Table 28-3). Lesions associated with perforation are more complex in nature. ACC type B or C lesions, calcified lesions, and chronic total occlusions (CTOs) are more likely to sustain perforation (see Table 28-3).[28,29] Women and older adults are at greater risk of perforation.[4]

Mechanisms

Two basic mechanisms are responsible for perforation: guidewire penetration and vessel rupture. *Vessel rupture* is usually caused by balloon or stent mismatch with oversizing of the dilation catheter. Occasionally, an appropriately sized catheter will result in perforation as a result of extensive dissection, lack of vessel wall integrity, or calcification. Early balloon angioplasty studies found increasing the balloon/artery ratio to greater than 1.2:1 increased perforation risk.[4] Use of atherectomy devices such as an eximer laser or rotational atherectomy also increased perforation risk.[31] Recanalization of CTOs has become a common setting for perforation, usually as a result of small guidewire perforations, particularly with the use of stiffer and more hydrophilic guidewires to perform subintimal dissection.[28]

Ellis graded perforations (Table 28-4) are separated into three classes of severity that range from small endovascular leaks into the adventia (grade I) to frank extravasation into the pericardial space (grade III). Grade I perforations are frequently caused by guidewires, but atheroablative devices and stents can cause small endovascular leaks. Occasionally, guidewires can cause very large distal perforations; therefore extreme vigilance should be maintained, particularly when using stiff and hydrophilic guidewires into distal tortuous vessels. Grade II and III perforations are usually caused by high-pressure balloon inflations, oversized balloon catheters, stents, or the use of atheroablative devices (Fig. 28-5).

Prognosis

Perforation severity predicts prognosis. Grade III perforations can quickly result in cardiac tamponade, rapid hemodynamic collapse, MI, and/or death (Table 28-5).[4,28-31,33,34,36] Either immediate covered stent implantation or referral for emergency CABG is often indicated.

TABLE 28-3 Incidence and Outcome of Coronary Perforation Across Reported Studies

Authors/Years Studied	N	Perforation Incidence (%)	Tamponade (%)	CABG (%)	MI (%)	Death (%)
Kiernan JT et al (2000-2008)[28]	14,281	0.48	18	3	7.4	5.9
Fasseas P et al (1990-1991)[29]	16,298	0.58	11.6	10.5	12.6	7.5
Aljuni SC et al (1988-1992)[30]	8,932	0.4	17	37	26	9
Dippel EJ et al (1995-1999)[31]	6,214	0.58	22	22	NA	11
Ellis SG et al (1990-1991)[32]	12,900	0.4	24	24	16	5
Gruberg L et al (1990-1999)[33]	30,746	0.27	31	39	34	10
Gunning MG et al (1995-2001)[34]	6,245	0.8	46	15	NA	12
Javaid A et al (1996-2005)[35]	38,559	0.19	19	35	NA	17
Shimony A et al (2001-2008)[36]	9,568	0.59	15.8	7	NA	7
Stankovic G et al (1993-2001)[37]	5,728	1.5	12	13	18	8
Ramana RK et al (2001-2004)[38]	4,886	0.5	4	20	32	8
Witzke CF et al (1995-2003)[39]	12,658	0.3	18	5	5	2.6

CABG, Coronary artery bypass graft; *MI,* myocardial infarction; *N,* number of procedures; *NA,* not available.

TABLE 28-4 Ellis Classification of Coronary Perforations

Grade	Description	Possible Clinical Sequelae
I	Focal extraluminal crater without extravasation limited to media or adventitia	Usually benign, may rarely cause delayed cardiac tamponade
II	Pericardial or myocardial blush without contrast in pericardium; limited extravasation producing a patch of blushing or staining within the myocardium or pericardium	
III	Persistent extravasation with streaming or jet of contrast	High risk of increased morbidity and mortality
IIIA	Directed toward pericardium	High risk of acute cardiac tamponade
IIIB	Directed toward myocardium (e.g., ventricular cavity)	More benign course; possible fistula formation

(With permission from Klein LW: Coronary artery perforation during interventional procedures. *Catheter Cardiovasc Interv* 68:713-717, 2006.)

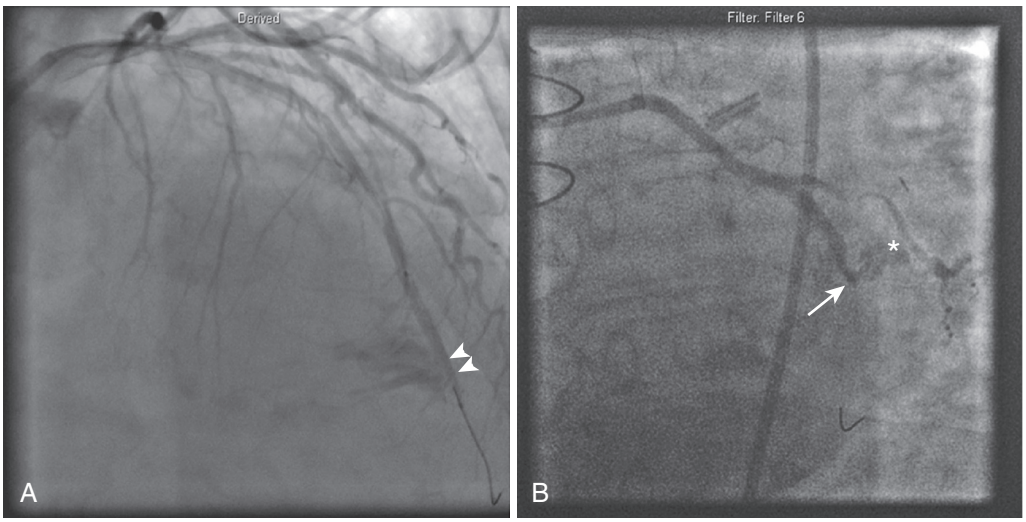


FIGURE 28-5 Coronary perforations. **A,** Distal perforation in the left anterior descending artery leading to extravasation (*arrowheads*) while treating a severe plaque. **B,** Perforation in a midobtuse marginal branch as a result of rotational atherectomy with extravasation into the pericardium (*asterisk;* Video 28-2).

TABLE 28-5 Coronary Stent Embolization Is Associated With Significant Major Adverse Cardiac Events

	Incidence (%)	N	Death (%)	MI (%)	CABG (%)
Brilakis ES et al[40]	0.32	38	3	11	5
Bolte J et al[41]	1.7	387	6.2	3.9	17
Cantor WJ et al[42]	8.3	108	2.8	5	16
Eggebrecht H et al[43]	0.9	20	15	NA	15

CABG, Coronary artery bypass graft; *MI,* myocardial infarction; *N,* number of patients; *NA,* not available

Diagnosis

Given the dire consequences of coronary perforation, the interventionalist must be especially attuned to recognizing this complication early. Patients may experience severe chest pain, dizziness, or nausea disproportional to symptoms typically associated with balloon inflation. ST-segment changes may persist after balloon deflation. Vasovagal reactions may also accompany perforations along with severe bradycardia and hypotension.[44] Awareness and vigilance after PCI is vital because cardiac tamponade as late as 24 hours after PCI has been reported.[4,45] Late tamponade risk can be minimalized with careful "final" angiograms that visualize all instrumented vessels and their branches.

Management

Grade I perforations can generally be treated with reversal of anticoagulation and/or prolonged balloon inflation at or proximal to the perforated vessel segment. Guidewire perforations are often best treated by balloon occlusion but have been treated with delivery of occlusive coils, fat, or beads. Occasionally, grade I perforations can resolve without an intervention, but small endovascular leaks may persist and require the use of a covered stent or referral to emergent CABG. Grade III perforations are catastrophic and more likely require urgent pericardiocentesis, deployment of a polytetraflouroethylene (PTFE) stent, and/or referral for emergent surgery.[44]

Once a perforation occurs, the first step is to remain calm and advance a balloon from the guide catheter across the perforation without losing the guidewire position. If the perforation results from a guidewire, balloon inflation proximal to the perforation is indicated. This highlights an essential interventional cardiology fundamental: balloons should remain in the guide or within the lesion following any inflation until angiography confirms no perforation is present. When perforation is recognized, balloon expansion to a pressure sufficient to occlude flow (usually 2 to 4 atm) is the first step. Once the vessel is occluded, the patient's hemodynamics may normalize; however, aggressive treatment with IV fluids, atropine, vasopressors, and perhaps mechanical circulatory support may be required.

When treating perforations, anticoagulation should be immediately stopped. If heparin was used as the anticoagulant, reversal with protamine is usually indicated. GP IIb/IIIa inhibitors must also be stopped, and abciximab should be reversed with an infusion of platelets. The effects of tirofiban and eptifibatide cannot be reversed with platelet infusions, but both have a shorter half-life compared with abciximab. Although IIb/IIIa inhibitors can increase bleeding complications, they have not been demonstrated to increase the incidence or severity of perforations.[31] Direct thrombin inhibitors such as bivalirudin are commonly utilized for procedural anticoagulation, and its effects cannot be reversed with protamine. Thus far bivalirudin has not been associated with an increased hazard of death or life-threatening complications for high-risk PCI.[46] Infusion of fresh frozen plasma may be the only means to reverse anticoagulation with bivalirudin; this, however, requires a time delay to thaw the blood products.[47]

The presence of coronary perforation should trigger urgent echocardiography. If a large pericardial effusion is present and is associated with tamponade physiology, emergent pericardiocentesis is indicated. Should echocardiography not be available, the diagnosis of tamponade on clinical grounds, use of right heart catheterization, or fluoroscopy of the heart borders may be helpful.

A major advance in the treatment of coronary perforation is the development of PTFE-covered stents. Prior to the advent of such stents, the presence of a grade III perforation often required emergency CABG and carried significant mortality.[45] The currently available PTFE stent (JoStent Graftmaster; Abbott Vascular, Santa Clara, CA) is a PTFE graft layered between two bare-metal stents that can exclude perforations. The initial experience using PTFE grafts was reported in a small case series that demonstrated a decrease in cardiac tamponade and emergency CABG.[48] PTFE-covered stents are bulky, and delivery into tortuous vessels can be challenging. A separate guide catheter for the PTFE-covered stent delivery is recommended because most guide catheters cannot accommodate both an angioplasty balloon and a PTFE-stent graft simultaneously (Fig. 28-6). Therefore a two-guide technique has been developed wherein contralateral access is established and a separate guide catheter is used to deliver the stent. A wire from the second guide catheter is advanced down the coronary vessel, and the angioplasty balloon is momentarily deflated to allow guidewire passage. The PTFE-stent is then quickly advanced across the perforation and is deployed after the removal of the angioplasty balloon. The two-guide catheter technique has been documented to decrease adverse event rates, and it offers the operator the luxury of more time to position the stent (Video 28-3).[49] Side-branch vessels near the perforation site may be excluded by the PTFE-covered stent, which may result in a periprocedural MI.[48] IVUS should be routinely be used to verify adequate covered-stent expansion because deploying this dual-stent layer may require aggressive post dilation (≥8 atm). Occasionally, collateral filling may cause persistent extravasation despite exclusion of the perforation with a stent graft, and surgical management or occlusion of the supplying collateral may be required.

Perforations in small vessels can be addressed with either additional prolonged balloon inflations; by injection of thrombin, polyvinyl alcohol, gelfoam, or collagen; or with embolization by microcoils or beads.[50,51] Figure 28-7 offers a suggested strategy for the management of coronary perforation.

DEVICE EMBOLIZATION

Incidence

Embolization of material such as coronary stents and guidewire fragments is a potentially catastrophic complication of PCI. Stents are the most common device embolized, with an incidence that ranges from 3% for first-generation, hand-crimped stents to a much lower 0.32% rate for current manufacturer-mounted stent delivery systems.[40,52]

Mechanism

Extreme tortuosity, angulation, and calcification increase the risk of stent embolization due to dislodgement from delivery balloons. For this reason, stents are more frequently lost in the right coronary artery and circumflex artery and less commonly in the left anterior descending (LAD) artery.[40,53] In today's era of PCI, recently deployed stents proximal to the targeted zone of deployment pose a risk of catching the edges of an undeployed stent; thus care must be taken when advancing and retracting stents.

Treatment

Numerous approaches are available for the removal of embolized stents. If possible, maintain guidewire position through the center of the stent; this will facilitate retrieval using one of many commercially available snares (Fig. 28-8). Another option is to advance a small-diameter balloon through the unexpanded stent, inflate the balloon, and attempt to drag the stent back into the guide catheter. A third approach is to pass a second wire alongside the embolized stent and attempt to enter one of the struts; then attach a single torqueing device to both wires, which is used to twist the wires together, followed by withdrawal of the wire-wrapped stent from the artery. A fourth approach is to deploy the embolized stent in its unintended location. Retrieval devices such as biliary forceps or bioptomes can easily damage the arterial wall and should be avoided or handled with great care. Deploying a new stent alongside the embolized stent such that the dislodged stent is embedded into the arterial wall is a reasonable option should retrieval be difficult, but this technique may be

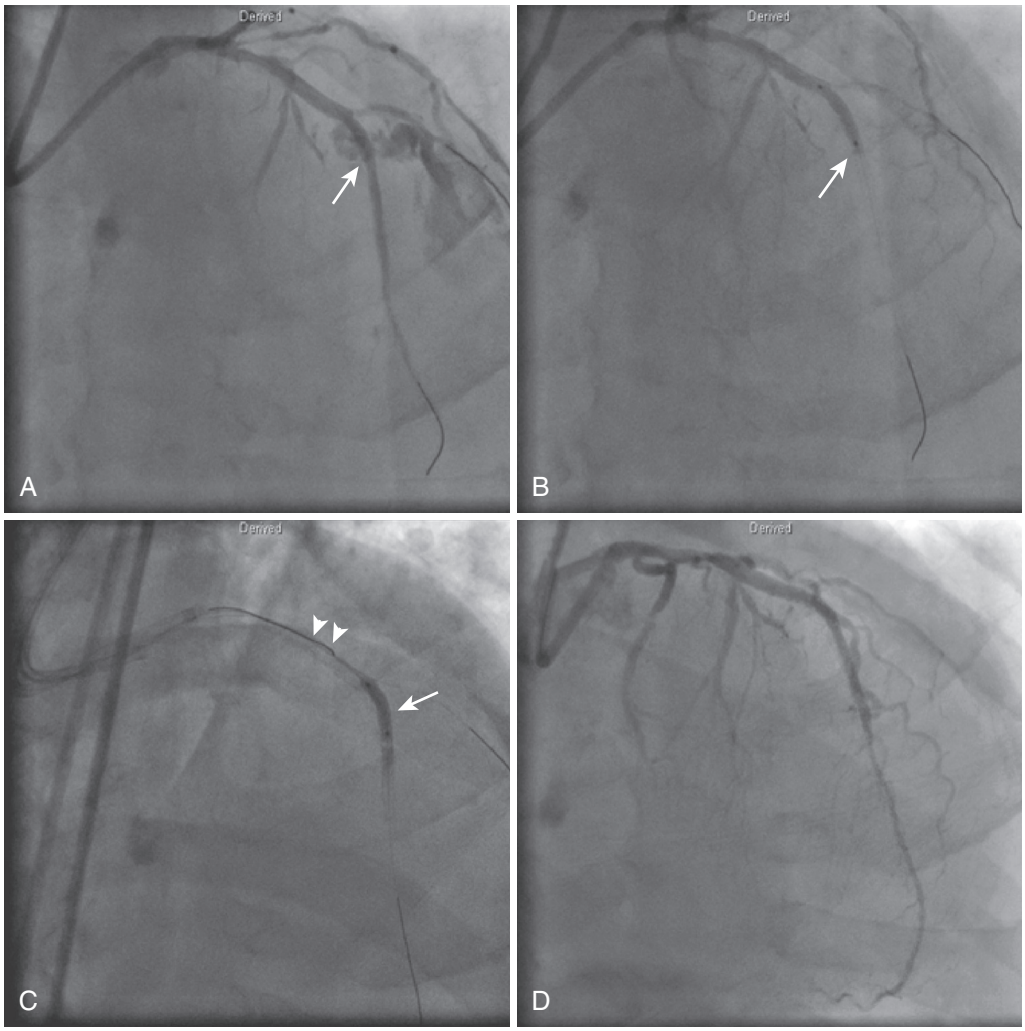


FIGURE 28-6 Successful exclusion of a coronary perforation with a polytetrafluoroethylene (PTFE)-covered stent graft. **A,** An Ellis class III perforation at the middle of the left anterior descending artery (LAD) with streaming into the pericardial space (*arrow*). **B,** Balloon tamponade of the perforation. **C,** Dual guide technique is shown as the original coronary wire is withdrawn (*arrowheads*) while a JoStent (Abbott Vascular, Santa Rosa CA; *arrow*) covered stent graft is deployed in the mid-LAD to exclude the perforation. **D,** Final angiogram demonstrates no extravasation after stent graft deployment (Video 28-3).

associated with an elevated risk of periprocedural MI, death, and referral for CABG.[41]

Retained Percutaneous Angioplasty Equipment Components

The incidence of retained coronary angioplasty equipment components is reported to be 0.2% in a single-center series.[54] Materials such as angioplasty balloons and guidewire fragments have embolized down coronary vessels. The successful recovery of fragments utilizes techniques similar to retrieving embolized stents.[55,56] In one report, four patients with retained guidewire fragments and one patient with a gold band from a balloon catheter did not suffer ischemic complications.

Prognosis

Embolization of coronary stents is associated with worse prognosis and an increased risk of adverse cardiac events (see Table 28-5).[40,41,53] Successful retrieval is associated with good prognosis; however, unsuccessful management or retrieval results in high rates of periprocedural MI, emergent referral for CABG, and death.[41] Peripheral embolization of stents is rarely associated with significant clinical sequelae. In one noninvasive assessment of 20 patients with peripheral stent embolization, no peripheral vascular complications were reported over a mean duration of 5 years.[53]

EMERGENCY CORONARY BYPASS SURGERY

Incidence

The incidence of emergency CABG has decreased from 3.7% during the balloon angioplasty era to 0% in the most recent NHLBI registry (Fig. 28-1).[1] Individual single-center registries showed an incidence of 0.4% to 0.5% (Table 28-6).[57-59] Recent data from the NHLBI Dynamic Registry describes an incidence of 0.7% for early CABG within 30 days of PCI.[1] Patient characteristics associated with emergent CABG included cardiogenic shock, acute MI, multivessel disease, and a prior history of MI. Procedural variables that distinguish patients referred for emergent CABG include ACC type C lesions, placement of an IABP, dissection, perforation, and abrupt closure. Analysis from one single-center study found that most patients referred for CABG had at least one or two high-risk characteristics, and those with four high-risk factors had a 9.3% incidence of emergent CABG.[59]

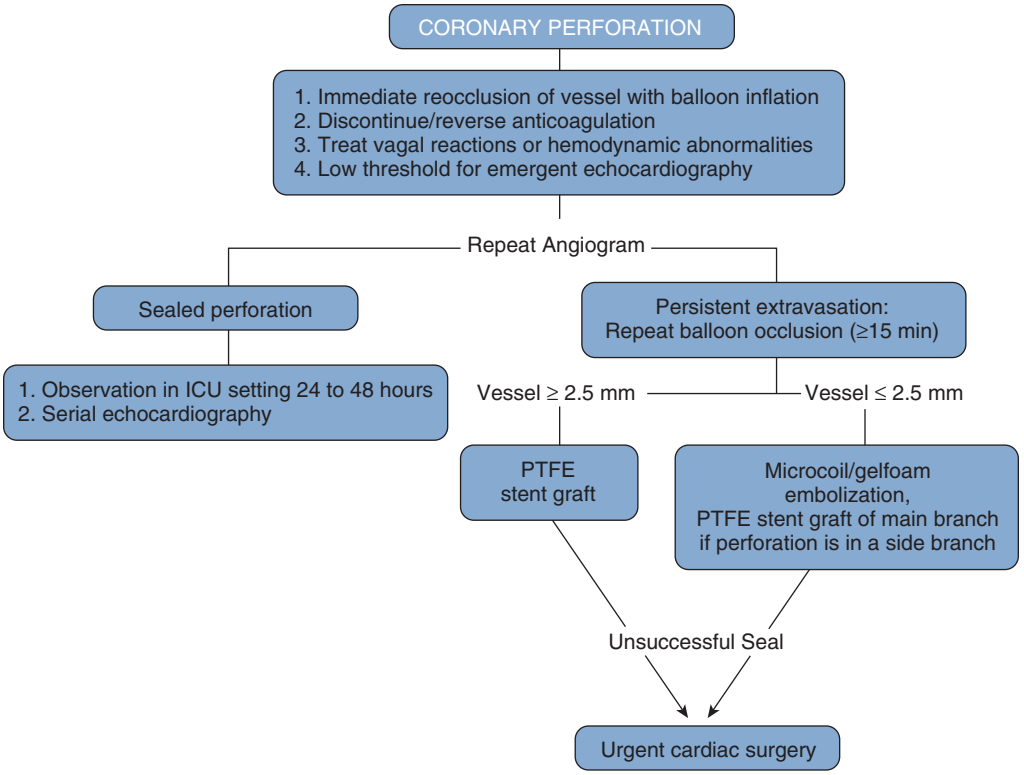


FIGURE 28-7 Suggested algorithm for management of coronary perforation. *ICU,* Intensive care unit; *PTFE,* polytetrafluoroethylene. (From Klein LW: Coronary artery perforation during interventional procedures. *Catheter Cardiovasc Interv* 68:713-717, 2006.)

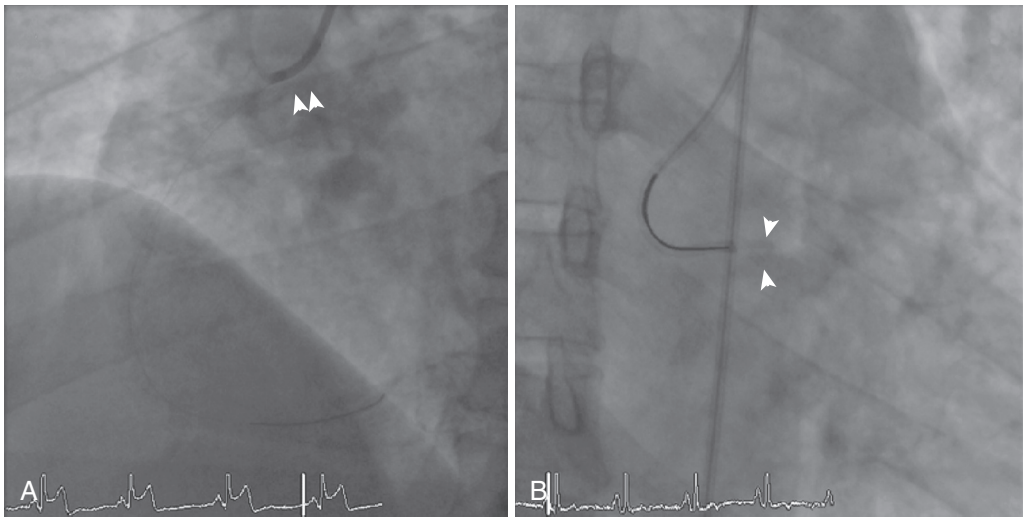


FIGURE 28-8 Snaring of an embolized coronary stent at the right coronary ostium. **A,** A coronary stent (*arrowheads*) was stripped from the balloon and is located at the right coronary ostium. **B,** Using a gooseneck snare, the stent is retrieved and retracted into the guide (Video 28-4).

TABLE 28-6 Unadjusted Rates of Major Adverse Cardiac Events Following Emergent Coronary Artery Bypass Graft for Failed Percutaneous Coronary Intervention in Contemporary Retrospective Single-Center Registries

	Time Period	Incidence (%)	N	Death (%)	MI (%)	Stroke (%)
Yang EH et al[57]	1995-2003	0.5	77	13	NA	NA
Seshadri N et al[58]	1992-2000	0.6	113	15	12	53
Roy P et al[59]	1994-2008	0.4	90	7.8	5.7	10

MI, Myocardial infarction; *N,* number of patients; *NA,* not available

TABLE 28-7 Incidence and Implications of Periprocedural Myocardial Infarction From Major Studies

Authors	N	Cardiac Marker Cutoff Level	Incidence (%)	Follow-Up Implication
Abdelmeguid et al[62]	4484	CK 1–2× ULN	5.8	Death (RR 1.27)
Abdelmeguid et al[63]	4664	CK 2–5× ULN	2.6	Death (RR 2.19)
Kong et al[64]	2812	CK 5× ULN CK 1–1.5× ULN CK 1.5–3× ULN CK >3× ULN	1.3 2.3 3.8 2.9	Death (RR 1.05)
Ghazzal et al[65]	15637	CK 1–2× ULN CK 2–3× ULN CK >3× ULN	4.6 1.1 1.6	Death (OR 1.84)
Tardiff et al[66]	1616	CK-MB >1× ULN	18.0	Death/MI/revasc. 6-month end point 1–3× ULN, 32.4% 3–5× ULN, 37.9% 5-10× ULN, 35.3% >10× ULN, 43.6%
Waksman et al[67]	3265	CK-MB >2× ULN, ST/T changes or CP	4.7	Death 7.8%
Simoons et al[68]	5025	CK-MB 1–3× ULN	13.2	Death (log enzyme ratio OR 1.82)
Roe et al[69]	2384	CK-MB > 3× ULN CK-MB 1–3× ULN CK-MB 3–5× ULN CK-MB 5–10× ULN CK-MB >10× ULN	6.6 21.3 6.0 7.1 9.5	Death (OR 1.06)
Mehran et al[70]	2256	CK-MB >4 ng/mL	25.8	NR
Stone et al[71]	7147	CK-MB >4 ng/mL	14	Death (adjusted OR 8.00)
Dangas et al[72]	4085	CK-MB >4 ng/mL	36.9	Death (OR 1.5)
Ajani et al[73]	1326	CK-MB >4 ng/mL	45	Death/MI/TVR (OR 1.57)
Brener et al[74]	3478	CK-MB >8.8 ng/mL	24	Death (OR 1.89)
Ellis et al[75]	8409	CK-MB >8.8 ng/mL	17.2	Death
Brener et al[76]	3573	CK-MB >8.8 ng/mL	38	Death (HR 1.1)
Hong et al[77]	1693	CK-MB 4–20 ng/mL CK-MB >20 ng/mL	32.1 15.2	Death (OR 5.5)
Natarajan et al[78]	1128	cTnI 1–4× ULN cTnI >5× ULN	7.6 9.1	NR
Nallamothu et al[79]	1157	 cTnI 1 to <3× ULN cTnI 3 to <5× ULN cTnI 5 to <8× ULN cTnI ≥ 8× ULN	 16 4.6 2 6.5	Death cTnI 5 to <8× ULN OR 3.4 cTnI ≥ 8× ULN OR 2.7
Fuchs et al[80]	1129	Tn-I 1–3× ULN Tn-I >3× ULN	15 15.5	 Death/MI/TVR Tn-I >3× ULN 6.4%
Cavallini et al[81]	3494	cTnI > 0.15 ng/dL CK-MB >5 ng/mL	44.2 16.0	Death (OR 1.9)

Data from Herrman J: Peri-procedural myocardial injury: 2005 update. *Eur Heart J* 26:2493-2519, 2005.
CK-MB, Creatine kinase myoglobin; *CP,* chest pain; cTnI, cardiac troponin-I; *HR,* hazard ratio; *MI,* myocardial infarction; *N,* number of patients; *NR,* not recorded; *OR,* odds ratio; *revasc.,* revascularization; *RR,* relative risk; Tn-I, troponin-I; *TVR,* target-vessel revascularization; *ULN,* upper limit of normal.

Prognosis

Emergent CABG following PCI is associated with significant morbidity and mortality with a death rate ranging between 7.8% and 14% among three single-center studies. Q-wave myocardial infarctions (QWMIs), stroke, and/or renal insufficiency commonly complicate emergent CABG procedures.[57] QWMIs account for most of the patient deaths, followed by cardiac arrhythmias, suggesting that delay in perfusion while transitioning to surgery is the most common mechanism of demise.[57] Therefore it is advisable to attempt all possible solutions expeditiously, and if success from PCI does not appear likely, request emergency CABG sooner, rather than later; also, strongly consider IABP, left ventricular (LV) support device insertion, and/or aggressive pharmacologic support to maintain perfusion pressure en route to surgery.

MYOCARDIAL INFARCTION

Incidence

Periprocedural myonecrosis during PCI is common and occurs with a 0% to 47% incidence based on reported series.[60] The definition of MI varies among studies with respect to biomarker assay, threshold values, frequency of blood specimen sampling, and use of ECG data among studies, which results in wide ranges of reported incidence.[61] Whether myonecrosis is directly responsible for late adverse outcomes or is simply a symptom of disease severity is debated. However, the prognostic significance of higher biomarker values is reproducible across many studies (Table 28-7). Currently, the accepted universal definition for a periprocedural MI is peak creatine kinase MB (CK-MB)

TABLE 28-8 Definition of Clinically Relevant Myocardial Infarction After Both Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting Procedures

1. In patients with normal baseline CK-MB	The peak CK-MB measured within 48 hours of the procedure rises to ≥10× the local laboratory ULN *or* to ≥5× ULN with new pathologic Q-waves in two or more contiguous leads or new persistent LBBB *or* in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70× the local laboratory ULN *or* ≥35× ULN with new pathologic Q-waves in two or more contiguous leads *or* new, persistent LBBB.
2. In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling	The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent preprocedure level.
3. In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling	The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

From Moussa ID, Klein LW, Shah B, et al: Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol* 62:1563-1570, 2013.
CK-MB, Creatine kinase MB; *cTn,* cardiac troponin; *cTn-I,* cardiac troponin-I; *cTn-T,* cardiac troponin-T; *LBBB,* left bundle branch block; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention; *ULN,* upper limit of normal.

TABLE 28-9 Mechanisms of Periprocedural Myonecrosis

Procedure-Related Complications
- Side-branch occlusion
- Flow-limiting dissection
- Abrupt closure
- Macroscopic embolization
- No-reflow phenomenon
- Microscopic embolization

Lesion-Specific Characteristics
- Large thrombus burden
- Plaque volume
- Plaque vulnerability

Patient-Specific Characteristics
- Arterial inflammation
- Aspirin resistance
- Genetic predisposition

From Bhatt DL, Topol EJ: Does creatinine kinase-MB elevation after percutaneous coronary intervention predict outcomes in 2005? Periprocedural cardiac enzyme elevation predicts adverse outcomes. *Circulation* 112:906-915, 2005.

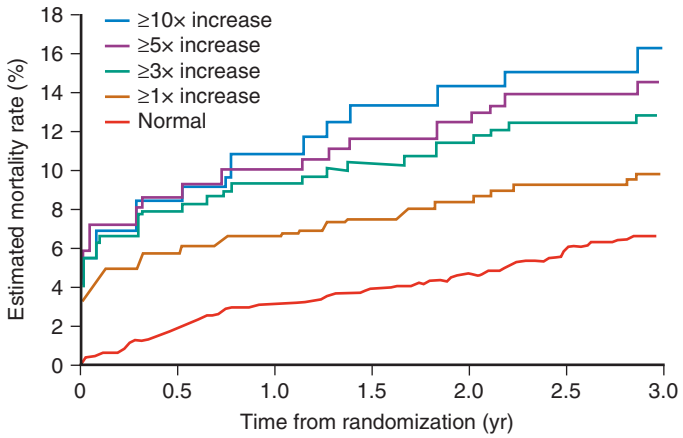


FIGURE 28-9 Mortality for patients with onefold to tenfold increases in periprocedural creatinine kinase elevation. The *P*-values for comparisons are onefold or greater, $P = .02$; threefold or greater, $P < .001$; fivefold or greater, $P < .001$; and tenfold or greater, $P < .001$. *CPK,* Creatinine phosphate kinase; *MI,* myocardial infarction. (From Topol EJ, Ferguson JJ, Weisman HF, et al: Long-term protection from mycardial ischemic events in a randomized trial of brief integrin beta$_3$ blockade with percutaneous coronary intervention. EPIC Investigator Group. Evaluation of Platelet IIb/IIIa Inhibition for Prevention of Ischemic Complication. *JAMA* 278:479-484, 1997.)

that is 10 or more times the local laboratory upper limit of normal (ULN) or five or more times the ULN with new pathologic Q-waves in two contiguous leads (Table 28-8).[82]

Mechanism

Obvious causes of periprocedural MI include side-branch occlusion, distal macroembolization, no-reflow phenomenon, abrupt occlusion, prolonged balloon inflations, and hypotension (Table 28-9). Distal microembolization occurs frequently, and the extent of myonecrosis has been shown to be proportional to the plaque burden and degree of calcification.[70] Microvascular embolization is reflected by worsening myocardial perfusion grade, and impaired perfusion grade is directly proportional to a larger infarct size by magnetic resonance imaging (MRI).[83] Doppler coronary flow with delayed enhancement MRI studies give further credence to the importance of distal embolization and microvascular obstruction as the cause of most post-PCI biomarker elevations.[84,85]

Of note, when optimizing stent expansion, greater cross-sectional areas were linked to higher postprocedure CK-MB elevation, suggesting that aggressive stent expansion increases the risk of plaque disruption and subsequent distal embolization.[86] Advancing and implanting bulkier devices, such as stents, has been associated with larger periprocedural MIs.[8] Improvement in adjunctive pharmacology during PCI, such as with GP IIb/IIIa inhibitors, significantly decreased MI rate following PCI, presumably by mitigating the no-reflow phenomenon and inhibiting platelet adhesion.[87,88]

The use of mechanical atherectomy devices are more likely to result in periprocedural MI. As coronary lesions are debulked, plaque is "pulverized" and sent downstream into the IC vascular bed. Whereas most embolized particles are small and pass harmlessly through the coronary microcirculation, atherectomy is associated with somewhat increased periprocedural MI and no-reflow phenomenon when compared with balloon angioplasty.[89]

Prognosis

Periprocedural enzyme elevation measured as CK-MB and troponin elevation is directly related to adverse events, including death and QWMI (see Table 28-9, Fig. 28-9).[90,91] This has been observed in multicenter trials and in a meta-analysis of multiple ACS and stable coronary disease trials.[92]

Prevention

Periprocedural myocardial necrosis appears to be part of the "collateral damage" in undertaking PCI, but multiple pharmacologic and device developments have emerged to attenuate the incidence of this complication. Pharmacologic advances such as GP IIb/IIIa inhibitors, $P2Y_{12}$ receptor inhibitors, and statins decrease periprocedural MI. The use of distal embolic protection during vein graft interventions has been shown to significantly reduce periprocedural MI.

GP IIb/IIIa inhibitors target the common final receptor for platelet cross-linking and thrombus formation. Abciximab, a murine monoclonal antibody specific for platelet IIb/IIIa receptors, causes an 80% blockade of platelet function[93] and was the first agent to demonstrate a reduction in periprocedural MI (8.6% vs. 5.2%, $P = .013$) when using balloon angioplasty or atherectomy to perform PCI.[94] These results were consistently reproduced with the implantation of stents in subsequent trials—such as EPISTENT, Evaluation in PTCA to Improve Long-Term Outcome With Abciximab GP IIb/IIIa Blockade (EPILOG), and c7E3 FAB Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE)—each with greater than 50% reductions in periprocedural MI compared with PCI with heparin and aspirin alone (Fig. 28-10).[8,88,95] Similar reductions of periprocedural MI were observed with synthetic small-molecule GP IIb/IIIa inhibitors such as eptifibatide and tirofiban. A 40% reduction in MI was seen at 48 hours (5.4% vs. 9.0%, $P = .0015$) in the Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrilin Therapy (ESPRIT) trial, and most of the clinical benefit of eptifibatide in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial were attributed to reductions in periprocedural MI.[96,97] Tirofiban was observed to reduce periprocedural MI when administered in a high-dose fashion in the Additive Value of Tirofiban Administered With the High-Dose Bolus in the Prevention of Ischemic Complications During High-Risk Coronary Angioplasty (ADVANCE) trial.[98]

Adequate platelet inhibition appears to be the key to success with respect to preventing periprocedural MI, with not only blocking GP IIb/IIIa receptors but also inhibiting $P2Y_{12}$-mediated platelet activation. This was first observed with pretreatment using ticlodipine and then clopidogrel in the PCI subset of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, in which a 44% reduction in MI was seen at 30 days.[99,100] Preprocedural loading with 300 mg of clopidogrel was found to reduce the primary end point of MI, death, and target-vessel revascularization (TVR) by 38% if given at least 6 hours prior to PCI.[101,102] A high loading dose (600 mg) of clopidogrel caused a 50% reduction in periprocedural MI, likely due to achievement of therapeutic inhibition of platelets more rapidly.[103] As expected, resistance to either aspirin or clopidogrel increases the hazard of periprocedural MI.[104] Tailoring anticoagulation strategies by adding eptifibatide for patients without optimal clopidogrel response may reduce periprocedural MI.[105]

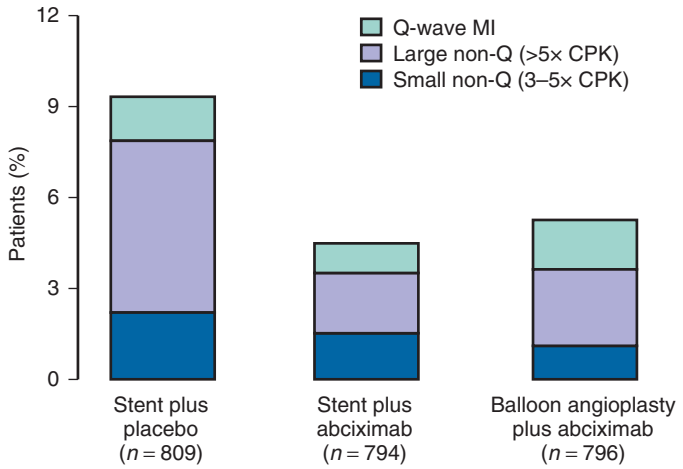


FIGURE 28-10 Incidence and type of myocardial infarction for each treatment group. (From the EPISTENT Investigators: Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet* 352:87-92, 1998.)

In addition to optimizing antiplatelet therapy prior to PCI, pretreatment with statins appears to prevent myocardial injury in patients undergoing both elective and emergent PCI.[106,107] Loading patients with atorvastatin 40 mg for 1 week prior to PCI caused a 72% reduction in periprocedural MI (3% vs. 18%, $P = .025$) during elective PCI in the Atorvastatin for Reduction of Myocardial Damage During Angioplasty (ARMYDA) study.[106] The mechanism of myonecrosis attenuation may be related to the decrease in expression of vascular cell adhesion molecule 1 (VCAM-1) and intracellular adhesion molecule 1 (ICAM-1) after PCI.[108] Even when patients are already receiving statin therapy, reloading with high doses of statins provided added reduction of periprocedural MI.[109]

Because many periprocedural MIs are caused by distal embolization, use of embolic protection devices (EPDs) has been investigated in several settings; however, the benefits have only been observed in saphenous vein graft (SVG) interventions. In the Saphenous Vein Graft Angioplasty Free of Emboli Randomized Trial (SAFER), a total of 801 patients undergoing elective SVG PCI were randomized to distal protection using the GuardWire (Medtronic Vascular, Santa Rosa, CA), resulting in a 41% reduction in periprocedural MI compared with those without EPDs.[110] Proximal protection and aspiration using the Proxis device (St. Jude Medical, St. Paul, MN) produced comparable rates of periprocedural MI, and its use was found to be noninferior to distal embolic protection devices when used in SVG interventions.[111] Unfortunately, the Proxis device is no longer available.

The benefits of distal embolic protection have not been reproduced in native coronary vessels. The Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD) trial randomized 501 patients to receiving either distal embolic protection using the GuardWire Plus distal protection device (Medtronic Vascular) combined with aspiration thrombectomy or usual care for STEMI.[112] Despite the use of the GuardWire Plus and aspiration thrombectomy, no differences were observed with respect to death, MI, or infarction size. Lack of efficacy in the setting of STEMI was attributed to the delay in reperfusion seen in the treatment group using distal EPDs. Similarly, use of FilterWire EX (Boston Scientific, Natick, MA) distal protection during ACSs did not confer any decrease of infarct size or reduction of major adverse cardiac events (MACEs) in the Protection Devices in PCI–Treatment of Myocardial Infarction for Salvage of Endangered Myocardium (PROMISE) study.[113]

Periprocedural MI remains a common complication that predicts future adverse outcomes. Judicious revascularization, optimization of pharmacologic therapy, and use of EPDs when appropriate may reduce its incidence.

CORONARY NO-REFLOW PHENOMENON

Incidence and Diagnosis

Coronary no-reflow phenomenon is the inability to perfuse myocardium after the opening of a previously occluded or stenosed epicardial coronary artery.[114] No-reflow phenomenon is suspected to result from a combination of endothelial damage, platelet and fibrin embolization, vasospasm, and tissue edema that overwhelms the coronary microcirculation. Reperfusion-related injury is hypothesized to contribute to a no-reflow state via infiltration of the microcirculation with neutrophils and platelets. The incidence of no-reflow phenomenon ranges from 0.6% to 2% and is more frequently observed when using stents or atherectomy and when performing PCI in SVGs.[115,116] Risk factors for no-reflow phenomenon include the angiographic presence of thrombus, cardiogenic shock, increased reperfusion time, hyperglycemia, and leukocytosis.[117-119] Diagnosis of no reflow is made angiographically

TABLE 28-10 Thrombus in Myocardial Infarction (TIMI) Grading System for Describing Coronary Flow

TIMI Grade	Description
0	No antegrade flow is present beyond the point of occlusion.
I	Contrast material is able to pass through the area of obstruction but fails to opacify the distal coronary bed.
II	Contrast is able to penetrate the area of obstruction and fills the distal coronary bed; however, it is perceptibly slower than other coronary vessels unaffected by the coronary obstruction.
III	Antegrade flow into the distal coronary bed of the obstructed artery is as prompt as the flow in an uninvolved coronary vessel.

TABLE 28-11 Prevention of No-Reflow Phenomenon

- Use distal protection devices when treating saphenous vein graft lesions.
- When performing rotational atherectomy, routinely use nitroglycerin, verapamil, and heparin in combination with the flush solution.
- Consider pretreatment with a glycoprotein IIb/IIIa inhibitor during percutaneous coronary intervention in patients with acute coronary syndromes.
- Minimize balloon inflation and consider direct stenting in patients with bulky atheroma or saphenous vein grafts.
- Pretreat with verapamil or adenosine.
- Aspiration thrombectomy for thrombus-laden lesions.

by assessing flow, usually using the Thrombolysis in Myocardial Infarction (TIMI) grading system (Table 28-10); however, other systems of measuring microcirculatory myocardial perfusion are also available, such as myocardial blush score, TIMI frame count, and contrast echocardiography.

Prevention

To some degree, no-reflow phenomenon can be minimized or prevented during coronary intervention with diligent pharmacologic and mechanical pretreatment and posttreatment (Table 28-11). Pretreatment with IC calcium channel blockers is a helpful adjunct for treatment of SVGs.[120] Use of distal protection devices in the context of SVG PCI decreased the rate of no-reflow phenomenon to 4.8%, compared with 9.7%, when performing PCI without distal protection in the SAFER trial.[110] Rates of no reflow increase with the use of rotational atherectomy, likely due to the embolization of pulverized plaque into the microcirculation. In one small study, the use of preemptive intracoronary adenosine and nitroglycerin during rotational atherectomy decreased the rate of no reflow from 11.4% to 1.4%.[120,121] Recent evidence from a small study showed a 10-minute intragraft infusion of adenosine at 200 μg/minute decreased no-reflow phenomenon in elective vein-graft interventions.[122] Administration of abciximab prior to PCI for STEMI increased the proportion of patients with TIMI grade 3 flow both before and after PCI in the Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-Up (ADMIRAL) trial.[123] This increase in TIMI grade 3 flow translated into higher left ventricular ejection fraction (LVEF) and decreased the composite end point of death, TVR, and reinfarction among patients receiving abciximab. More recently, use of IC abciximab to improve reperfusion during STEMI did not increase the rate of TIMI grade 3 flow (IC abciximab 91.3% vs. no IC abciximab 91.5%; $P = .94$) or myocardial blush grade 3 (IC abciximab 80.7% vs. no IC abciximab 82.1%; $P = .71$).[124]

Another tool that may play a role in preventing no-reflow phenomenon and optimizing perfusion in the setting of STEMI is aspiration thrombectomy. The Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) was a prospective trial that randomized 1071 patients to either routine aspiration thrombectomy prior to coronary stenting versus stent implantation without thrombectomy.[125] Aspiration thrombectomy improved markers of reperfusion, such as myocardial blush score and ST-segment resolution, but outcomes with respect to death, reinfarction, TVR, and composite MACE rates were not found to be different at 30 days. Rates of MACE correlated with the degree of perfusion as measured by myocardial blush score and ST-segment resolution (Fig. 28-11). At 1 year, routine aspiration thrombectomy reduced the rate of cardiac death to 3.4%, compared with 6.7%, when performing routine primary PCI for reperfusion therapy.[126] Benefits of adjunctive thrombectomy during STEMI were reproduced in both meta-analysis and in a pooled patient analysis of 11 randomized clinical trials for both 30-day and 1-year MACCE rates, respectively.[127,128] However, the most recent prospective evaluations of aspiration thrombectomy—Thrombus Aspiration During ST-Segment Elevation Myocardial Infarction (TASTE) and Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction (INFUSE-AMI)—did not recapitulate the benefit seen with aspiration thrombectomy in the TAPAS trial.[124,129] No differences in TIMI grade 3 flow (aspiration 92.6% vs. no aspiration 90.1%; $P = .36$), myocardial blush grade 3 (aspiration 83.4% vs. no aspiration 79.3%; $P = .26$), and infarct size (aspiration median 17% vs. no aspiration 17.3%; $P = .51$) were observed in the INFUSE-AMI study.[124] Similarly, the TASTE trial revealed no differences with respect to hard clinical end points as the 30-day all-cause mortality did not change with aspiration (aspiration 2.8% vs. no aspiration 3.0%; $P = .63$).

TABLE 28-12 Management of No-Reflow Phenomenon as Suggested by the Society for Cardiovascular Angiography and Interventions

First-Line Management

- Adenosine (10 to 20 μg bolus)
- Verapamil (100 to 200 μg bolus or 100 μg/min up to 1000 μg total with temporary pacer on standby)
- Nitroprusside (50 to 200 μg bolus, up to 1000 μg total dose)

Evidence Less Strong

- Rapid, moderately forceful injection of saline or blood (to unplug microvasculature)
- Cardizem (0.5 to 2.5 mg over 1 min, up to 5 mg)
- Papaverine (10 to 20 μg)
- Nicardipine (200 μg)
- Nicorandil (2 μg)
- Epinephrine (50 to 200 μg)

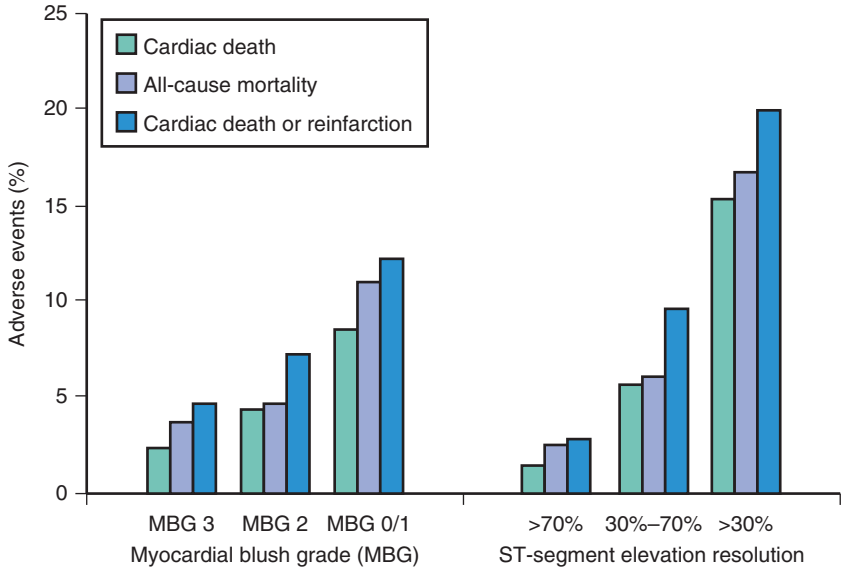
Never Shown to Be Effective

- Intracoronary nitroglycerin
- Coronary artery bypass graft (contraindicated)
- Stent placement (if site of original stenosis is widely patent)
- Thrombolytics (e.g., urokinase, tissue plasminogen activator)

From Klein LW, Kern MJ, Berger P, et al: Society of cardiac angiography and interventions: suggested management of the no-reflow phenomenon in the cardiac catheterization laboratory. *Catheter Cardiovasc Interv* 60:194-201, 2003.

Treatment

The first-line treatment for no-reflow phenomenon primarily consists of delivery of vasodilators—especially adenosine, calcium channel blockers, and/or nitroprusside—into the coronary microcirculation (Table 28-12). Should the dye column stop at midvessel, distal contrast injections through balloons or microcatheters should be performed to exclude dissection. Injection of vasodilators through an infusion catheter close to the distal bed may improve microcirculation drug delivery. No role has been found for referral for emergent CABG or thrombolytic therapy. If the stenosis is widely patent by angiography or IVUS, additional coronary stenting is not helpful. Patients with



Rate of cardiac death (%)	2–4	4–4	8–5 $P = .003$	1–4	5–6	15–3 $P < .0001$
Rate of all-cause mortality (%)	3–7	4–7	11–0 $P = .001$	2–6	6–0	16–8 $P < .0001$
Rate of cardiac death or reinfarction (%)	4–7	7–3	12–2 $P = .004$	2–8	9–5	20–0 $P < .0001$

FIGURE 28-11 Cardiac death, all-cause mortality, and the combined end point of cardiac death and nonfatal reinfarction are inversely proportional to myocardial blush score and degree of ST-segment resolution, proving that outcomes are directly related to the quality of perfusion. (From Vlaar PJ, Svilaas T, van der Horst IC, et al: Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study [TAPAS]: a 1-year follow-up study. *Lancet* 371:1915-1920, 2008.)

cardiogenic shock may require IABP or LV support devices to maintain adequate systemic perfusion pressure.

Prognosis

No-reflow phenomenon is associated with a larger infarct size, reduced LVEF, and death.[130-132] Retrospective analysis in patients with no-reflow phenomenon undergoing primary PCI have an in-hospital and 6-month mortality increase of sixfold and tenfold, respectively. The adjusted odds for death at 6 months was 5.4 times higher in patients with no-reflow phenomenon.[132]

AIR EMBOLISM

Incidence

Injection of air into the coronary artery is potentially fatal and can result in "air lock," which causes abrupt occlusion of the vessel along with possible cardiac arrest and MI. Almost always iatrogenic, the incidence of this complication is approximately 0.1% to 0.3% (Video 28-5).[133] Air embolism usually results from the inadequate aspiration of catheters or the entrainment of air during equipment exchanges. Occasionally, rupture of an inadequately prepared coronary balloon or introduction of air through an intracardiac defect can allow a paradoxic embolism into the coronary circulation.

Diagnosis

The degree of danger associated with air embolism is proportional to the amount of air that enters the coronary circulation. Once air is embolized, air lock can prevent perfusion of the distal coronary bed (Fig. 28-12). Air embolism may manifest as chest pain; hypotension; transient ECG changes consistent with myocardial ischemia; arrhythmias (bradycardia, heart block, ventricular tachycardia, and ventricular fibrillation); and even cardiac arrest. The diagnosis of air embolism is made angiographically, and the bolus generally divides into smaller bubbles that cause a slow-flow phenomenon in epicardial vessels.[133]

TABLE 28-13 Treatment of Air Embolism

- Ventilate with 100% oxygen.
- Treat aggressively with intravenous fluids, atropine, or vasopressors for hemodynamic support.
- Consider intraaortic balloon counterpulsation for hemodynamic support.
- Dissipate the "airlock" with wires or balloon catheters.
- Consider catheter aspiration.
- Treat no-reflow phenomenon with standard vasodilators (adenosine, verapamil, nitroprusside).

Treatment

Resolution of air embolism can be accomplished faster by ventilating with 100% oxygen (Table 28-13). Increasing the mean arterial pressure will assist in forcing air bubbles into the coronary microcirculation, thus overcoming the air lock. Forceful injection of saline or contrast can also assist in dissipating the air, and balloons can be used to pulverize large bubbles. Thrombectomy catheters can be used to aspirate bubbles from the epicardial vessel. While waiting for an air embolus to resolve, the patient will often become profoundly hypotensive and may complain of chest discomfort. Expedient treatment of hypotension with systemic vasopressors such as norepinephrine or phenylephrine can be life saving. IABP counterpulsation may also be useful. Of course, the most efficacious means of dealing with air embolism is prevention by meticulous aspiration and flushing of catheters between equipment exchanges.[134]

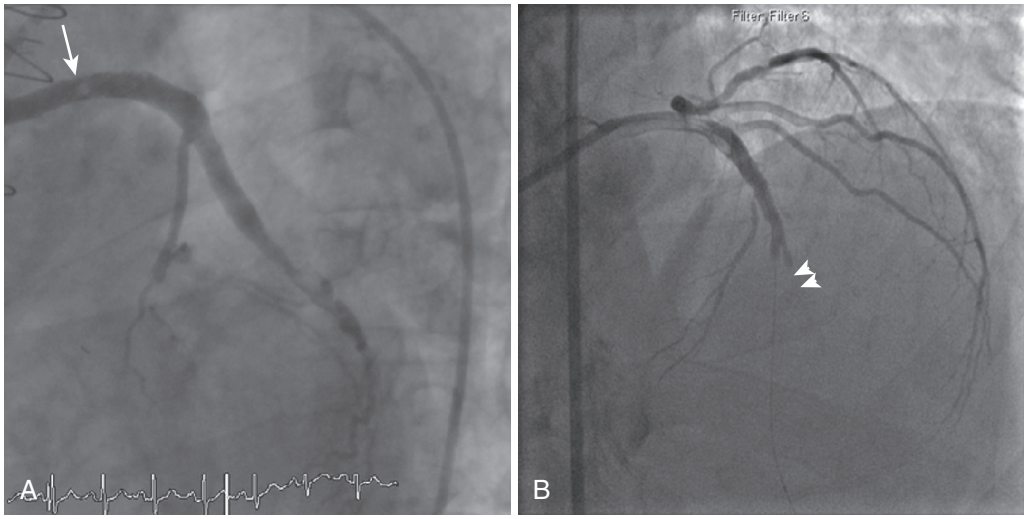


FIGURE 28-12 Air embolism. **A,** Air embolism (*arrow*) from inadequate flushing of a distal protection filter. **B,** "Airlock" created by a large air embolus causing cessation of flow in the left anterior descending artery (*arrowheads;* Video 28-5).

TABLE 28-14 Commonly Used Pretreatment Regimen for Contrast Allergy

- Prednisone 50 mg orally 13, 7, and 1 hr prior to procedure or intravenous hydrocortisone 100 mg 1 hr prior to procedure
- Cimetidine 300 mg orally 1 hr prior
- Diphenhydramine 50 mg orally 1 hr prior
- Montelukast 10 mg orally 1 hr prior
- Nonionic low osmolar or isoosmolar contrast agent

RADIOCONTRAST HYPERSENSITIVITY

Incidence and Prognosis

Allergy to contrast medium is a common but rarely serious complication in the cardiac catheterization laboratory. Since the advent of low-osmolar nonionic agents, the incidence of contrast intolerance has significantly declined. The risk of allergy to contrast agents is estimated to be 4% to 12% for ionic contrast media and 1% to 3% for nonionic contrast agents.[135] The reported incidence of severe contrast reactions is 0.23% with a mortality of 1 per 55,000 cases.[136] Reactions from contrast media include minor events such as nausea, vomiting, and localized urticaria with pruritus; moderate reactions are characterized by laryngeal or facial edema and mild bronchospasm. Severe reactions are true emergencies and manifest as respiratory or cardiac arrest and shock. Occasionally, contrast allergy may manifest solely as persistent hypotension during a cardiac procedure. Approximately 2% to 5% of patients may develop delayed reactions characterized by rash 1 hour to 1 week after contrast exposure.[137] Patients may experience pruritus, maculopapular rash, urticaria, angioedema, and/or fever. Often, identification of the agent responsible for the allergy may be confounded because of concomitant delivery of antibiotics or treatment with antithrombotic agents, such as clopidogrel.

Prevention and Treatment

Prophylactic measures can decrease the incidence and severity of contrast reactions but do not entirely eliminate the risk. Pretreatment of patients with contrast allergy usually consists of corticosteroids and antihistamines (Table 28-14). Mild reactions may be treated with a similar regimen; however, moderate reactions such as laryngeal edema, bronchospasm, or hypotension require immediate administration of intramuscular (IM) epinephrine 0.1 to 0.3 mL (1:1000 dilution) or IV epinephrine 1 mg (1:10,000 dilution) to prevent progressive symptoms.[138] Severe bronchospasm, laryngeal edema, or cardiac arrest are treated with IV epinephrine diluted 1:10,000 at a dose of 1 to 3 mL (Table 28-15). Overdose of IV epinephrine may manifest as tachycardia, tremor, pallor, and hypertensive emergency. Preexisting beta-blocker therapy may blunt the response of epinephrine and increases the risk of a severe reaction. Supplemental oxygen, endotracheal intubation, aggressive fluid resuscitation, administration of corticosteroids, and use of an epinephrine drip may be required to stabilize the patient. Such patients should be monitored in the intensive care unit until the reaction subsides.[139]

TABLE 28-15 Treatment of Anaphylactoid Reactions to Contrast Media

MILD
Nausea, Vomiting, and Localized Urticaria with Pruritus; Self-Limiting
• Observation
MODERATE
Laryngeal or Facial Edema and Mild Bronchospasm

• Epinephrine
  • 1:1000 dilution at 0.1 to 0.3 mL intramuscularly
  • 1:10,000 dilution at 1 to 3 mL intravenously
• Diphenhydramine 25 to 50 mg intravenously

SEVERE
Respiratory or Cardiac Arrest and Anaphylactoid Shock
• ACLS resuscitation (airway, breathing, circulation) • Epinephrine drip at 10 to 20 μg/min up to 30 min after symptom resolution • Aggressive intravenous fluids

From Nayak KR, White AA, Cavendish JJ, et al: Anaphylactioid reactions to radiocontrast agents: prevention and treatment in the cardiac catheterization laboratory, *J Invasive Cardiol* 21:548-551, 2009.
ACLS, Advanced cardiac life support.

BLEEDING

Bleeding rates vary depending on the definitions used, but bleeding is a relatively common complication: major bleeding occurred in 1.7% of all-comers in an analysis of patients from 2004 through 2011 in the CathPCI Registry.[140] Focused analysis of ACS trials showed that TIMI

TABLE 28-16 Bleeding Academic Research Consortium (BARC) Definitions of Bleeding

Type 0: No bleeding
Type 1: Bleeding that is not actionable
Bleeding that does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional; may include bleeding episodes that lead to self-discontinuation of medical therapy (e.g., warfarin) by the patient without consulting a health care professional
Type 2: Actionable bleeding
Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for types 3, 4, or 5 but does meet at least one of the following criteria: it (1) requires nonsurgical medical intervention by a health care professional, (2) leads to hospitalization or increased level of care, or (3) prompts evaluation
Type 3: Serious bleeding
Type 3a:
Overt bleeding plus a hemoglobin drop of 3 to 5 g/dL (provided the hemoglobin drop is related to the bleed)
Any transfusion with overt bleeding
Type 3b:
Cardiac tamponade
Bleeding that requires surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
Bleeding that requires vasoactive agents
Type 3c:
Intracranial hemorrhage (does not include microbleeds or hemorrhage transformation, does include intraspinal bleeding)
Subcategories confirmed by autopsy, imaging, or lumbar puncture
Intraocular bleed that compromises vision
Type 4: Coronary artery bypass graft–related bleeding
Perioperative intracranial bleeding within 48 hours
Reoperation after closure of sternotomy for the purpose of controlling bleeding
Transfusion of 5 or more units of whole blood or packed red blood cells within a 48-hour period
Chest tube output of 2 L or more within a 24-hour period
Type 5: Fatal bleeding
Type 5a
Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b
Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

minor/major bleeding occurred in approximately 2.3% of patients in a pooled registry of studies, and 4.1% patients with STEMI suffered TIMI major bleeding in the HORIZONS trial.[141,142] Given the multiple definitions of bleeding in the literature, a universal definition was formed by the Bleeding Academic Research Consortium (BARC) and was subsequently validated (Table 28-16).[143,144] Predictors of bleeding from multiple analyses included advanced age, female sex, severe renal impairment, glycoprotein inhibitor use, larger sheath size, peak activated clotting time, simultaneous right heart catheterization, low-molecular-weight heparin use, elevated white blood cell count, procedure duration, and postprocedure heparin use.[145-148]

Bleeding adversely impacts prognosis; the presence of bleeding was associated with an in-hospital mortality of 5.58% versus 0.57% ($P < .001$) of nonbleeding patients.[140] Patients at high risk for bleeding have more comorbidities and often come to medical attention urgently, features that compound the risk of mortality from bleeding events. Patients at high risk for bleeding with a subsequent bleeding event had a 6.54% higher rate of death relative to those at low risk for bleeding ($P < .001$).[140] Non–access-site bleeding further increases the hazard of death and elevates the in-hospital mortality rate to 8.25%,[140] and mortality is proportional to bleeding severity. In a post-hoc pooled analysis of several acute coronary syndrome studies, no significant difference in mortality was observed between TIMI minor bleeding and no bleeding in ACSs, but a fivefold increase in mortality was seen with severe bleeding.[141] Increased mortality associated with TIMI major bleeding mostly occurred in the first 30 days. Even after excluding the early deaths, a 1.5-fold increase in 6-month mortality persisted in patients with severe bleeding compared with ACS patients without bleeding.[141] Similarly, ischemic end points after TIMI major bleeding—such as early hazard toward MI (adjusted hazard ratio [HR] 4.44) and stroke (adjusted HR 6.46)—were most prominent in the first 30 days.[141] Retroperitoneal bleeding, a particularly devastating event with an in-hospital mortality of 6.4%, is fortunately rare (0.4%).[149] Increased early mortality associated with bleeding may originate from (1) the requirement to discontinue antiplatelet therapy, (2) the increased metabolic stress of having poor oxygen delivery as a result of anemia, (3) possible hypotension, and possibly (4) blood transfusion; these are independently associated with a fourfold and threefold increase in death and MI, respectively, even after adjusting for covariates and nadir hemoglobin concentration.[150]

Strategies to mitigate bleeding include appropriate patient selection, tailored pharmacology, access-site management, and use of radial access. Avoiding inappropriate revascularization candidates by using prospective risk calculators is valuable because the in-hospital mortality numbers needed to harm (NNH) for a bleeding event in high-risk patients and in those with non–access-site bleeding were 21 and 16, respectively.[151,152] Appropriate pharmacology selection and drug dosing remains problematic; as many as 22.3% of patients with chronic renal failure are given contraindicated medications.[153] Bleeding avoidance strategies, such as the use of vascular closure devices (VCDs) and bivalirudin administration, appear to work incrementally.[154] When analyzing cohorts at high risk for bleeding using VCDs only, bivalirudin only, and VCDs plus bivalirudin, the combined approach was associated with the lowest rate of periprocedural bleeding (VCDs 4.6% vs. bivalirudin 3.8% vs. VCD plus bivalirudin 2.3%; $P < .001$).[154] Femoral access using ultrasound guidance may help mitigate some bleeding complications because it decreases the number of puncture attempts and subsequent vascular complications, but micropuncture technique does not appear to significantly impact vascular complications or bleeding.[155,156] Finally, radial access resulted in a 50% decrease in access-site–related major bleeding, and the benefits of radial access are magnified in ACSs, particularly with STEMI, in which radial puncture decreased access-site–related bleeding 60% in the Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE-STEACS) study.[157,158] However, given the 6.1% to 10.0% rate of crossover from radial to femoral access, strategies for mitigating femoral access bleeding remain valuable.[157-159]

CONCLUSION

Avoidance, recognition, and management of procedural complications are central to maintaining competence as an interventional cardiologist. Although the specific complications described in this chapter represent some of the most important and common mishaps, this is not an exhaustive listing. Complications can never be completely avoided. No matter how experienced the interventionalist, complications will teach humility and provide a source of continuing education throughout a clinician's career.

REFERENCES

1. Venkitachalam L, Kip KE, Selzer F, et al: Twenty-year evolution of percutaneous coronary intervention and its impact on clinical outcomes: a report from the National Heart, Lung, and Blood Institute-Sponsored, Multicenter 1985-1986 PTCA and 1997-2006 Dynamic Registries. *Circ Cardiovasc Interv* 2:6–13, 2009.
2. Huber MS, Mooney JF, Madison J, Mooney MR: Use of a morphologic classification to predict clinical outcome after dissection from coronary angioplasty. *Am J Cardiol* 68:467–471, 1991.
3. Klein L: Coronary complications of percutaneous coronary intervention: a practical approach to the management of abrupt closure. *Catheter Cardiovasc Interv* 64:395–401, 2005.
4. Ellis SG, Roubin GS, King SB, 3rd, et al: Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty. *Circulation* 77:372–379, 1988.
5. Lincoff AM, Popma JJ, Ellis SG, et al: Abrupt vessel closure complicating coronary angioplasty: clinical, angiographic and therapeutic profile. *J Am Coll Cardiol* 19:926–935, 1992.
6. de Feyter PJ, de Jaegere PPT, Murphy ES, Serruys PW: Abrupt coronary artery occlusion during percutaneous transluminal coronary angioplasty. *Am Heart J* 123:1633–1642, 1992.
7. Ellis SG: Coronary lesions at increased risk. *Am Heart J* 130:643–646, 1995.
8. Topol EJ: Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet* 352: 87–92, 1998.
9. Boersma E, Harrington RA, Moliterno DJ, et al: Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 359: 189–198, 2002.
10. Schomig A, Kastrati A, Mudra H, et al: Four-year experience with Palmaz-Schatz stenting in coronary angioplasty complicated by dissection with threatened or present vessel closure. *Circulation* 90:2716–2724, 1994.
11. George BS, Voorhees WD, Roubin GS, et al: Multicenter investigation of coronary stenting to treat acute or threatened closure complicating percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 22:135–143, 1993.
12. Roubin GS, Cannon AD, Agrawal SK, et al: Intracoronary stenting for acute and threatened closure complicating percutaneous transluminal coronary angioplasty. *Circulation* 85:916–927, 1992.
13. Aoki J, Lansky AJ, Mehran R, et al: Early stent thrombosis in patients with acute coronary syndromes treated with drug-eluting and bare metal stents: the Acute Catheterization and Urgent Intervention Triage Strategy trial. *Circulation* 119:687–698, 2009.
14. Stone GW, Lansky AJ, Pocock SJ, et al: Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. *N Engl J Med* 360:1946–1959, 2009.
15. Mauri L, Hsieh W-H, Massaro J, et al: Stent Thrombosis in Randomized Trials of Drug-Eluting STents. *N Engl J Med* 356:1020–1029, 2007.
16. Spaulding C, Daemen J, Boersma E, et al: Pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 356:989–997, 2007.
17. Kedhi E, Joesef S, McFadden E, et al: Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *Lancet* 375:201–209, 2010.
18. Genereux P, Stone GW, Harrington RA, et al: Impact of intraprocedural stent thrombosis during percutaneous coronary intervention: insights from the CHAMPION PHOENIX Trial (Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention). *J Am Coll Cardiol* 63:619–629, 2014.
19. Xu Y, Qu X, Fang W, Chen H: Prevalence, correlation and clinical outcome of intra-procedural stent thrombosis in patients undergoing primary percutaneous coronary intervention for acute coronary syndrome. *J Interv Cardiol* 26:215–220, 2013.
20. Dangas GD, Caixeta A, Mehran R, et al: Frequency and predictors of stent thrombosis after percutaneous coronary intervention in acute myocardial infarction. *Circulation* 123:1745–1756, 2011.
21. Choi SY, Witzenbichler B, Maehara A, et al: Intravascular ultrasound findings of early stent thrombosis after primary percutaneous intervention in acute myocardial infarction: a Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) substudy. *Circ Cardiovasc Interv* 4:239–247, 2011.
22. Nakano M, Yahagi K, Otsuka F, et al: Causes of early stent thrombosis in patients presenting with acute coronary syndrome: an ex vivo human autopsy study. *J Am Coll Cardiol* 63:2510–2520, 2014.
23. Ge L, Airoldi F, Iakovou I, et al: Clinical and angiographic outcome after implantation of drug-eluting stents in bifurcation lesions with the crush stent technique: importance of final kissing balloon post-dilation. *J Am Coll Cardiol* 46:613–620, 2005.
24. Iakovou I, Schmidt T, Bonizzoni E, et al: Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 293:2126–2130, 2005.
25. Chechi T, Vecchio S, Vittori G, et al: ST-segment elevation myocardial infarction due to early and late stent thrombosis. *J Am Coll Cardiol* 51:2396–2402, 2008.
26. Biondi-Zoccai GG, Sangiorgi GM, Chieffo A, et al: Validation of predictors of intraprocedural stent thrombosis in the drug-eluting stent era. *Am J Cardiol* 95:1466–1468, 2005.
27. Biondi-Zoccai GG, Agostoni P, Sangiorgi GM, et al: Incidence, predictors, and outcomes of coronary dissection left untreated after drug-eluting stent implantation. *Eur Heart J* 27:540–546, 2006.
28. Kiernan TJ, Yan BP, Ruggeiro N, et al: Coronary artery perforations in the contemporary interventional era. *J Interv Cardiol* 22:350–353, 2009.
29. Fasseas P, Orford JL, Panetta CJ, et al: Incidence, correlates, management, and clinical outcome of coronary perforation: analysis of 16,298 procedures. *Am Heart J* 147:140–145, 2004.
30. Ajluni S, Glazier S, Blankenship L, O'Neill WW: Perforations after percutaneous coronary interventions: clinical, angiographic, and therapeutic observations. *Catheter Cardiovasc Diagn* 32:206–212, 1994.
31. Dippel EJ, Kereiakes DJ, Tramuta DA, et al: Coronary perforation during percutaneous coronary intervention in the era of abciximab platelet glycoprotein IIb/IIIa blockade: an algorithm for percutaneous management. *Catheter Cardiovasc Interv* 52:279–286, 2001.
32. Ellis SG, Ajluni S, Arnold AZ, et al: Increased coronary perforation in the new device era. Incidence, classification, management, and outcome. *Circulation* 90:2725–2730, 1994.
33. Gruberg L, Pinnow E, Flood R, et al: Incidence, management, and outcome of coronary artery perforation during percutaneous coronary intervention. *Am J Cardiol* 86:680–682, 2000.
34. Gunning MG, Williams IL, Jewitt DE, et al: Coronary artery perforation during percutaneous intervention: incidence and outcome. *Heart* 88:495–498, 2002.
35. Javaid A, Buch AN, Satler LF, et al: Management and outcomes of coronary artery perforation during percutaneous coronary intervention. *Am J Cardiol* 98:911–914, 2006.
36. Shimony A, Zahger D, Van Straten M, et al: Incidence, risk factors, management and outcomes of coronary artery perforation during percutaneous coronary intervention. *Am J Cardiol* 104:1674–1677, 2009.
37. Stankovic G, Orlic D, Corvaja N, et al: Incidence, predictors, in-hospital, and late outcomes of coronary artery perforations. *Am J Cardiol* 93:213–216, 2004.
38. Ramana R, Arab D, Joyal D, et al: Coronary artery perforation during percutaneous coronary intervention: incidence and outcomes in the new interventional era. *J Invasive Cardiol* 17:606–608, 2005.
39. Witzke C, Martin-Herro F, Clarke SC, et al: The changing pattern of coronary perforation during percutaneous coronary intervention in the new device era. *J Invasive Cardiol* 16:297–301, 2004.
40. Brilakis ES, Best PJM, Elesber AA, et al: Incidence, retrieval methods, and outcomes of stent loss during percutaneous coronary intervention. *Catheter Cardiovasc Interv* 65:333–340, 2005.
41. Bolte J, Neumann U, Pfafferott C, et al: Incidence, management, and outcome of stent loss during intracoronary stenting. *Am J Cardiol* 88:565–567, 2001.
42. Cantor WJ, Lazzam C, Cohen EA, et al: Failed coronary stent deployment. *Am Heart J* 136:1088–1095, 1998.
43. Eggebrecht H, Haude M, Birgelen CV, et al: Nonsurgical retrieval of embolized coronary stents. *Catheter Cardiovasc Interv* 51:432–440, 2000.
44. Klein LW: Coronary artery perforation during interventional procedures. *Catheter Cardiovasc Interv* 68:713–717, 2006.
45. Fejka M, Dixon SR, Safian RD, et al: Diagnosis, management, and clinical outcome of cardiac tamponade complicating percutaneous coronary intervention. *Am J Cardiol* 90:1183–1186, 2002.
46. Romaguera R, Sardi G, Laynez-Carnicero A, et al: Outcomes of coronary arterial perforations during percutaneous coronary intervention with bivalirudin anticoagulation. *Am J Cardiol* 108: 932–935, 2011.
47. Annapoorna SK, Oana CR, Kunal S, et al: Changing outcomes and treatment strategies for wire induced coronary perforations in the era of bivalirudin use. *Catheter Cardiovasc Interv* 74:700–707, 2009.
48. Lansky AJ, Yang Y-M, Khan Y, et al: Treatment of coronary artery perforations complicating percutaneous coronary intervention with a polytetrafluoroethylene-covered stent graft. *Am J Cardiol* 98:370–374, 2006.
49. Ben-Gal Y, Weisz G, Collins MB, et al: Dual catheter technique for the treatment of severe coronary artery perforations. *Catheter Cardiovasc Interv* 75:708–712, 2009.
50. Gaxiola E, Browne K: Coronary artery perforation repair using microcoil embolization. *Catheter Cardiovasc Diagn* 43:474–476, 1998.
51. Pravin KG: Delayed and repeated cardiac tamponade following microleak in RCA successfully treated with intra arterial sterile glue injection. *Catheter Cardiovasc Interv* 73:797–800, 2009.
52. Schatz R, Baim D, Leon M, et al: Clinical experience with the Palmaz-Schatz coronary stent. Initial results of a multicenter study. *Circulation* 83:148–161, 1991.
53. Kammler J, Leisch F, Kerschner K, et al: Long-term follow-up in patients with lost coronary stents during interventional procedures. *Am J Cardiol* 98:367–369, 2006.
54. Hartzler GO, Rutherford BD, McConahay DR: Retained percutaneous transluminal coronary angioplasty equipment components and their management. *Am J Cardiol* 60:1260–1264, 1987.
55. Patel T, Shah S, Pandya R, et al: Broken guidewire fragment: a simplified retrieval technique. *Catheter Cardiovasc Interv* 51:483–486, 2000.
56. Hung C, Tsai C, Hou CJ-Y: Percutaneous transcatheter retrieval of retained balloon catheter in distal tortuous coronary artery. *Catheter Cardiovasc Interv* 62:471–475, 2004.
57. Yang EH, Gumina RJ, Lennon RJ, et al: Emergency coronary artery bypass surgery for percutaneous coronary interventions: changes in the incidence, clinical characteristics, and indications from 1979 to 2003. *J Am Coll Cardiol* 46:2004–2009, 2005.
58. Seshadri N, Whitlow PL, Acharya N, et al: Emergency coronary artery bypass surgery in the contemporary percutaneous coronary intervention era. *Circulation* 106:2346–2350, 2002.
59. Roy P, de Labriolle A, Hanna N, et al: Requirement for emergent coronary artery bypass surgery following percutaneous coronary intervention in the stent era. *Am J Cardiol* 103:950–953, 2009.
60. Herrmann J: Peri-procedural myocardial injury: 2005 update. *Eur Heart J* 26:2493–2519, 2005.
61. Thygesen K, Alpert JS, White HD, et al: Universal definition of myocardial infarction. *Circulation* 116:2634–2653, 2007.
62. Abdelmeguid AE, Topol EJ, Whitlow PL, et al: Significance of mild transient release of creatine kinase–MB fraction after percutaneous coronary interventions. *Circulation* 94:1528–1536, 1996.
63. Abdelmeguid AE, Ellis SG, Sapp SK, et al: Defining the appropriate threshold of creatine kinase elevation after percutaneous coronary interventions. *Am Heart J* 131:1097–1105, 1996.
64. Kong TQ, Jr, Davidson CJ, Meyers SN, et al: Prognostic implication of creatine kinase elevation following elective coronary artery interventions. *JAMA* 277:461–466, 1997.
65. Ghazzal Z, Ashfaq S, Morris DC, et al: Prognostic implication of creatine kinase release after elective percutaneous coronary intervention in the pre-IIb/IIIa antagonist era. *Am Heart J* 145:1006–1012, 2003.
66. Tardiff BE, Califf RM, Tcheng JE, et al: Clinical outcomes after detection of elevated cardiac enzymes in patients undergoing percutaneous intervention. *J Am Coll Cardiol* 33:88–96, 1999.
67. Waksman R, Ghazzal Z, Baim DS, et al: Myocardial infarction as a complication of new interventional devices. *Am J Cardiol* 78:751–756, 1996.
68. Simoons ML, van den Brand M, Lincoff M, et al: Minimal myocardial damage during coronary intervention is associated with impaired outcome. *Eur Heart J* 20:1112–1119, 1999.
69. Roe MT, Mahaffey KW, Kilaru R, et al: Creatine kinase-MB elevation after percutaneous coronary intervention predicts adverse outcomes in patients with acute coronary syndromes. *Eur Heart J* 25:313–321, 2004.
70. Mehran R, Dangas G, Mintz GS, et al: Atherosclerotic plaque burden and CK-MB enzyme elevation after coronary interventions : intravascular ultrasound study of 2256 patients. *Circulation* 101:604–610, 2000.
71. Stone GW, Mehran R, Dangas G, et al: Differential impact on survival of electrocardiographic q-wave versus enzymatic myocardial infarction after percutaneous intervention: a device-specific analysis of 7147 patients. *Circulation* 104:642–647, 2001.
72. Dangas G, Mehran R, Feldman D, et al: Postprocedure creatine kinase-MB elevation and baseline left ventricular dysfunction predict one-year mortality after percutaneous coronary intervention. *Am J Cardiol* 89:586–588, 2002.
73. Ajani AE, Waksman R, Sharma AK, et al: Usefulness of periprocedural creatinine phosphokinase-MB release to predict adverse outcomes after intracoronary radiation therapy for in-stent restenosis. *Am J Cardiol* 93:313–317, 2004.
74. Brener SJ, Ellis SG, Schneider J, Topol EJ: Frequency and long-term impact of myonecrosis after coronary stenting. *Eur Heart J* 23:869–876, 2002.
75. Ellis SG, Chew D, Chan A, et al: Death following creatine kinase-MB elevation after coronary intervention: identification of an early risk period: importance of creatine kinase-MB level, completeness of revascularization, ventricular function, and probable benefit of statin therapy. *Circulation* 106:1205–1210, 2002.
76. Brener SJ, Lytle BW, Schneider JP, et al: Association between CK-MB elevation after percutaneous or surgical revascularization and three-year mortality. *J Am Coll Cardiol* 40:1961–1967, 2002.
77. Hong MK, Mehran R, Dangas G, et al: Creatine kinase-MB enzyme elevation following successful saphenous vein graft intervention is associated with late mortality. *Circulation* 100: 2400–2405, 1999.
78. Natarajan MK, Kreatsoulas C, Velianou JL, et al: Incidence, predictors, and clinical significance of troponin-I elevation without creatine kinase elevation following percutaneous coronary interventions. *Am J Cardiol* 93:750–753, 2004.
79. Nallamothu BK, Chetcuti S, Mukherjee D, et al: Prognostic implication of troponin I elevation after percutaneous coronary intervention. *Am J Cardiol* 91:1272–1274, 2003.
80. Fuchs S, Kornowski R, Mehran R, et al: Prognostic value of cardiac troponin-I levels following catheter-based coronary interventions. *Am J Cardiol* 85:1077–1082, 2000.

81. Cavallini C, Savonitto S, Violini R, et al: Impact of the elevation of biochemical markers of myocardial damage on long-term mortality after percutaneous coronary intervention: results of the CK-MB and PCI study. *Eur Heart J* 26:1494–1498, 2005.
82. Moussa ID, Klein LW, Shah B, et al: Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol* 62:1563–1570, 2013.
83. Choi JW, Gibson CM, Murphy SA, et al: Myonecrosis following stent placement: association between impaired TIMI myocardial perfusion grade and MRI visualization of microinfarction. *Catheter Cardiovasc Interv* 61:472–476, 2004.
84. Bahrmann P, Werner GS, Heusch G, et al: Detection of coronary microembolization by Doppler ultrasound in patients with stable angina pectoris undergoing elective percutaneous coronary interventions. *Circulation* 115:600–608, 2007.
85. Porto I, Selvanayagam JB, Van Gaal WJ, et al: Plaque volume and occurrence and location of periprocedural myocardial necrosis after percutaneous coronary intervention: insights from delayed-enhancement magnetic resonance imaging, thrombolysis in myocardial infarction myocardial perfusion grade analysis, and intravascular ultrasound. *Circulation* 114:662–669, 2006.
86. Iakovou I, Merhan R, Mintz G, et al: Increased CKMB release is a trade-off for optimal stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol* 39:28–29, 2002.
87. Topol EJ, Mark DB, Lincoff AM, et al: Outcomes at 1 year and economic implications of platelet glycoprotein IIb/IIIa blockade in patients undergoing coronary stenting: results from a multicentre randomised trial. *Lancet* 354:2019–2024, 1999.
88. The EPILOG Investigators: Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 336:1689–1697, 1997.
89. Topol EJ, Leya F, Pinkerton CA, et al: A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease. *N Engl J Med* 329:221–227, 1993.
90. De Labriolle A, Lemesle G, Bonello L, et al: Prognostic significance of small troponin I rise after a successful elective percutaneous coronary intervention of a native artery. *Am J Cardiol* 103:639–645, 2009.
91. Javaid A, Buch AN, Steinberg DH, et al: Does creatine kinase-MB (CK-MB) isoenzyme elevation following percutaneous coronary intervention with drug-eluting stents impact late clinical outcomes? *Catheter Cardiovasc Interv* 70:826–831, 2007.
92. Nienhuis MB, Ottervanger JP, Bilo HJG, et al: Prognostic value of troponin after elective percutaneous coronary intervention: a meta-analysis. *Catheter Cardiovasc Interv* 71:318–324, 2008.
93. Gold HK, Gimple LW, Yasuda T, et al: Pharmacodynamic study of F(ab')2 fragments of murine monoclonal antibody 7E3 directed against human platelet glycoprotein IIb/IIIa in patients with unstable angina pectoris. *J Clin Invest* 86:651–659, 1990.
94. The EPIC Investigators: Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 330:956–961, 1994.
95. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 349:1429–1435, 1997.
96. The PURSUIT Trial Investigators: Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 339:436–443, 1998.
97. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet* 356:2037–2044, 2000.
98. Valgimigli M, Percoco G, Barbieri D, et al: The additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high-risk coronary angioplasty: the ADVANCE trial. *J Am Coll Cardiol* 44:14–19, 2004.
99. Steinhubl SR, Lauer MS, Mukherjee DP, et al: The duration of pretreatment with ticlopidine prior to stenting is associated with the risk of procedure-related non–Q-wave myocardial infarctions. *J Am Coll Cardiol* 32:1366–1370, 1998.
100. Mehta SR, Yusuf S, Peters RJG, et al: Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 358:527–533, 2001.
101. Steinhubl SR, Berger PB, Mann JT, 3rd, et al: Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 288:2411–2420, 2002.
102. Hochholzer W, Trenk D, Bestehorn H-P, et al: Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. *J Am Coll Cardiol* 48:1742–1750, 2006.
103. Patti G, Colonna G, Pasceri V, et al: Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. *Circulation* 111:2099–2106, 2005.
104. Chen W-H, Lee P-Y, Ng W, et al: Aspirin resistance is associated with a high incidence of myonecrosis after non-urgent percutaneous coronary intervention despite clopidogrel pretreatment. *J Am Coll Cardiol* 43:1122–1126, 2004.
105. Cuisset T, Frere C, Quilici J, et al: Glycoprotein IIb/IIIa inhibitors improve outcome after coronary stenting in clopidogrel nonresponders: a prospective, randomized study. *J Am Coll Cardiol Intv* 1:649–653, 2008.
106. Pasceri V, Patti G, Nusca A, et al: Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: results from the ARMYDA (Atorvastatin for Reduction of MYocardial Damage during Angioplasty) study. *Circulation* 110:674–678, 2004.
107. Patti G, Pasceri V, Colonna G, et al: Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial. *J Am Coll Cardiol* 49:1272–1278, 2007.
108. Patti G, Chello M, Pasceri V, et al: Protection from procedural myocardial injury by atorvastatin is associated with lower levels of adhesion molecules after percutaneous coronary intervention: results from the ARMYDA-CAMs (Atorvastatin for Reduction of MYocardial Damage during Angioplasty-Cell Adhesion Molecules) substudy. *J Am Coll Cardiol* 48:1560–1566, 2006.
109. Di Sciascio G, Patti G, Pasceri V, et al: Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention: results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) randomized trial. *J Am Coll Cardiol* 54:558–565, 2009.
110. Baim DS, Wahr D, George B, et al: Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. *Circulation* 105:1285–1290, 2002.
111. Mauri L, Cox D, Hermiller J, et al: The PROXIMAL trial: proximal protection during saphenous vein graft intervention using the proxis embolic protection system: a randomized, prospective, multicenter clinical trial. *J Am Coll Cardiol* 50:1442–1449, 2007.
112. Stone GW, Webb J, Cox DA, et al: Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. *JAMA* 293:1063–1072, 2005.
113. Gick M, Jander N, Bestehorn H-P, et al: Randomized evaluation of the effects of filter-based distal protection on myocardial perfusion and infarct size after primary percutaneous catheter intervention in myocardial infarction with and without ST-segment elevation. *Circulation* 112:1462–1469, 2005.
114. Rezkalla SH, Kloner RA: No-reflow phenomenon. *Circulation* 105:656–662, 2002.
115. Abbo KM, Dooris M, Glazier S, et al: Features and outcome of no-reflow after percutaneous coronary intervention. *Am J Cardiol* 75:778–782, 1995.
116. Piana R, Paik G, Moscucci M, et al: Incidence and treatment of "no-reflow" after percutaneous coronary intervention. *Circulation* 89:2514–2518, 1994.
117. Yip HK, Chen MC, Chang HW, et al: Angiographic morphologic features of infarct-related arteries and timely reperfusion in acute myocardial infarction: predictors of slow-flow and no-reflow. *Chest* 122:1322–1332, 2002.
118. Kojima S, Sakamoto T, Ishihara M, et al: The white blood cell count is an independent predictor of no-reflow and mortality following acute myocardial infarction in the coronary interventional era. *Ann Med* 36:153–160, 2004.
119. Iwakura K, Ito H, Kawano S, et al: Predictive factors for development of the no-reflow phenomenon in patients with reperfused anterior wall acute myocardial infarction. *J Am Coll Cardiol* 38:472–477, 2001.
120. Klein LW, Kern MJ, Berger P, et al: Society of cardiac angiography and interventions: suggested management of the no-reflow phenomenon in the cardiac catheterization laboratory. *Catheter Cardiovasc Interv* 60:194–201, 2003.
121. Moses JW, Whitlow PL, Kuntz RE, et al: Myocardial infarction after rotational atherectomy: predictors and influence on late outcome in the STRATAS trial. *J Am Coll Cardiol* 31:455, 1998.
122. Kapoor N, Yalamanchili V, Siddiqui T, et al: Cardioprotective effect of high-dose intragraft adenosine infusion on microvascular function and prevention of no-reflow during saphenous vein grafts intervention. *Catheter Cardiovasc Interv* 83:1045–1054, 2014.
123. Montalescot G, Barragan P, Wittenberg O, et al: Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 344:1895–1903, 2001.
124. Stone GW, Maehara A, Witzenbichler B, et al: Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. *JAMA* 307:1817–1826, 2012.
125. Svilaas T, Vlaar PJ, van der Horst IC, et al: Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med* 358:557–567, 2008.
126. Vlaar PJ, Svilaas T, van der Horst IC, et al: Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. *Lancet* 371:1915–1920, 2008.
127. De Luca G, Dudek D, Sardella G, et al: Adjunctive manual thrombectomy improves myocardial perfusion and mortality in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: a meta-analysis of randomized trials. *Eur Heart J* 29:3002–3010, 2008.
128. Burzotta F, De Vita M, Gu YL, et al: Clinical impact of thrombectomy in acute ST-elevation myocardial infarction: an individual patient-data pooled analysis of 11 trials. *Eur Heart J* 30:2193–2203, 2009.
129. Frobert O, Lagerqvist B, Olivecrona GK, et al: Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 369:1587–1597, 2013.
130. Gibson CM, Murphy SA, Rizzo MJ, et al: Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. *Circulation* 99:1945–1950, 1999.
131. Ross AM, Coyne KS, Moreyra E, et al: Extended mortality benefit of early postinfarction reperfusion. *Circulation* 97:1549–1556, 1998.
132. Mehta RH, Harjai KJ, Boura J, et al: Prognostic significance of transient no-reflow during primary percutaneous coronary intervention for ST-elevation acute myocardial infarction. *Am J Cardiol* 92:1445–1447, 2003.
133. Khan M, Schmidt DH, Bajwa T, Shalev Y: Coronary air embolism: incidence, severity, and suggested approaches to treatment. *Catheter Cardiovasc Diagn* 36:313–318, 1995.
134. Dib J, Boyle AJ, Chan M, Resar JR: Coronary air embolism: a case report and review of the literature. *Catheter Cardiovasc Interv* 68:897–900, 2006.
135. Canter LM: Anaphylactoid reactions to radiocontrast media. *Allergy Asthma Proc* 26:199–203, 2005.
136. Goss J, Chambers C, Heupler F, Jr: Systemic anaphylactoid reactions to iodinated contrast media during cardiac catheterization procedure: guidelines for prevention, diagnosis and treatment. *Catheter Cardiovasc Diagn* 34:99–104, 1995.
137. Yasuda R, Munechika H: Delayed adverse reactions to nonionic monomeric contrast-enhanced media. *Invest Radiol* 33:1–5, 1998.
138. Sampson HA, Munoz-Furlong A, Bock SA, et al: Symposium on the definition and management of anaphylaxis: summary report. *J Allergy Clin Immunol* 115:584–591, 2005.
139. Nayak KR, White AA, Cavendish JJ, et al: Anaphylactoid reactions to radiocontrast agents: prevention and treatment in the cardiac catheterization laboratory. *J Invasive Cardiol* 21:548–551, 2009.
140. Chhatriwalla AK, Amin AP, Kennedy KF, et al: Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. *JAMA* 309:1022–1029, 2013.
141. Eikelboom JW, Mehta SR, Anand SS, et al: Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* 114:774–782, 2006.
142. Stone GW, Witzenbichler B, Guagliumi G, et al: Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. *Lancet* 377:2193–2204, 2011.
143. Mehran R, Rao SV, Bhatt DL, et al: Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 123:2736–2747, 2011.
144. Ndrepepa G, Schuster T, Hadamitzky M, et al: Validation of the bleeding academic research consortium definition of bleeding in patients with coronary artery disease undergoing percutaneous coronary intervention. *Circulation* 125:1424–1431, 2012.
145. Doyle BJ, Ting HH, Bell MR, et al: Major femoral bleeding complications after percutaneous coronary intervention: incidence, predictors, and impact on long-term survival among 17,901 patients treated at the Mayo Clinic from 1994 to 2005. *JACC Cardiovasc Interv* 1:202–209, 2008.
146. Moscucci M: Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 24:1815–1823, 2003.
147. Feit F, Voeltz MD, Attubato MJ, et al: Predictors and impact of major hemorrhage on mortality following percutaneous coronary intervention from the REPLACE-2 trial. *Am J Cardiol* 100:1364, 2007.
148. Kirtane AJ, Piazza G, Murphy SA, et al: Correlates of bleeding events among moderate- to high-risk patients undergoing percutaneous coronary intervention and treated with eptifibatide: observations from the PROTECT-TIMI-30 trial. *J Am Coll Cardiol* 47:2374–2379, 2006.
149. Trimarchi S, Smith DE, Share D, et al: Retroperitoneal hematoma after percutaneous coronary intervention: prevalence, risk factors, management, outcomes, and predictors of mortality: a report from the BMC2 (Blue Cross Blue Shield of Michigan Cardiovascular Consortium) registry. *JACC Cardiovasc Interv* 3:845–850, 2010.
150. Rao S, Jollis JG, Harrington R, et al: Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA* 292:1555–1562, 2004.
151. Mehta SK, Frutkin AD, Lindsey JB, et al: Bleeding in patients undergoing percutaneous coronary intervention: the development of a clinical risk algorithm from the National Cardiovascular Data Registry. *Circ Cardiovasc Interv* 2:222–229, 2009.
152. Mehran R, Pocock SJ, Nikolsky E, et al: A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol* 55:2556–2566, 2010.
153. Tsai TT, Maddox TM, Roe MT, et al: Contraindicated medication use in dialysis patients undergiong percutaneous coronary intervention. *JAMA* 302:2458–2464, 2009.
154. Marso SP, Amin AP, House JA, et al: Association between use of bleeding avoidance strategies and risk of periprocedural bleeding among patients undergoing percutaneous coronary intervention. *JAMA* 303:2156–2164, 2010.
155. Seto AH, Abu-Fadel MS, Sparling JM, et al: Real-time ultrasound guidance facilitates femoral arterial access and reduces

vascular complications: FAUST (Femoral Arterial Access With Ultrasound Trial). *JACC Cardiovasc Interv* 3:751–758, 2010.
156. Ben-Dor I, Maluenda G, Torguson R, et al: A novel, minimally invasive access technique versus standard 18-gauge needle set for femoral access. *Catheter Cardiovasc Interv* 79:1180–1185, 2012.
157. Jolly SS, Yusuf S, Cairns J, et al: Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet* 377:1409–1420, 2011.
158. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al: Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *J Am Coll Cardiol* 60:2481–2489, 2012.
159. Grossman PM, Gurm HS, McNamara R, et al: Percutaneous coronary intervention complications and guide catheter size: bigger is not better. *JACC Cardiovasc Interv* 2:636–644, 2009.

29 Periprocedural Myocardial Infarction and Embolism-Protection Devices

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KEY POINTS

- Periprocedural myocardial necrosis remains a common complication of percutaneous coronary intervention (PCI).
- The 2012 Third Universal Definition document defines a myocardial infarction (MI) associated with PCI as elevation of troponin values above five times the 99th percentile of upper reference limit (URL) in patients with normal baseline values or a rise of troponin values above 20% if the baseline values are elevated and are stable or falling.
- Given the adverse prognostic implications, it is important to develop strategies to prevent, rather than treat, periprocedural MI (PMI).
- Successful strategies to prevent PMI include pharmacologic and nonpharmacologic approaches.
- The primary pharmacologic interventions that have achieved significant success in preventing PMI include aggressive antiplatelet therapy, primarily intravenous (IV) glycoprotein IIb/IIIa inhibitors and oral thienopyridine inhibitors, and statin therapy.
- Nonpharmacologic approaches include the use of embolic protection devices (EPDs) in the setting of saphenous vein graft (SVG) intervention and carotid stenting.
- With more innovation in EPD design, and with supporting data, the potential exists for future application of EPDs in other settings of coronary and peripheral intervention.

PERIPROCEDURAL MYOCARDIAL INFARCTION

- The contemporary definition of PMI is based on the rise and fall of biomarkers—such as total creatine kinase (CK), creatine kinase MB (CK-MB), and troponin—after PCI in addition to clinical, electrocardiography (ECG), and imaging evidence of myonecrosis.
- The incidence of PMI varies according to the type of assayed biomarker (CK-MB, troponin I [Tn I], or troponin T [Tn T]) and the preset threshold for diagnosis.
- Larger PMIs are infrequent and usually follow angiographically documented complications, such as side-branch closure or no-reflow phenomenon, but smaller and more common PMIs often follow apparently uncomplicated procedures.
- The primary underlying mechanisms of PMI are side-branch occlusions and distal embolization into the downstream microcirculation of the PCI-related vessel, with platelet aggregation/activation playing a significant role in subsequent myonecrosis.
- Risk factors for development of PMI include acute presentation, heightened systemic inflammation, and advanced coronary and/or noncoronary atherosclerotic disease. Atheroablation devices (directional or rotational) are associated with higher rates of PMI, followed by stents and then balloon angioplasty.
- PMI is associated with increased late mortality, and the association is more robust when the CK-MB or troponin levels exceed five times the upper limit of normal (ULN).
- Potent antiplatelet therapies (IV glycoprotein IIb/IIIa inhibitors, direct thrombin inhibitors, and/or oral thienopyridine inhibitors) decrease the incidence of PMI, especially in high-risk procedures.
- Pretreatment with statins reduces the incidence of PMI because of their antiinflammatory effects.
- EPDs have been proven to reduce PMI in saphenous vein graft PCI.

EMBOLISM PROTECTION DEVICES

- EPDs include distal occlusive balloons, filter devices, and proximal flow occlusion/reversal systems; all aim to trap embolized debris from the angioplasty site before it reaches the distal microvascular bed.
- Clinical trials have demonstrated that using an EPD during vein graft PCI leads to a significant reduction in PMI; it is also cost-effective and has thus become the standard of care in those patients.
- Several randomized trials failed to show any benefit of an EPD in the setting of PCI for acute MI, thus highlighting the complexity of the mechanisms of myonecrosis and injury in those settings.
- Good evidence suggests that EPDs reduce cerebral embolism during carotid stenting, but no conclusive randomized trial based on clinical end points has been undertaken to confirm that benefit.
- Comparison of carotid stenting that includes embolic protection with carotid endarterectomy results in similar outcomes in patients with asymptomatic disease and in the hands of experience operators.
- Use of a proximal EPD during carotid stenting may be associated with a lower risk of stroke, although randomized comparative trials are lacking at this time.

Periprocedural myocardial necrosis remains the most common complication of PCI. Such myonecrosis can range from a clinically silent minor elevation of cardiac enzymes to a major MI with short- and/or long-term consequences. With advances in pharmacologic therapies and in interventional technology, the incidence of early major cardiac events (MACEs)—such as large MI (both ST-elevation MI [STEMI] and non–ST-elevation MI [NSTEMI]) and death—has fallen to less than 3%, even in complex multivessel PCI.[1,2] The reduced incidence of these complications can be attributed in large part to the role of coronary stents in treatment of abrupt closure and the aggressive antiplatelet therapies more commonly utilized over the last two decades. This improvement in outcomes is remarkable considering the ever-increasing number and complexity of patients and lesions treated with PCI today compared with 20 to 30 years ago. However, the frequency with which any periprocedural myonecrosis is detected has increased, primarily because of the development and widespread adoption of sensitive biomarkers of myocardial damage. As such, the exact definition and clinical significance of the periprocedural release of cardiac markers are topics for active debate, in both real-world and clinical trial settings.

DEFINITION

The definition of *periprocedural myocardial infarction* (PMI) is continuing to evolve with changing and improving biomarker assays and a better understanding of the prognostic significance of these events.

Currently, commonly used definitions for the diagnosis of PMI are based on one of two documents: the Third Universal Definition of Myocardial Infarctions[3] and the definition proposed by the Society of Cardiac Angiography and Interventions (SCAI) expert consensus document.[4]

Both definitions are based on identifying the rise and fall of cardiac biomarkers following PCI in addition to corroborating clinical, ECG, imaging, and/or angiographic evidence of myonecrosis. They differ in the various thresholds considered enough to make the diagnosis and in how they indicate a clinically relevant change in prognosis. It is important to note that both definitions of PMI are complicated by the current practice of earlier referral of acute MI patients and those with an acute coronary syndrome (ACS) to the catheterization laboratory. Importantly, the prognostic implication of elevated biomarkers after PCI cannot be known unless the baseline level is taken into account. In patients with elevated biomarker levels at baseline, prognosis is more directly linked to the baseline biomarker level than to the post-procedural level. In fact, biomarker elevation before PCI is the more important determinant of long-term mortality. In those situations, detection of abnormal levels of cardiac markers after PCI may not necessarily be related to the procedure but are simply a reflection of the ongoing myonecrosis caused by the thrombotic event that led to the clinical presentation. In ACS patients, biomarker levels may rise after a normal initial sample, which commonly coincides with the time when angiography and PCI are performed.[5] For these reasons, both definitions include specific criteria to extend the definition of PMI to those who were referred to PCI in the setting of ACS or STEMI.

The Third Universal Definition of Myocardial Infarction: Definition of Periprocedural Myocardial Infarction

The aim of this document is to redefine MI based on contemporary evidence and to standardize the definition in various clinical settings. The 2012 Third Universal Definition document[3] proposed the following updated definition for PMI: an MI associated with PCI is arbitrarily defined by elevation of troponin values greater than five times the 99th percentile (URL) in patients with normal baseline values (≤99th percentile URL) or a rise of troponin values greater than 20% if the baseline values are elevated and are stable or falling. The required enzymatic criteria should be associated with (i) symptoms consistent with myocardial ischemia; (ii) new ischemic ECG changes or new left bundle branch (LBBB) block; (iii) angiographic loss of patency of a major coronary artery or a side branch, a persistent slow- or no-flow state, or embolization; or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality. PCI-related MI (type 4) is distinguished from spontaneous MI (type 1), secondary MI (type 2), and MI associated with sudden death (type 3) or coronary artery bypass grafting (CABG; type 5). A documented stent thrombosis is recognized as a type 4b MI, whereas an MI associated with restenosis greater than 50% is type 4c (Table 29-1).

When a troponin value is elevated but less than or equal to five times the 99th percentile URL after PCI, and the troponin value was normal before the PCI, or when the troponin value is more than times the 99th percentile URL in the absence of ischemic, angiographic, or imaging findings, the task force suggested that the term *myocardial injury* should be used.

Notably, the universal definition states that troponin is the preferred biomarker, the prognostic significance of which is less well validated than CK-MB in the setting of post-PCI myonecrosis. A large body of literature has demonstrated that post-PCI CK and CK-MB elevations have serious adverse prognostic implications, even in absence of pathologic Q-waves.[6-9] Three meta-analyses to examine the prognostic impact of periprocedural elevated CK-MB have confirmed a proportionate increase in early and late mortality with rising values.[10-12] The use of abnormal troponin assays to diagnose type 4a MI is supported by some datasets, although supporting evidence is not as wide ranging as has been demonstrated on the basis of abnormal CK-MB. Troponin is a particularly sensitive biomarker used ubiquitously for risk stratification in patients with ACS, but its widespread adoption has by itself increased the incidence of spontaneous MI and PMIs by 40% to 50%. In contrast to its predictive value in type 1 MI (ACS), existing data on peri- or post-PCI troponin elevation do not establish a clear association with an adverse prognosis. To make the definition more clinically relevant, the biomarker threshold for PMI was raised from greater than three times the 99th percentile URL in the earlier version of the Universal Definition document[13] to greater than five times the 99th percentile URL in the most recent one.[3] Nonetheless, the more recently recommended threshold remains arbitrary, and critics argue that any diagnosis of PMI should be associated with meaningful, well-defined prognostic significance.

TABLE 29-1 Categories of Myocardial Infarction Related to Percutaneous Coronary Intervention as Defined in the Third Universal Definition of Myocardial Infarction 2012

Category	Description/ Definition
Type 4a: MI related to PCI	MI associated with PCI is arbitrarily defined by elevation of cardiac troponin values greater than 5 times the 99th percentile URL in patients with normal baseline values or a rise of cardiac troponin values greater than 20% if the baseline values are elevated and are stable or falling. *In addition, one of the following features needs to be present:* (i) Symptoms suggestive of myocardial ischemia (ii) New ischemic electrocardiographic changes or new left bundle branch block (iii) Angiographic loss of patency of a major coronary artery or a side branch or persistent slow-flow or no-flow or embolization (iv) Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality
Type 4b: MI related to stent thrombosis	MI associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
Type 4c: MI related to restenosis	MI with evidence of 50% or more stenosis at coronary angiography or a complex lesion associated with a rise and/or fall of troponin values above the 99th percentile URL and no other significant obstructive CAD of greater severity following (i) initially successful stent deployment or (ii) initially successful PTCA (diameter stenosis <50% at the end of the procedure).

Thygesen K, Alpert JS, Jaffe AS, et al: Third universal definition of myocardial infarction. *J Am Coll Cardiol* 60:1581-1598, 2012.
CAD, Coronary artery disease; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention; *PTCA,* percutaneous transluminal coronary angioplasty; *URL,* upper reference limit.

The Society of Cardiac Angiography and Interventions Expert Consensus Proposed Definition of Periprocedural Myocardial Infarction

To address the limitations of the universal definition of PMI discussed above, an expert consensus group from the SCAI[4] proposed an alternate definition of *clinically relevant* MI after PCI, defined as "an event associated with a worsened prognosis." To this end, the document recommended that CK-MB be the preferred biomarker to assess clinically relevant PMI, defined as a CK-MB 10 or more times the ULN. A lower threshold (≥5× ULN) may be accepted in the patient in whom new pathologic Q-waves in two or more contiguous leads (or new, persistent LBBB) develop after PCI, although further study is required to validate this threshold. If CK-MB assays are not available, the

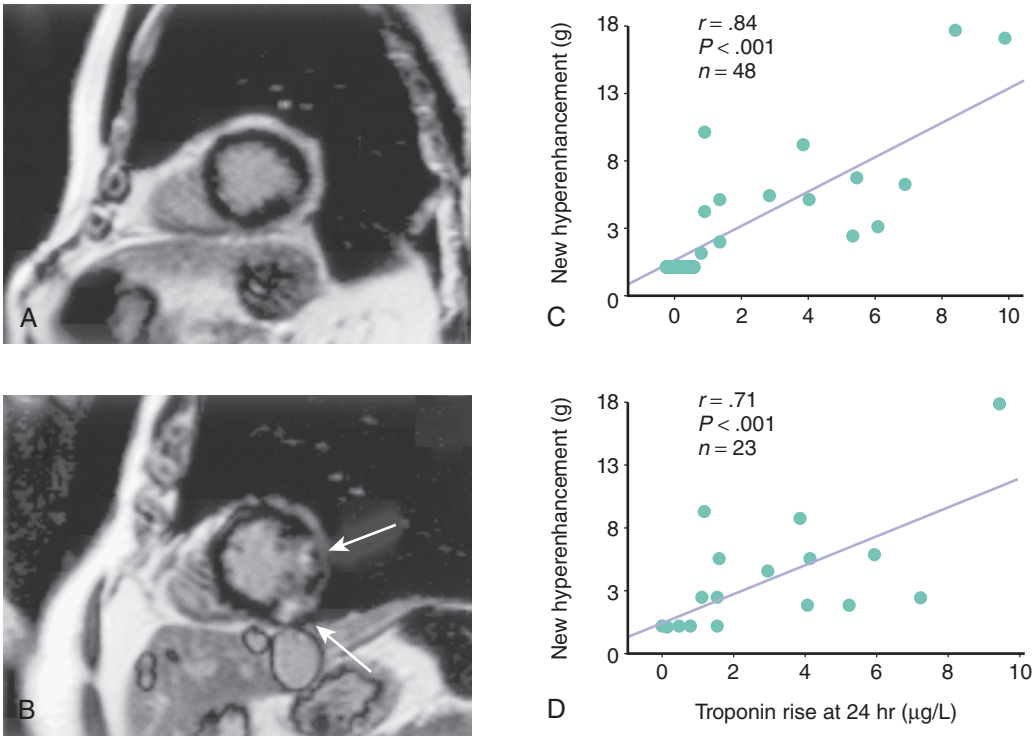


FIGURE 29-1 **A,** Apical ventricular short-axis image in a patient showing no hyperenhancement before left circumflex/obtuse marginal bifurcation percutaneous coronary intervention (PCI). **B,** Image demonstrates two regions of new hyperenhancement in the distribution of the obtuse marginal branch artery after PCI (*arrows*). Correlation between 24-hour post-PCI troponin I value versus mass of new myocardial hyperenhancement both early (**C**) and late (**D**) after PCI. (From Selvanayagam JB, Porto I, Channon K, et al: Troponin elevation after percutaneous coronary intervention directly represents the extent of irreversible myocardial injury: insights from cardiovascular magnetic resonance imaging. *Circulation* 111:1027-1032, 2005.)

consensus document suggests a troponin level of 70 or more times the ULN to diagnose a type 4a MI. The authors selected this high troponin threshold so that the prognostic implication would be comparable to that associated with a CK-MB elevation of 10 or more times the ULN.

The following recommendations were made to diagnose post-PCI MI in ACS patients in whom the baseline level has not returned to normal: (1) in patients with elevated troponin (or CK-MB) in whom the biomarker levels are stable or falling, a new CK-MB elevation by an absolute increment of 10 or more times the ULN (or ≥70× ULN for troponin) from the previous nadir level should be evident; (2) in patients with elevated troponin (or CK-MB) in whom the biomarker levels have *not* been shown to be stable or falling, there should be a further rise in CK-MB or troponin beyond the most recently measured value by an absolute increment of 10 or more times the ULN in CK-MB or 70 or more times the ULN in troponin plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new-onset or worsening heart failure or sustained hypotension. Chest pain alone is insufficient to be used as a criterion. In this definition, no specific angiographic or imaging criteria are given to corroborate the enzymatic, clinical, and ECG thresholds.

Enzyme Elevation and Evidence of Myonecrosis: The Value of Imaging Studies

Although substantial debate surrounds the clinical significance of minor biomarker elevation after PCI, solid evidence suggests that any biomarker level elevation following PCI corresponds to irreversible myocardial injury, both qualitatively and quantitatively. In a small study that used late gadolinium enhancement (LGE) on magnetic resonance (MR) imaging to directly visualize areas of myonecrosis, Ricciardi and colleagues[14] reported MR evidence of LGE (equivalent to ~2 g of myocardium) in nine of nine patients who had a minor procedure-related CK-MB elevation (~2× ULN). In the five control patients who did not have any CK-MB elevation, no MR evidence of LGE was found in the target vessel perfusion territory. Of note, none of the patients in whom LGE was detected as evidence of myonecrosis developed Q-waves on ECG.

In a more contemporary and rigorous study, 48 patients underwent cardiac MR imaging (CMRI) before and after PCI to detect newly developed LGE as evidence of procedure-related myonecrosis.[15] Half the patients underwent a third MR scan at a median of 8 months. Findings were correlated with serum troponin levels recorded 24 hours after the index PCI. All patients were preloaded with clopidogrel and received abciximab at the time of PCI, but the incidence of troponin elevation above the ULN was 37% (14 patients). Evidence of LGE was present in the target vessel territory in all 14 patients. In those with no troponin elevation after PCI, no evidence of LGE was found on MR scans. A linear correlation was also apparent between the troponin level at 24 hours after PCI and the mass (in grams) of newly hyperenhanced myocardium, both on the early post-PCI scan and on the delayed 8-month scan, thus confirming the correlation between periprocedural biomarker release and irreversible myocardial damage (Fig. 29-1).[15]

In addition to confirming the irreversible nature of the myocardial injury, the location of MR hyperenhancement in relation to the PCI target segment may give insight into the pathophysiologic mechanism underlying PMI. When the hyperenhancement is visualized in proximity of the treated segment, side-branch occlusion (SBO) is the more likely explanation. But in cases in which the myocardial injury/damage is downstream from the treated segment, PMI can be best explained by distal microembolization and adverse platelet and inflammatory reactions in the microcirculation.[14,16]

TABLE 29-2 Incidence of Periprocedural Myocardial Infarction in Selected Large Patient Series

Reference	N	Type of PCI	Biomarker Definition of PMI	Incidence of PMI (%)
Harrington et al[6]	1,012	PTCA DCA	CK-MB ×2 ULN	3.8 10.3
Abdelmeguid et al[7]	4,664	PTCA, DCA	CK 2–5× ULN	2.6
Ellis et al[8]	8,409	PCI	CK-MB > 8.8	17.2
Ghazzal et al[9]	15,637	PCI	CK 1–2× ULN CK > 3× ULN	4.6 1.6
Simoons et al[10]	5,025	PTCA	CK-MB 1–3× ULN	13.2
Ioannidis et al[11]				
Roe et al[12]	2,384	PCI	CK-MB 1–3× ULN CK-MB 3–5× ULN CK-MB 5–10× ULN CK-MB > 10× ULN	21.3 6.0 7.1 9.5
Stone et al[67]	7,147	PTCA Stent Ablation Ablation+stent	CK-MB > 4	25.1 34.4 37.8 48.8
Natarajan et al[161]	1,128	PCI	Tn I > 0.5	16.8
Nallamothu et al[20]	1,157	PCI	Tn I 1–3× ULN Tn I 3–5× ULN Tn I 5–8× ULN Tn I ≥ 8× ULN	16.0 4.6 2.0 6.5
Cavallini et al[18]	3,494	PCI	Tn I > 0.15 CK-MB > 5	44.2 16.0
Testa et al[162]	7,578	PCI	Tn > 99% URL Tn > 3× URL	28.7 14.5

CK-MB, Creatine kinase MB; *DCA,* directional coronary atherectomy; *PCI,* percutaneous coronary intervention; *PMI,* periprocedural myocardial infarction; *PTCA,* percutaneous transluminal coronary angioplasty; *Tn,* troponin; *TnI,* trpononin I; *ULN,* upper limit of normal; *URL,* upper reference limit.

INCIDENCE

As with its definition, the reported incidence of PMI has varied widely from one published report to another (Table 29-2). This variation can be attributed to several factors, but the predominant predictors are the choice of biomarker assayed and the threshold value used to diagnose PMI.

In a randomized trial of PCI and coronary artery bypass grafting (CABG) for triple-vessel disease, 75% of PCI and 100% of CABG patients had biomarker level elevation despite successful revascularization. Use of ultrasensitive troponin resulted in nearly all such patients reaching criteria for a type 4a MI, whereas using CK-MB, only about 15% were classified as such.[17] In other studies composed of less complex patients, an appreciable elevation of cardiac troponin above the ULN following PCI was still noted in about 40% to 50%.[18] In one meta-analysis of 15 studies that included more than 7500 patients with normal baseline troponin levels, troponin elevation occurred in 29% of the procedures.[19] When applying the older universal definition of PMI (any troponin elevation > 3× URL), the incidence of PMI is 14.5%. In a patient series that excluded patients with initially positive markers, the average incidence of PMI using CK-MB, troponin T, and troponin I greater than the ULN was 23%, 23%, and 27%, respectively.[16]

When the incidence of PMI is reported for a consecutive series of patients undergoing PCI (irrespective of their clinical condition after the procedure), it is invariably higher than in other series, in which biomarkers were assayed only in patients who developed certain symptoms or signs of ischemia. This is the result of detection of a fairly larger proportion of clinically silent events, with small-magnitude biomarker release.[7] The American College of Cardiology (ACC)/American Heart Association (AHA) PCI guidelines update published in 2011 recommended that for those patients who have signs or symptoms suggestive of MI during or after PCI, or for asymptomatic patients with significant persistent angiographic complications (e.g., large SBO, flow-limiting dissection, no-reflow phenomenon, or coronary thrombosis), CK-MB and/or troponin should be measured (class I recommendation). A class IIb recommendation is proposed for routine measurement of cardiac biomarkers in all patients after PCI.[2] Using a lower biomarker cutoff value to define PMI increases its epidemiologic incidence.[12,20] Other important factors that contribute to the heterogeneity of the conclusions of the various published series include the widely disparate baseline and procedural characteristics in the studied populations, inclusion or exclusion of patients with antecedent myocardial infarction, and the timing of blood sampling.[5,16]

Discrepancies may be found in the reported incidences of PMI according to the time frame in which various reports were published, the anticoagulation/antiplatelet therapy used, and the devices used for PCI. Large Q-wave PMIs were reduced from 2.1% in the Bypass Angioplasty Revascularization Investigation (BARI) trial population to 0.8% in BARI-like patients selected from the more contemporary National Heart, Lung, and Blood Institute (NHLBI) dynamic registry, in which the reduction was primarily driven by contemporary liberal use of stents that effectively treated abrupt closure and flow-limiting dissections.[21] Additionally, in the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) randomized controlled trial,[22] abciximab use reduced Q-wave PMI during stenting by more than 40% (1.4% vs. 0.8%).

UNDERLYING PATHOPHYSIOLOGIC MECHANISMS

MR myocardial imaging in patients who develop biomarker release after PCI reveals two different types of PMI, according to the distribution of hyperenhancement indicative of acute injury. In the more commonly seen *distal type* of PMI, hyperenhancement is in the distal distribution downstream from the treated segment. In the *proximal type* of PMI, the injury is primarily detected adjacent to the treated

segment.[14,23] Proximal PMI is usually linked to flow impairment in a side branch arising from the treated segment, whereas the more commonly seen distal PMI results from microvascular obstruction in the distribution of the artery subjected to PCI.

Distal Embolization and Periprocedural Myocardial Infarction

Although distal embolization associated with endothelial injury has been recognized for years, the importance of this phenomenon in relation to PCI was not fully appreciated until the last decade.[24] Significant distal embolization can cause no-reflow phenomenon after PCI in large part as a result of microvascular dysfunction, because evidence of myocardial ischemia and reduced antegrade coronary flow are present in the absence of an occlusive epicardial stenosis or side-branch compromise. In a report of patients undergoing PCI for NSTEMI, those with a postprocedural troponin I elevation were significantly more likely to have reduced tissue-level perfusion than those without a troponin I elevation. Platelet aggregates have been identified in the distal microcirculation and in atherosclerotic debris retrieved from arteries downstream from the site of angioplasty using filter devices (Fig. 29-2).

Clinically, intravascular ultrasound (IVUS) studies provided further insight into the relationship between embolization of plaque material and PMI. Prati and coworkers[25] examined the relationship between change in plaque volume before and after stenting and the degree of CK-MB release in 54 patients. In patients with unstable angina, the reduction in plaque volume was more significant, but more important, such reduction significantly correlated with CK-MB release even after adjusting for other variables that influence PMI. A more recent and sophisticated analysis of 62 patients undergoing complex PCI by Porto and colleagues[23] demonstrated a significant association between the change in target lesion plaque area by IVUS and the mass of myonecrosis assessed by hyperenhancement on MR imaging after PCI. The authors also correlated impaired microvascular flow (thrombolysis in myocardial infarction [TIMI] perfusion grade 0 or 1) with MR evidence of hyperenhancement downstream from the treated segment, hence suggesting that particulate matter from the atherosclerotic plaque disrupted by angioplasty drifts downstream and leads to microvascular obstruction and myonecrosis.

The development and clinical utilization of embolic protection devices (EPDs) has provided additional evidence of distal embolization because particulate matter from the atherosclerotic plaque subjected to angioplasty could be collected, measured, and analyzed. The embolized material has been found to primarily consist of debris comprising atherosclerotic plaque and thrombotic elements, with particles that range in size from about 50 to more than 600 µm. Neutrophils and macrophages have also been identified. Although these devices are more frequently used in the setting of PCI in saphenous vein grafts (SVGs), distal embolization in routine native vessel PCI is probably just as common, with debris that is very similar in quantity and composition.[26,27]

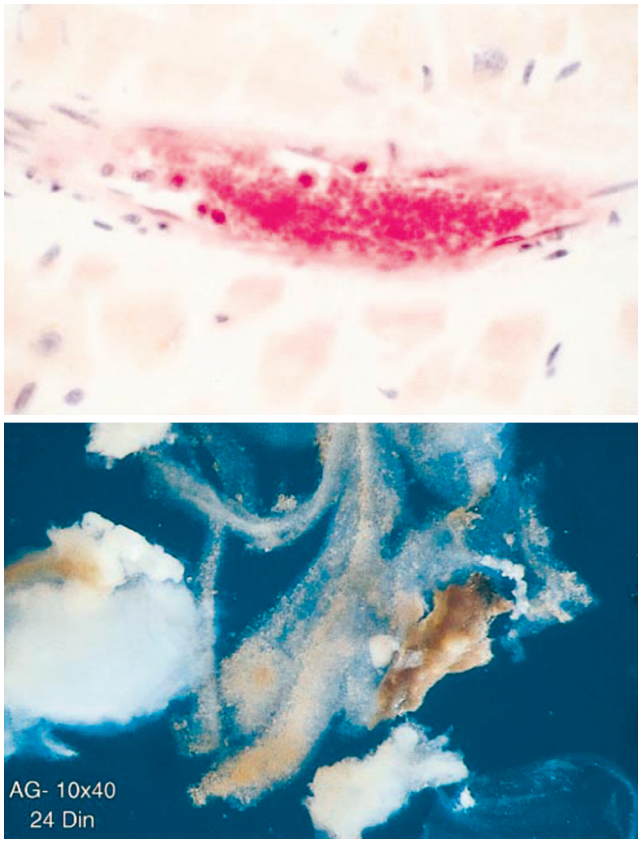


FIGURE 29-2 **A,** Histologic specimen of intramyocardial microvessel filled with platelets; the specimen stained positive for platelet glycoprotein (GP) IIb/IIIa from a patient who suffered sudden cardiac death. **B,** Atherosclerotic particulate embolic material retrieved from percutaneous coronary revascularization with an Angioguard guidewire filter. (From Topol EJ, Yadav JS: Recognition of the importance of embolization in atherosclerotic vascular disease. *Circulation* 101:570-580, 2000.)

The Role of the Platelet

Platelet activation plays a critical role in the development and perpetuation of coronary microvascular obstruction following PCI. By definition, the interventional devices used to treat an epicardial stenosis will result in a break in the endothelial surface and a release of debris into the coronary bloodstream. The exposed intraplaque contents stimulate platelet activation and aggregation at the site of the PCI and probably also in the downstream microvasculature. Thus the platelet aggregates that plug the microcirculation not only cause mechanical obstruction but also lead to biochemical responses due to their interaction with the injured endothelium, the neutrophils, and more platelets. The release of vasoactive substances such as serotonin and endothelin-1 from the activated platelets and the injured endothelium lead to intense microvascular vasoconstriction, which accentuates the ischemic injury and resultant myonecrosis.[16,24]

One study of aspirin resistance emphasized the role of platelet aggregation in the pathophysiology of PMI. Patients deemed to be resistant to aspirin therapy were found to have a significantly higher incidence of PMI defined as any increase in CK-MB (51.7% vs. 24.6%, $P = .006$).[28] The odds of developing PMI in this cohort of 151 patients presenting for nonurgent PCI increased threefold if they were found to be aspirin resistant before the procedure.[28]

Periprocedural ST-Segment–Elevation Myocardial Infarction

A PCI-related infarction presenting with ST-segment elevation is caused by acute and total occlusion of a relatively sizable epicardial coronary branch. This is most commonly the result of abrupt closure of a branch or acute stent thrombosis. On occasion, embolization of large thrombus or atheroma may occlude the distal vessel and cause STEMI; such embolization is more common in degenerated SVG interventions than in native vessel interventions.

Other Pathophysiologic Mechanisms

Distal embolization of plaque debris and platelet activation, with all its local metabolic consequences, are probably the primary mechanisms leading to distal PMI in the absence of PCI complications such as side-branch closure or flow-limiting dissections. However, other intriguing mechanisms may interact with embolism and platelet activation. These

mechanisms have been suggested by analysis of coronary sinus blood samples obtained before and after PCI, thus reflecting the local metabolic derangements that result from the intervention. For instance, evidence of neutrophil activation is present in the coronary sinus samples after PCI as is an increase in serum levels of C-reactive protein (CRP) and interleukin 6 (IL-6). The increase in inflammatory marker levels was associated with post-PCI troponin release.[29] This demonstrates a local inflammatory response at the level of the myocardium in response to PCI and suggests a potential contribution to the process of myocyte damage.[16,29] Concentration of isoprostanes (stable end products of oxygen free radical–mediated lipid peroxidation) also increased in coronary sinus blood following PCI, which demonstrates an increase in oxygen free radical production during PCI.[30] The extent to which this inflammatory response and increased oxidative stress contribute to myonecrosis remains unclear.

RISK FACTORS PREDISPOSING TO PERIPROCEDURAL MYOCARDIAL INFARCTION

Clinical trials to examine the role of newer interventional devices, glycoprotein (GP) IIb/IIIa inhibitors, and/or newer anticoagulants—as well as large PCI registries—have provided significant insight into the incidence and significance of PMI. Based on these studies, certain subsets of patients have been identified to be at higher risk of PMI. These subsets can be identified based on clinical, lesion-related, procedural, or device-related variables.

Clinical Characteristics

The risk of PMI is significantly increased in patients with evidence of more severe atherosclerotic disease. Multivessel and/or more diffuse coronary artery disease (CAD) is associated with an approximately 50% increase in the relative risk of developing PMI.[9,12,31] IVUS evidence of increased plaque burden is also a risk factor for development of PMI,[23,25] which may explain why diabetics are at a higher risk.[32] Notably, evidence of advanced noncardiac atherosclerotic disease has been associated with an even higher relative risk of PMI.[31] Other patient risk factors such advanced age and preexisting renal dysfunction are probably indicative of more advanced atherosclerotic disease.

The clinical presentation at the time of PCI may also play a role in determining the risk of PMI and other adverse events during and after the procedure. Patients with ACSs are more likely to develop PMI.[16] However, studies to examine the incidence of PMI in this patient population have been limited by methodologic difficulties. First, it is more complex to define PMI when patients present with elevated markers before PCI; therefore most of the studies on this topic excluded these patients from the analysis. Second, even if patients with elevated markers are excluded, it is conceivable that those with negative markers who were referred to PCI within minutes to hours of presentation may have been having a spontaneous infarction that was only appreciated after the PCI.[12,16]

A heightened systemic inflammatory state before PCI is also a major predictor of adverse outcomes, which include PMI. Most of the evidence in support of this hypothesis has been based on correlations between pre-PCI CRP levels and evidence of PMI. A small study of 85 patients with stable angina undergoing PCI demonstrated that PMI, defined by an elevated troponin level, is significantly more frequent in patients with elevated CRP (46% of those with elevated CRP, but only 18% of those with a normal CRP, developed the complication).[33] Chew and colleagues[34] examined the relationship between preprocedural CRP and the adverse events (death and MI) in the first 30 days following PCI in a larger series of 727 consecutive patients. The highest quartile of CRP was predictive of worse outcome (odds ratio [OR], 3.68; 95% confidence interval [CI], 1.5 to 9.0) and that association persisted even after adjusting for other variables that influence outcome. The event-free survival curves separated within 24 hours and were primarily driven by a reduction in MI, suggesting that patients with elevated CRP are more susceptible to development of PMI (Fig. 29-3).

Lesion-Related Risk Factors

SVG lesions are notorious for the risk of development of PMI, probably as a result of the increased incidence of both macroembolization and microembolization with subsequent slow flow and no-reflow phenomenon. In the absence of an EPD, the risk of PMI (defined as CK-MB >3× ULN) in the contemporary era can be as high 13.7%. This rate almost doubles if the threshold cutoff value to define PMI is any increase in CK-MB.[35] The introduction of EPDs in the last few years has significantly reduced the risk of PMI in those patients.[35-37]

Several lesion characteristics are traditionally associated with a higher risk of PMI, primarily features suggestive of lesion instability such as eccentricity, irregular contour, or visible thrombosis. Complex lesions (ACC/AHA type C) usually contain one or more of those features and are thus associated with a significantly increased risk of PMI.[7,38] In a small study, the value of the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score in predicting PMI was assessed and compared with other lesion-scoring systems. This particular angiographic scoring system expressed lesion severity and complexity, which can be estimates of disease severity. Not surprisingly, increasing SYNTAX scores were associated with increased risk of PMI. Using receiver operator curve (ROC) analysis, a score of 17 or higher predicted PMI with a sensitivity of 75% and a specificity of 70%.[39]

Lesions that involve the ostium of a major side branch are usually among the more complex lesion types and are more prone to result in PMI because of the higher risk of side-branch closure. Other lesion characteristics that confer a higher risk of PMI include those features that suggest a higher plaque burden such as multiplicity of lesions, long lesions, and diffusely diseased arteries. Lesions with a larger necrotic core, as identified by IVUS and virtual histology (IVUS-VH) imaging, may confer a higher risk of PMI; this is because the necrotic core components include fragile tissues such as foam cells, organized intramural hemorrhage, and cholesterol crystals that may embolize and potentiate thrombosis.[40] In this study, embolization of small particles liberated during stenting was detected as high-intensity transient signals (HITS) with a Doppler guidewire (Fig. 29-4). Tanaka and associates[41] utilized optimal coherence tomography (OCT) to image the culprit plaques in NSTEMI patients undergoing PCI. Plaques with thinner caps (<70 μ) and larger lipid cores (>90 degree arc of the vessel

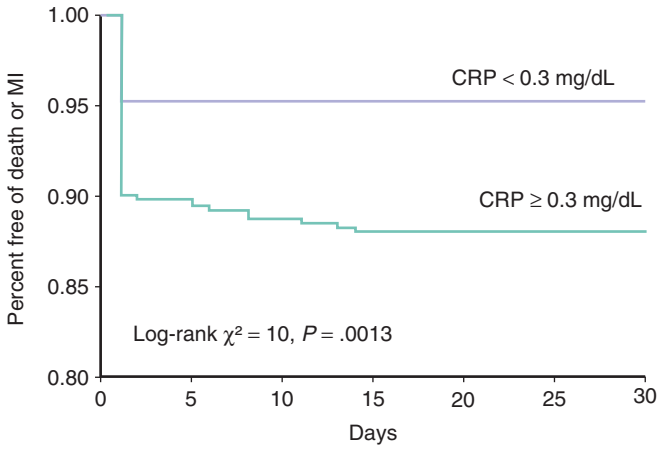


FIGURE 29-3 Kaplan-Meier survival curves for 30-day death or myocardial infarction (MI) stratified by baseline C-reactive protein (CRP). The majority of the events and the separation of the curves occur within the first one to two days; that is, the difference is primarily driven by the incidence of periprocedural myocardial infarction. (From Chew DP, Bhatt DL, Robbins MA, et al: Incremental prognostic value of elevated baseline C-reactive protein among established markers of risk in percutaneous coronary intervention, *Circulation* 104:992-997, 2001.)

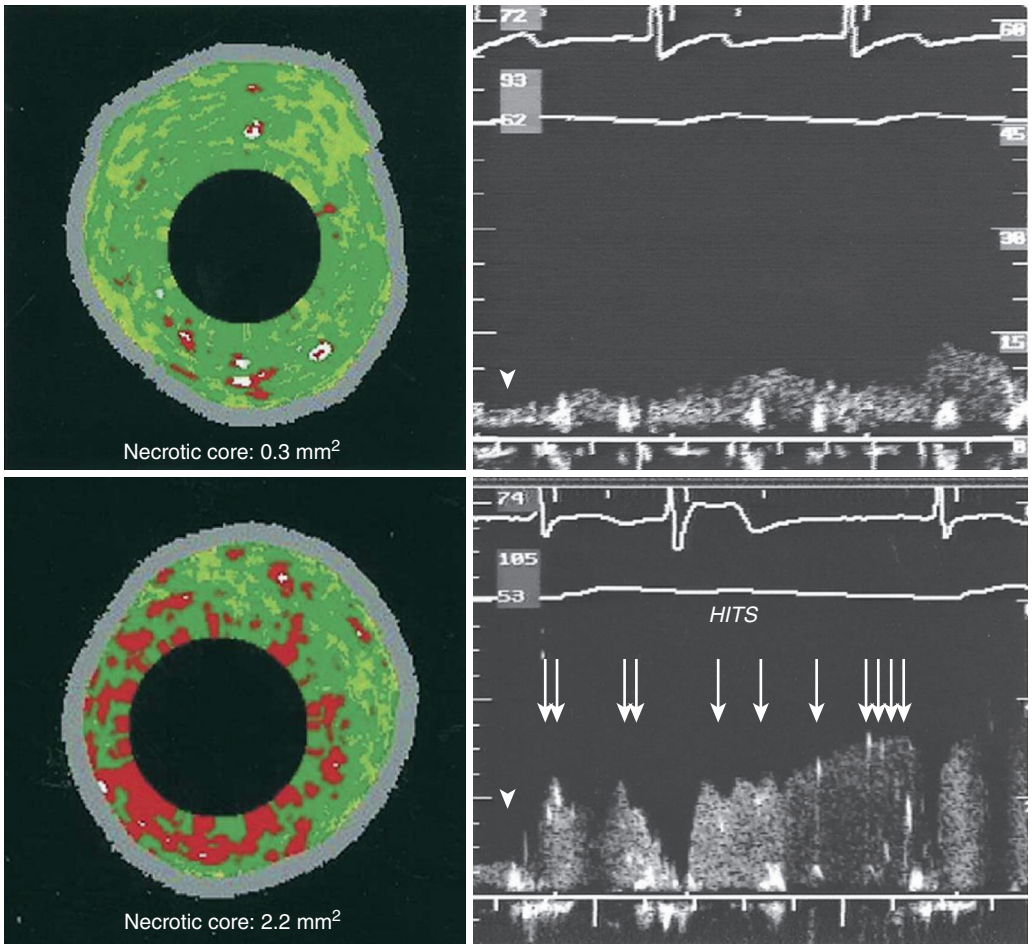


FIGURE 29-4 Plaques with a larger necrotic core, as identified by intravascular ultrasound and virtual histology (IVUS-VH) imaging, are more likely to cause distal embolization. The largely fibrotic plaque with minimal necrotic core (*top left*) results in minimal high-intensity transient signals (HITS; *top right*) detected by a Doppler wire placed distal to the lesion during stenting. Conversely, stenting of a plaque with a larger necrotic core (*bottom left*) results in significantly more HITS. (From Kawamoto T, Okura H, Koyama Y, et al: The relationship between coronary plaque characteristics and small embolic particles during coronary stent implantation. *J Am Coll Cardiol* 50:1635-1640, 2007.)

circumference) were more highly associated with periprocedural no-reflow phenomenon.

Procedural Complications and Risk of Periprocedural Myocardial Infarction

Side-branch occlusion, flow-limiting dissections, and transient abrupt closure have been the most recognizable procedural complications that result in relatively large PMIs.[7,9,38,42] However, these complications are rare, and most detected PMIs follow routine procedures with no obvious angiographic complications.[16,24] With universal availability of stents and their routine use, abrupt closure has become quite rare—fewer than 1% of cases in contemporary PCI.[24] The effectiveness of stenting and the availability of potent antiplatelet therapies are probably the primary mechanisms by which large (Q-wave) PMIs and need for emergent coronary surgery have been reduced by almost 50%.[21,43] Abrupt closure and no-reflow phenomenon have not been found to affect outcome when treated promptly, with no subsequent PMIs.[42]

SBO has been and remains the most common angiographically recognizable procedural complication to result in PMI.[7,9] Unlike abrupt closure, the incidence of SBO has not decreased with routine use of coronary stenting. In fact, with increasing stent use, SBO has become the most likely cause of acute occlusion during PCI.[44] SBO has been reported in 13% to 19% of cases in which a stent was placed across a major side branch (>1 mm), and most occur after poststent high-pressure dilation. Side branches that arise from within native coronary artery lesions are at a fivefold to tenfold higher risk for occlusion. Other predictors include branch ostial disease, branch artery size, and balloon/artery ratio. Proposed mechanisms for SBO include plaque shift (the so-called snowplow effect), branch artery ostial dissection or spasm, and/or thrombus formation.[45] A major SBO can be associated with large (possibly Q-wave) infarctions, but even smaller SBOs have been associated with evidence of small areas of MR hyperenhancement, diagnostic of small areas of PMI. The distribution of hyperenhancement in these cases is different from that seen with distal embolization downstream of the target lesion for PCI. With SBO, hyperenhancement is adjacent, rather than distal to, the location of the PCI. The likelihood of development of new hyperenhancement increases 16-fold when SBO can be angiographically recognized.[23]

Some intriguing observations have been made regarding SBO and PMI in the era of PCI for complex lesions using drug-eluting stents. In the Randomized Trial Evaluating Slow-Release Formulation TAXUS Paclitaxel-Eluting Coronary Stents to Treat De Novo Coronary Lesions (TAXUS V) trial, which randomized 1172 patients to receive a paclitaxel-eluting or a bare-metal stent, complex lesion subsets (>35% type C) were treated in both groups, and more than 30% of patients received more than one stent. In the subgroup of patients who received multiple stents, the incidence of 30-day MI was significantly higher

with paclitaxel-eluting stents (8.3% vs. 3.3%, $P = .047$). Core laboratory angiographic analysis of this patient subset revealed a significantly higher incidence of side-branch compromise or occlusion with paclitaxel-eluting stents than with bare-metal stents (42.6% vs. 30.6%, $P = .03$), resulting a higher incidence of less than TIMI grade 3 flow in the paclitaxel-eluting stent group. Why paclitaxel-eluting stents are associated with more side-branch compromise and subsequent PMI remains unclear. Possible explanations include the increasing thickness of the stent struts caused by the drug-eluting polymer, increased platelet deposition, and/or paclitaxel-induced spasm.[46] A comparison of paclitaxel- and everolimus-eluting stents demonstrates the importance of the strut and polymer thickness. A post-hoc analysis of the Clinical Evaluation of the Investigational Device XIENCE V Everolimus-Eluting Coronary Stent System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions (SPIRIT III) randomized trial[47] compared the incidence of PMI in 113 patients who received the thinner strut and thinner polymer everolimus-eluting stent to 63 patients who received the paclitaxel-eluting stent, in whom a small side branch was "jailed" by the deployed stent. PMI defined as any increase in CK-MB above the ULN was much lower in the everolimus-eluting stent group (9.0% vs. 29.7%, $P = .01$).

Risk of Periprocedural Myocardial Infarction by Interventional Device

Some of the earliest investigations to spark interest in PMI and its significance were in the context of comparing newer interventional devices to standard balloon angioplasty. Data from the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT-I) demonstrated that directional coronary atherectomy (DCA) was associated with more abrupt closure, evidence of PMI, and subsequently a higher rate of clinical adverse events compared with balloon angioplasty.[6,48] These findings were confirmed in the Balloon Versus Optimal Atherectomy Trial (BOAT), in which a more refined technique of DCA was supposed to demonstrate its superiority to percutaneous transluminal coronary angioplasty (PTCA). However, the incidence of PMI was still significantly higher with DCA than with PTCA (16% vs. 6%).[49] DCA is associated with more distal embolization, particularly in SVG interventions.[50] There is also evidence of a higher degree of platelet activation with DCA,[51] with its subsequent mechanical obstruction and thrombotic and inflammatory responses in the downstream microcirculation. Similarly, owing to its mechanism of action, rotational atherectomy is associated with more platelet activation and more distal embolization of plaque debris than balloon angioplasty.[52]

Although the routine use of coronary stents has dramatically reduced the incidence of most PCI complications—such as abrupt closure, flow-limiting dissections, need for emergent bypass surgery, and restenosis—stenting increases the incidence of PMI compared with balloon angioplasty, with a relative risk increase of about 20%.[16,24,53] In patients who underwent PCI of the left anterior descending coronary artery (LAD) and were randomly assigned to balloon angioplasty or stenting, evidence was found of a higher degree of platelet and neutrophil surface activation after stenting.[54] High-pressure inflations aiming to overexpand stents and reduce restenosis can actually lead to higher CK-MB levels. In a study of approximately 1000 patients undergoing IVUS-guided stenting, the incidence of PMI (defined as CK-MB 3× ULN) was 16%, 18%, and 25% in three groups of patients, in whom the final stent/reference lumen area was less than 70%, 70% to 100%, and greater than 100%, respectively.[55] Increasing stent length was also associated with increased biomarker release in a smaller study of patients who underwent elective PCI.[56]

PROGNOSTIC IMPLICATIONS OF PERIPROCEDURAL MYOCARDIAL INFARCTION

Although much controversy surrounds the definition and prevalence of PMI with everyday PCI, there is no dispute that significant PMI is associated with an increased mortality risk. Controversy still exists about the pathophysiologic mechanisms that underlie this association and also the definition and size of PMI that would confer such increased risk. However, convincing evidence suggests that any PMI is associated with some degree of increased risk of death, particularly with longer follow-up durations.

The pioneering work of Abdelmeguid and coworkers[7] demonstrated that CK and CK-MB elevation after PCI (primarily balloon angioplasty and DCA in this report) are associated with an approximate 30% relative increase in 3-year mortality. Three-year follow-up of the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial patients, who underwent angioplasty and DCA as well, revealed an incremental long-term risk of death with increasing degrees of PMI. Among the 2001 patients enrolled in the trial, the mortality risk increased from 7.3% in those with no CK elevation to 13.1% when CK was greater than three times the ULN and again to 16.5% with CK greater than 10 times the ULN.[57] In the EPISTENT trial, in which stenting was routinely used in two thirds of the patients, the 1-year mortality doubled between patients with minimal to no PMI (CK-MB >1× ULN) to those with CK-MB greater than three to ten times the ULN (1.5% vs. 3.4%).[22] Subsequently, similar conclusions were made by examining outcomes of patients enrolled in PCI clinical trials and large-scale single-center patient registries (see Table 29-2).[6,8,9,12,22,58]

Although the association between PMI and mortality has not been disputed, the mechanisms that can explain this association are not clear. The magnitude of myonecrosis is limited, but it may provide a nidus for arrhythmogenesis. On the other hand, it has been suggested that the association between PMI and late mortality merely represents a reflection of increased risk in a group of patients with more advanced disease.[5] The latter hypothesis can be criticized by the fact that aggressive preprocedural platelet inhibition (by thienopyridine pretreatment or IV GP IIb/IIIa inhibitors) reduces PMI and subsequent risk of death and adverse events, suggesting that this is a modifiable risk.

The threshold above which a PMI is considered prognostically significant has been a subject of some debate. It has been traditional to consider a PMI when the CK-MB exceeds three times the ULN, although the recent PCI guidelines suggest CK-MB greater than five times the ULN should be the threshold for defining a PMI.[59] In the large series of Ghazzal and colleagues,[9] minor elevation of total CK (<3× ULN) did not confer a statistically significant increase in risk of late mortality. Brener and coworkers[60] suggested that only massive CK-MB release (>10× ULN) predicts an increased risk of death over a 3-year period. However, strong evidence shows that smaller CK-MB elevations are associated with increasing risk of death. Abdelmeguid and colleagues[7] examined that question specifically and concluded that any increase in CK-MB above normal limits confers some degree of risk. In a later meta-analysis, any increase in CK-MB, even less than three times the ULN, was associated with a statistically significant increase in the risk of death (OR 1.5). Patients with a CK-MB level three to five times the ULN and those with levels more than five times the ULN had an even higher relative risk of dying over the 3-year follow-up.[11] Similarly, in the large meta-analysis by Roe and colleagues,[12] the increased mortality risk was associated with increasing CK-MB expressed as a continuous variable—that is, with no specific thresholds above or below which the risk changes (Fig. 29-5). A more recent analysis of 5268 patients undergoing elective PCI, using both troponin T and CK-MB postprocedure levels, demonstrated an association of the elevated biomarker levels with 3-month mortality. The optimal thresholds that predicted mortality in this analysis were troponin T greater than 25 times the ULN and CK-MB greater than five times the ULN.[61]

Frequently, very large PMIs (i.e., CK-MB levels > 8 to 10× ULN) are associated with significant complications or an unsuccessful procedural result. The association between PMI and mortality has been attributed to the impact of an unsuccessful procedure on mortality and not to an independent effect. In a study of approximately 6000 patients, the incidence of PMI was three times more frequent when the procedure was unsuccessful, and the size of the infarction was also significantly larger. After adjusting for the success of the procedure—defined

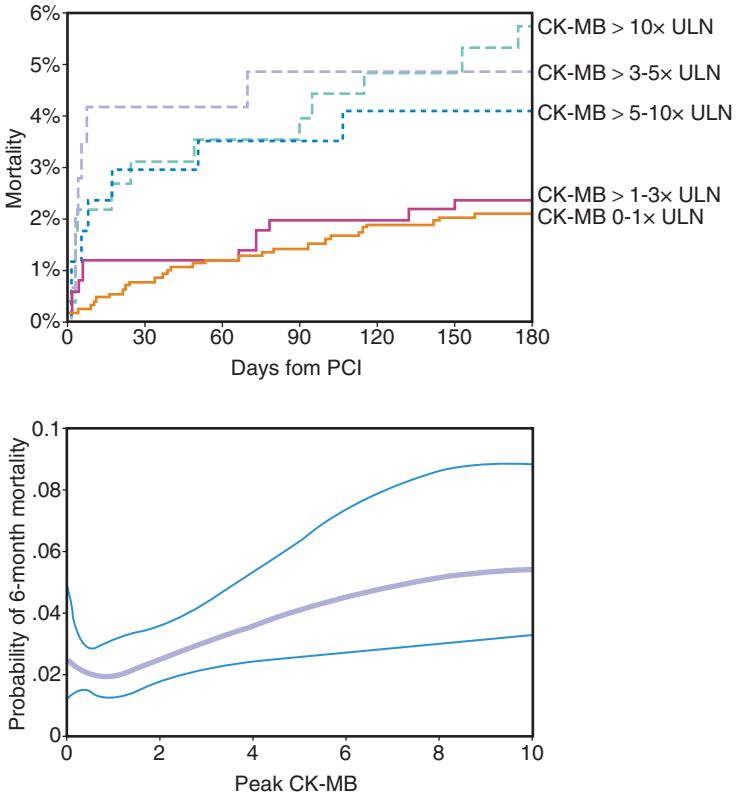


FIGURE 29-5 *Top:* Kaplan-Meier curves for 6-month unadjusted mortality after percutaneous coronary intervention (PCI) for increments of post-PCI creatine kinase MB (CK-MB). *Bottom:* Continuous unadjusted relationship between peak CK-MB (expressed as times the upper limit of normal [×ULN]) and 6 months mortality. The thin or blue lines represent the 95% confidence intervals. (From Roe MT, Mahaffey KW, Kilaru R, et al: Creatine kinase-MB elevation after percutaneous coronary intervention predicts adverse outcomes in patients with acute coronary syndromes. *Eur Heart J* 25:313-321, 2004.)

as residual stenosis of less than 50%, achievement of TIMI grade 3 flow, absence of significant residual dissection, no need for urgent revascularization, and no stent thrombosis within 24 hours—the presence or absence of PMI was not statistically related to 1-year mortality.[62] However, the study only examined 1-year mortality, and in many investigations that have examined PMI, the effect on mortality was observed with longer-term follow-up. In addition, the initial studies by Abdelmeguid and colleagues[7,38] that established a relationship between PMI and death have excluded unsuccessful procedural results from their analyses. In the recent CK-MB and PCI study[18] to examine the significance of post-PCI troponin elevation, unsuccessful procedures doubled the odds of 2-year mortality; yet the effect of post-PCI CK-MB levels remained a strong and significant predictor of mortality.

The association between mortality and PMI defined by elevated serum troponin levels has been studied, although less extensively. The updated PCI guidelines propose that a PMI becomes clinically significant if the troponin level exceeds five times the ULN. In a study of 1157 patients (>77% receiving stents), 1-year mortality risk increased only in the group of patients with troponin I levels eight or more times the ULN (≥16 ng/mL).[20] However, in a large multicenter prospective study of almost 3500 patients that addressed the significance of post-PCI troponin levels, a statistically significant association was found between troponin I elevation and 2-year mortality. As expected, the incidence of troponin I elevation after PCI was significantly higher than that of CK-MB, indicating the higher sensitivity of troponin I in detecting myonecrosis. Yet this high sensitivity appears to reduce the ability of troponin elevation to predict prognosis.[18] As for troponin T, a threshold of greater than 25 times the ULN appears similar to a CK-MB threshold of five times the ULN in predicting 90-day mortality.[61]

A contemporary analysis on the prognostic significance of PMI in patients from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial suggests that PMI is a marker of baseline risk, atherosclerosis burden, and procedural complexity but in most cases does not appear to have independent prognostic significance. In this analysis of the 1-year follow up of the ACUITY patients, development of a spontaneous MI was significantly associated with mortality, whereas a postprocedural MI was not.[63]

PREVENTION AND MANAGEMENT OF PERIPROCEDURAL MYOCARDIAL INFARCTION

In the majority of cases of PMI, the event is clinically silent and the diagnosis is made on the basis of routine collection of cardiac biomarkers after PCI. Therefore little can be done to treat the event by any specific measures different from those that should be used with any patient undergoing PCI—that is, effective beta-blockade, antiplatelet therapy, lipid lowering, and aggressive risk-factor control. During the procedure, recognition of a side-branch closure usually prompts an attempt at restoration of flow in that branch by balloon angioplasty and stenting if necessary. If distal embolization of thrombus is seen to impair distal flow, aspiration thrombectomy and/or intracoronary (IC) fibrinolytic therapy may improve flow. Embolization of atheromatous debris is not likely to respond to pharmacologic agents.[64] IC injection of vasodilators such as nitroglycerin, calcium channel blockers, nitroprusside, or adenosine can also improve flow by relieving arteriolar spasm and recruiting a larger microvascular bed. Whereas these maneuvers can improve epicardial flow, it is not clear whether they will impact the size or the prognostic significance of the PMI.[65,66] After the procedure, and in the event of a relatively large PMI (e.g., CK-MB ≥ 5× ULN), an additional day of telemetry monitoring and more adequate beta-blockade (with a target heart rate of about 60 beats/min) may be indicated.

Given the adverse prognostic implications, it is significantly more important to develop strategies to prevent, rather than treat, PMI. Successful strategies to prevent PMI include pharmacologic and nonpharmacologic approaches. The primary pharmacologic interventions that have achieved significant success include aggressive antiplatelet therapy (primarily IV GP IIb/IIIa inhibitors and oral thienopyridine

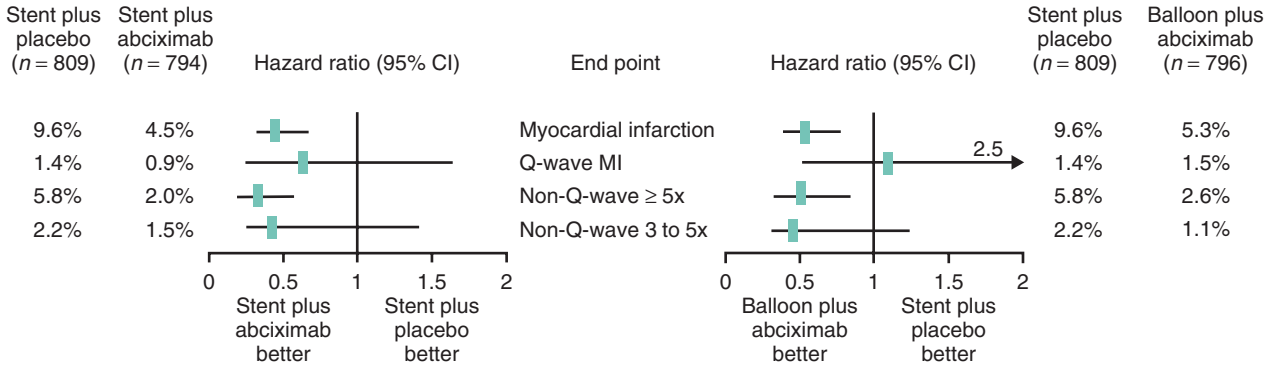


FIGURE 29-6 Kaplan-Meier estimates and hazard ratios (95% confidence interval [CI]) for myocardial infarction in the EPISTENT trial. (From the EPISTENT investigators: Randomized placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting [EPISTENT]. *Lancet* 352: 87-92, 1998.)

inhibitors) and statin therapy. Nonpharmacologic approaches include the use of EPDs in the setting of SVG intervention. Collectively, these therapies are integrated to prevent or at least reduce distal embolization and to protect the myocardium.

Intravenous Glycoprotein IIb/IIIa Platelet Inhibitors

Periprocedural utilization of GP IIb/IIIa platelet inhibitors provides immediate and near-complete inhibition of platelet aggregation. The IV administration of the appropriate doses and the targeting of the final common receptor for the aggregation process (the GP IIb/IIIa receptor) ensure both an extremely high bioavailability and a very predictable and complete response. Abciximab, the prototype of this class of antiplatelet agents, has been shown in multiple clinical trials to reduce the incidence of post-PCI myonecrosis. In the seminal trials (EPIC, Evaluation in PTCA to Improve Long-Term Outcome With Abciximab GP IIb/IIIa Blockade [EPILOG], and EPISTENT), the cutoff for defining PMI was CK-MB levels three times the ULN. The relative risk reduction in MI at 30 days ranged between 40% and 60%, with the curves separating as early as the first day, thus indicating a significant reduction in PMI.[37,67] In EPISTENT, administration of abciximab significantly reduced the risk of a larger PMI (CK-MB >5× ULN) irrespective of the device used, stent or balloon angioplasty (Fig. 29-6).[22] In the c7E3 FAB Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial,[68] refractory unstable angina patients were randomized to receive abciximab or placebo many hours before and during PCI. In this trial, the incidence of MI in the hours before undergoing PCI was reduced significantly in the abciximab arm. Additionally, the incidence of PMI was reduced by more than 50% in the abciximab arm (2.6% vs. 5.5%, $P = .009$). With rotational atherectomy, which consistently results in distal microembolization, abciximab bolus and infusion demonstrated a significant advantage over anticoagulation alone in reducing postprocedural CK and CK-MB rise.[52]

Similar effects have been demonstrated with the synthetic small-molecule GP IIb/IIIa inhibitors, eptifibatide and tirofiban. The impact of eptifibatide on PMI was significantly better when the dosing regimen was adjusted from one bolus in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) PCI trial[69] to the double-bolus regimen followed in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial,[70] thus emphasizing the importance of the near-complete inhibition required if an impact on distal embolization is to be expected. In the PURSUIT trial, the incidence of PMI was reduced by 25%, whereas the reduction with the double-bolus regimen was 40%. In both trials, PMI was defined as CK-MB greater than three times the ULN, and the incidence of PMI in the placebo group was very similar in both trials—about 9%. Similarly, in the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE),[71] which examined the role of tirofiban in patients with ACSs, a small but significant reduction was seen in PMI at the 48-hour mark. However, no statistically significant difference was seen in the incidence of the primary end point (30-day death, MI, or revascularization for recurrent ischemia and use of stents for threatened or abrupt closure) between tirofiban and placebo. With the higher-dose tirofiban bolus, a small study of 202 high-risk patients undergoing PCI demonstrated that PMI defined by troponin rise decreased by about 34% and average CK-MB level (expressed in absolute units) was reduced by more than 50%.[72]

Direct Thrombin Inhibitors (Bivalirudin)

Although it has been clearly established that intensive platelet inhibition does result in reduced PMI, concern has been raised about excess bleeding risk caused by such strategies. Recent focus on bleeding complications demonstrates a significant adverse prognostic implication to periprocedural bleeding on outcome, with convincing evidence of increased 1-year mortality in patients who suffer an early bleeding complication.[73] This recognition has encouraged the use of the direct thrombin inhibitor bivalirudin as the primary anticoagulant during PCI over the last several years. Large trials to compare bivalirudin with a combination of heparin and GP IIb/IIIa inhibitors demonstrated noninferiority of bivalirudin in reducing PMI and its clear superiority in reducing bleeding complications. It thus seems to strike a reasonable balance between reducing PMI and other ischemic complications without paying a price in the form of excess bleeding. In the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial, which examined the role of bivalirudin in low-risk PCI patients, the incidence of PMI was slightly higher, but not statistically significant, in the bivalirudin arm: 7.0% compared with 6.2% in the control arm of heparin and GP IIb/IIIa inhibitors.[74] In another large randomized trial of over 4500 low-risk PCI patients (those with stable clinical presentations), bivalirudin therapy was compared with unfractionated heparin, and both groups were preloaded with oral aspirin and clopidogrel. Neither anticoagulant strategy was superior in reducing ischemic complications (PMI 5.6% with bivalirudin vs. 4.8% with heparin), but bleeding complications were reduced in the bivalirudin arm (3.1% vs. 4.6%, $P = .008$).[75]

In the ACUITY trial, approximately 14,000 ACS patients treated with an early invasive strategy were randomized to one of three antithrombotic regimens: heparin plus a GP IIb/IIIa inhibitor; bivalirudin plus a GP IIb/IIIa inhibitor; or bivalirudin alone. Comparing those who received heparin and GP IIb/IIIa inhibitors to those who received bivalirudin alone, no difference was found in ischemic events, but bleeding complications were reduced by almost 50% at 30 days (5.7% vs. 3.0%, $P < .001$ for noninferiority, $P < .001$ for superiority of bivalirudin).[76]

In a prespecified analysis, the outcomes of the 7789 ACUITY patients who underwent PCI were analyzed according to the anticoagulation regimen they received. The results mirrored those of the main trial: no difference was found in PMI or other ischemic events, but a statistically significant reduction in bleeding complications was noted, leading to improved net clinical benefit in favor of bivalirudin alone. A post-hoc analysis of this subset demonstrated an important interaction between clopidogrel pretreatment and the choice of anticoagulant strategy. Of the 7789 PCI patients, 129 did not receive any clopidogrel, and 3493 received clopidogrel before angiography, 1572 at the time of PCI and 814 after PCI. Patients who received clopidogrel before angiography or within 30 minutes of PCI had similar ischemic complications, whether they were randomized to bivalirudin or heparin and GP IIb/IIIa inhibitors. However, when clopidogrel was not given, or when it was given more than 30 minutes after PCI, those randomized to bivalirudin experienced a higher incidence of ischemic events, mostly in the form of PMI (14.1% vs. 8.5%; risk ratio [RR], 1.7; 95% CI, 1.05 to 2.63).[77] This interaction between timing of clopidogrel therapy and bivalirudin use emphasizes the need for an effective antiplatelet therapy when direct thrombin inhibitors are used during PCI.

$P2Y_{12}$ Platelet Inhibitors

The proven benefit of IIb/IIIa platelet inhibitors in reducing PMI further supports the central role of platelet aggregation/activation in the pathophysiology of PMI. This is also further emphasized by the very high incidence of PMI and other adverse cardiac events in patients with aspirin resistance. Thus dual-antiplatelet therapy (DAPT) at the time of PCI has been advocated. The timing and dosing of these agents seems to have a significant impact on PMI and other post-PCI adverse events. Steinhubl and colleagues[78] reported a significant reduction in the incidence of PMI with pre-PCI administration of ticlopidine. The longer the duration of therapy, the lower the incidence was; and among patients pretreated with ticlopidine, the odds ratio for development of PMI was 0.18 when the duration of pretreatment was 3 or more days. Subsequently, the questions of dosing and duration of pretreatment with another thienopyridine inhibitor, clopidogrel, were addressed in the Clopidogrel for Reduction of Events During Observation (CREDO) trial. The study randomized patients undergoing elective PCI to receive a 300-mg clopidogrel loading dose or placebo 3 to 24 hours before PCI. All patients were taking aspirin, and most of them did undergo PCI. A second randomization to 28 days versus 9 months of DAPT was performed for those in the clopidogrel arm. The results demonstrated a reduction in 30-day major adverse events (primarily early MIs) only in patients who received the loading dose 6 or more hours before PCI (Fig. 29-7).[79] Thus the timing of the loading dose significantly impacted the beneficial effect of thienopyridine on PCI outcomes. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, 30% of patients underwent PCI at the discretion of the treating cardiologists. This PCI subgroup included 2658 patients with NSTEMI from non-U.S. centers where the time between admission for ACS and PCI averaged 10 days. In this setting, the 30-day incidence of MI was reduced by more than 50% in patients who received clopidogrel (2.9% vs. 6.2%), suggesting that a longer duration of pretreatment, particularly in high-risk patients, is associated with better protection against procedure-related MI.[80]

Several groups have demonstrated that a higher loading dose (600 mg) of clopidogrel can achieve two important goals: it can reach higher levels of platelet inhibition and can achieve that target within 2 hours of oral administration.[81] The improved efficacy of the higher loading dose is at least partly attributed to the fact that about one third of patients do not adequately respond to the inhibitory effect of the 300 mg dose.[81] The Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA-2) trial established the superiority of the 600-mg loading dose of clopidogrel in reducing PMI and improving 30-day outcomes. This study enrolled 255 patients undergoing PCI and randomized them to 300-mg versus 600-mg loading doses of clopidogrel 4 to 8 hours before PCI. The primary end point of death, MI, or urgent revascularization at 30 days was reduced by 66% in the high-loading-dose arm (4% vs. 12%, P =.04). The benefit was almost entirely due to the marked reduction in PMI; a reduction of approximately 50% in a multivariate model adjusting for all variables that influence the incidence of PMI (OR, 0.48; 95% CI, 0.15 to 0.97; P = .044).[82] It remains controversial whether a higher loading dose of clopidogrel (900 mg) can lead to further improvement in PMI and other ischemic complications.[83,84]

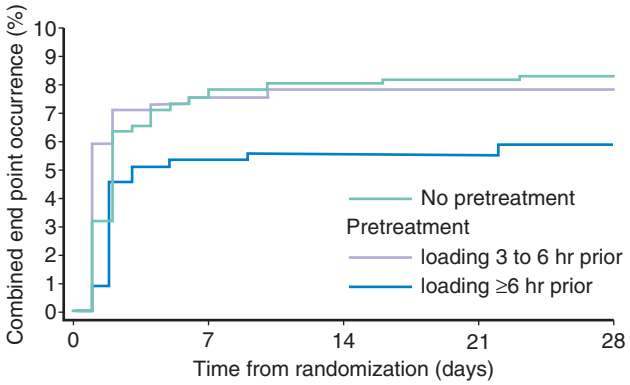


FIGURE 29-7 The 28-day combined end point (death, myocardial infarction, urgent revascularization) in the CREDO trial, stratified by use and timing of clopidogrel loading dose. The curves separate within 48 hours, primarily because of differences in incidence of periprocedural myocardial infarction. (From Steinhubl SR, Berger PB, Mann JT 3rd, et al: Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial, *JAMA* 288:2411-2420, 2002.)

The main criticism of the routine clopidogrel preloading strategy in patients undergoing coronary angiography is that a fraction of the patients will be referred to bypass surgery; these patients will have an increased risk of bleeding unless their bypass surgery is postponed for at least 5 days. Thus the Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty (ARMYDA)-5 PRELOAD trial tested the strategy of high-dose clopidogrel loading in the catheterization laboratory against high-dose preloading that was previously established. In this trial, 409 patients were randomized to receive a 600-mg preloading dose 4 to 8 hours before PCI or a 600-mg loading dose in the catheterization laboratory after obtaining diagnostic angiograms. The study revealed no difference in incidence of PMI between the two strategies (8.8% in laboratory vs. 9.3% preload groups, P = .99).[85] Point-of-care testing demonstrated that platelet reactivity remained high during the PCI and for the 2 hours that followed in patients treated in the catheterization laboratory, which is not consistent with the previously established association between better platelet inhibition and reduced incidence of PMI. The study was also criticized for the small sample size, which makes it underpowered to detect a difference between the groups.[86]

As the evidence for the effective platelet inhibition caused by clopidogrel mounted, questions arose regarding the need for the more expensive IV GP IIb/IIIa inhibitors in PCI. In sequential investigations, the Intracoronary Stenting and Antithrombotic Regimen Rapid Early Action for Coronary Treatment (ISAR-REACT) trials, the interaction between clopidogrel loading and abciximab infusion for peri-PCI platelet inhibition was examined in low-risk and then in higher-risk patient populations. In ISAR-REACT 1, more than 1000 stable patients were randomized to receive clopidogrel loading plus placebo versus clopidogrel loading plus abciximab bolus and infusion. At 30 days, no statistically significant difference was found between the two groups in the incidence of MI or death.[87] However, the very low incidence of adverse events in the placebo group diminished the statistical power of the study to detect differences between the groups. In the following

study, ISAR-REACT 2, more than 2000 patients with non–ST-segment–elevation ACSs were enrolled. All patients received clopidogrel pretreatment, and then half of them were randomized to abciximab bolus plus infusion. Unlike ISAR-REACT 1, a significant reduction was seen in the 30-day composite end point in favor of abciximab. This included more than a 20% reduction in infarctions, most of which were PMIs (8.1% vs. 10.5%). Based on the results of those two investigations, it seems that a more complete degree of platelet inhibition is needed in patients at higher risk of PMI and procedural complications. In addition to the more complete platelet inhibition ensured by the use of abciximab, its cross reactivity with αVβ3 (vitronectin) and αMβ2 (Mac-1) receptors may provide potent antiinflammatory effects. This appears to be associated with a significant reduction in the degree of rise of inflammatory markers such as CRP, IL-6, and tumor necrosis factor alpha (TNF-α) in the 1 to 2 days following PCI, an effect that may contribute to the reduction in PMI seen with abciximab use during PCI.[88]

The association of more effective platelet inhibition and improved outcomes in patients with ACS treated invasively has been further supported by results of clinical trials comparing prasugrel and ticagrelor to clopidogrel. Although the incidence of PMI was not directly reported, both agents were associated with a statistically significant lower incidence of ischemic events in the early phase after PCI, which are typically driven by periprocedural events.[89-91]

Cangrelor (AR-C69931MX) is a direct-acting and reversible intravenous $P2Y_{12}$ receptor antagonist. Cangrelor achieves almost complete and immediate inhibition of ADP-induced platelet aggregation when administered as a bolus. The plasma half-life is approximately 3 to 5 minutes, and platelet function is restored within an hour after cessation of infusion. The use of cangrelor in patients undergoing PCI was studied in two phase III trials, the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PCI and CHAMPION PLATFORM studies.[92,93] Cangrelor was not associated with a significant reduction in the primary efficacy end point in either of these trials but was associated with reductions in secondary end points, including the rate of stent thrombosis, with no excess in severe bleeding. The prospective, double-blind, active-controlled clinical trial Cangrelor versus standard therapy to achieve optimal Management of Platelet InhibitiON (CHAMPION PHOENIX)[94] was designed to evaluate prospectively whether cangrelor does indeed reduce ischemic complications of PCI. The modified intention-to-treat population comprised 10,942 patients, approximately 44% of whom presented with an ACS. Compared with those who received clopidogrel immediately before or after PCI, cangrelor—administered as an IV bolus and an infusion for 2 hours or for the duration of the procedure, whichever was longer—significantly reduced the rate of periprocedural complications of PCI, including stent thrombosis. A reduction in the rate of acute PMI accounted for most of the benefit. Importantly, the incidence of major bleeding or need for transfusion were not significantly different between the groups.[94] A pooled analysis of all three randomized trials of cangrelor demonstrated a significant reduction in major adverse cardiac events (MACEs, mostly PMI) by 19% and stent thrombosis by 41% at 48 hours after PCI.[95] Despite these findings, the Food and Drug Administration (FDA) advisory panel voted against the approval of the drug because of concerns regarding conflicting trial results and whether the risk/benefit profile was acceptable.

Impact of Statin Therapy

The inflammatory response of distal embolization and platelet aggregate interaction with leukocytes contributes to the degree of myonecrosis that is frequently seen after PCI. The observations made in PCI registries demonstrated a reduction in PMI in patients who were receiving statins at the time of their PCI.[96] Proposed mechanisms that can explain this finding include an antiinflammatory effect and the ability of statins to enhance nitric oxide production.[97] In an analysis of 803 patients undergoing rotational atherectomy, the incidence of any myonecrosis was reduced by statin therapy from 52% to 24%, and the incidence of PMI (CK-MB ≥ 3× ULN) was reduced from 22% to 7.5%.[98] These observations were eventually confirmed in two prospective randomized trials. In both trials, statin therapy was started several days before scheduled PCI in the active therapy arm. In one report on 451 patients, statin therapy was not restricted to any specific agents. Median post-PCI troponin level was 0.13 ng/mL in the statin group and 0.21 ng/mL in the control group ($P = .03$). Similarly, the incidence of troponin I more than five times the ULN was significantly reduced with statin therapy (23.5% vs. 32% in the control group, $P = .04$).[99] In the similarly designed Atorvastatin for Reduction of Myocardial Damage During Angioplasty (ARMYDA) trial, a smaller number of stable angina patients were randomized to receive atorvastatin versus placebo. A greater than 50% reduction was reported in incidence of PMI, as measured by CK-MB, troponin I, or myoglobin in the atorvastatin group.[100] In ARMYDA-2, an incremental benefit of statin and high-dose loading clopidogrel was found that led to a more impressive 80% reduction in PMI.[82]

A subgroup analysis of the ARMYDA trial confirms the antiinflammatory role of statins in reducing myonecrosis after PCI. In 138 patients, serum levels of adhesion molecules—intracellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), and e-selectin—were similar in patients in the atorvastatin group and the placebo group before PCI. Yet after PCI, the rise in ICAM and e-selectin were significantly attenuated with atorvastatin therapy. This attenuated rise in adhesion molecules paralleled the protective effect against myonecrosis, providing some evidence that the antiinflammatory effect of statins contributes to their observed protective effect against myonecrosis and early mortality, which cannot be attributed to its HMG-CoA reductase inhibitory effect.[101]

The impact of high-dose statin therapy can be demonstrated within days, confirming the existence of mechanisms of action other than lipid lowering. The Novel Approaches for Preventing or Limiting Events (Naples II) trial[102] recently reported that a single, high (80 mg) loading dose (within 24 h) of atorvastatin reduces the incidence of PMI in elective PCI. The incidence of PMI was 9.5% in the atorvastatin group and 15.8% in the control group (OR, 0.56; 95% CI, 0.35 to 0.89; $P = .014$).

Because most patients undergoing PCI are already on statins, the question of pretreatments seemed irrelevant. However, pleiotropic and antiinflammatory effects of statins seem to diminish with time. The Atorvastatin for Reduction of Myocardial Damage During Angioplasty–Acute Coronary Syndromes (ARMYDA-RECAPTURE) clinical trial[103] randomized more than 380 patients undergoing PCI to an intensive "reloading" of atorvastatin (80 mg 12 h before and 40 mg immediately before PCI) and a standard therapy group (standard daily dose of atorvastatin). All patients were pretreated with clopidogrel and aspirin. At 30 days, a significant reduction was observed in the composite end point in favor of atorvastatin reloading. The incidence of any postprocedure elevation in CK-MB and troponin was significantly lower in the reloading group (13% vs. 24%, $P = .017$, and 37% vs. 49%, $P = .021$, respectively). Similar to observations made with abciximab, the benefit of intensive atorvastatin therapy was restricted to patients who presented with ACS, probably because of the higher underlying risk of PMI. A meta-analysis of 14 randomized controlled trials including at total of 3146 patients with stable angina and NSTEMI noted that statin loading before PCI was associated with a 56% relative reduction in PMI (OR, 0.44; 95% CI, 0.35 to 0.56; $P < .00001$). The reduction in PMI was statistically significant regardless of the clinical presentation (Fig. 29-8).[104]

Other Pharmacologic Interventions

Controversy still exists about the role of preprocedural beta-blocker therapy and PMI. Evidence suggests that beta-blockade has a favorable impact on survival after PCI. Ellis and coworkers[105] supported this finding in a study of 6200 patients undergoing PCI, concluding that beta-blocker therapy improved survival in the post-PCI patients.

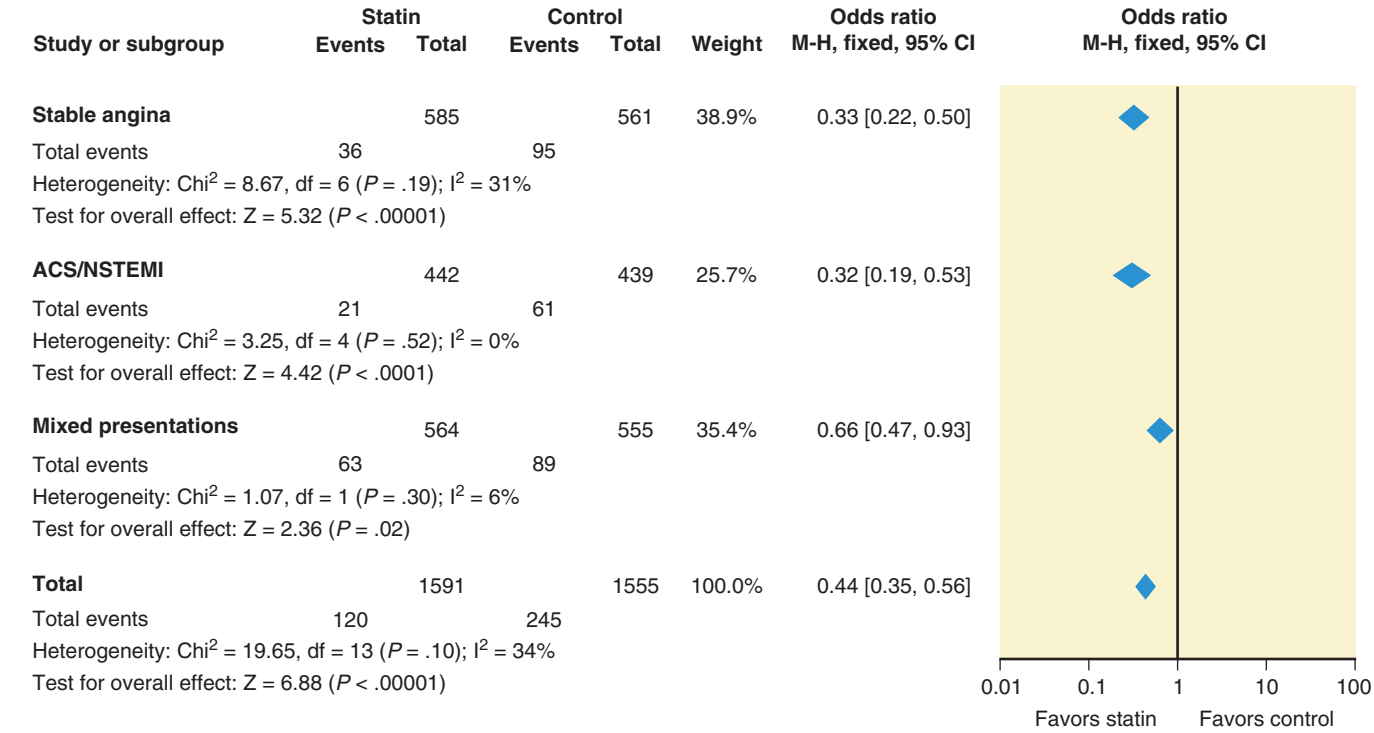


FIGURE 29-8 Impact of statin therapy on periprocedural myocardial infarction (PMI). Odds ratios of PMI in patients loaded with a statin before percutaneous coronary intervention (PCI) are compared with patients treated with statin therapy only after PCI. The figure depicts the results for the overall meta-analysis and the results for the trials that enrolled patients with stable angina, acute coronary syndrome (ACS), and a mixed population of patients. *CI,* Confidence interval; *df,* degrees of freedom; I^2, a measure of heterogeneity; *M-H,* Mantel-Haenszel method; *NSTEMI,* non-ST–elevation myocardial infarction; *Z,* Z score. (From Benjo AM, El-Hayek GE, Messerli F, et al: High-dose statin loading prior to percutaneous coronary intervention decreases cardiovascular events: a meta-analysis of randomized controlled trials. *Catheter Cardiovasc Interv* 85:53-60, 2015.)

However, after adjustment for multiple variables and using propensity analysis, no evidence suggested that patients with beta-blocker therapy had reduced risk or reduced size of PMI.

Adenosine administered via an IC or IV route produces a hyperemic effect and pharmacologically mimics preconditioning. A small randomized trial of 62 patients undergoing nonurgent PCI noted a reduction in PMI in patients randomized to receiving a 50 µg bolus of IC adenosine via the guiding catheter and before wire passage.[106] Larger trials are needed to confirm this potential benefit.

Trimetazidine, a piperazine derivative antianginal agent, exerts a significant vasodilatory effect and improves myocardial glucose utilization through inhibition of fatty acid metabolism. Given its cardioprotective benefits, it has been evaluated in a periprocedural context as well. A placebo-controlled study that randomized 266 patients to a loading dose of trimetazidine 30 minutes before PCI demonstrated a significant reduction in troponin I area under the curve, indicating reduced myonecrosis.[107] Based on these results, a larger study may be justifiable.

Nonpharmacologic Approaches

Very few mechanical options to prevent PMI are currently available. Direct stenting (without balloon predilation) was proposed to reduce plaque trauma and distal embolization. A small randomized study compared direct stenting to conventional predilation followed by stent deployment and demonstrated a significant reduction in PMI.[108] In a retrospective analysis that involved 311 stable angina patients, Nageh and associates[109] noted that direct stenting reduced postprocedural troponin I levels when compared with patients in whom predilation was used. Subsequent larger trials did not confirm any concrete advantages of this approach in reducing myonecrosis or any other adverse events.[110]

As mentioned previously, bifurcation stenosis interventions are particularly vulnerable for PMI, primarily as a result of SBO. Trials to evaluate a two-stent strategy versus a one-stent or provisional stent strategy (a one-stent strategy that allows the positioning of a second stent if required) have observed that PMI is more frequent with the two-stent strategy.[111]

The concept of ischemic preconditioning (ICP) and its role in myocyte protection is an intriguing one. Transient and repeated episodes of ischemia followed by reperfusion of the myocardium or any other muscle mass in the body can provide some protection against myocardial damage when a prolonged episode of ischemia ensues by limiting reperfusion injury. This concept has been shown to limit infarct size in patients undergoing bypass surgery.[112] In the Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent)[113] study, 242 stable angina patients undergoing elective PCI were randomized to receive remote IPC (induced by three 5-minute inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5-minute intervals of reperfusion) or a control (an uninflated cuff around the arm) before arrival in the catheterization laboratory. The primary outcome was troponin I level at 24 hours after PCI. The median troponin I level at 24 hours after PCI was lower in the remote IPC group compared with the control group (0.06 vs. 0.16 ng/mL; $P = .040$). After PCI, 42% of patients who underwent remote IPC had a normal troponin level, compared with 24% of the control group ($P = .01$). The mechanisms of protection induced by remote ischemic preconditioning are multifactorial; evidence shows an early opening of mitochondrial potassium channels[114] and a later antiinflammatory effect mediated by modified gene expression.[115]

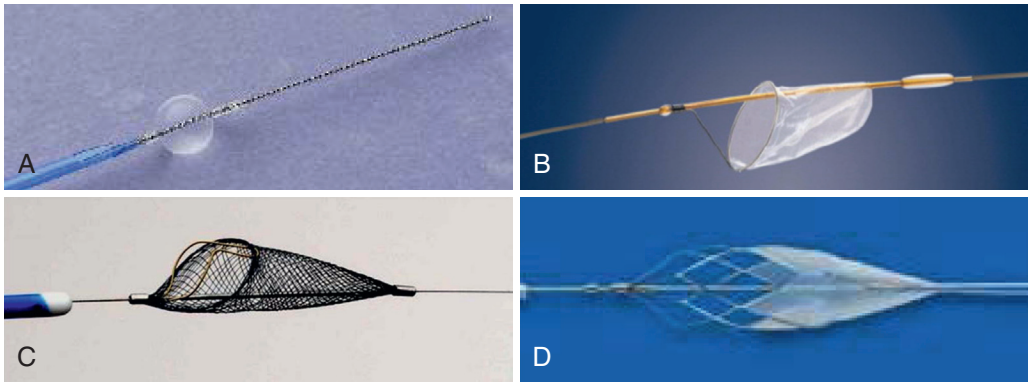


FIGURE 29-9 Examples of distal embolic protection devices. **A,** The PercuSurge GuardWire, from Medtronic, is the only balloon occlusive distal device. The FilterWire, from Boston Scientific (**B**); the Spider, from Covidien (**C**), and the Accunet, from Abbott Vascular (**D**) are all examples of distal filter devices.

Only two devices have noted benefit on periprocedural infarct size: embolic protection in the setting of SVG intervention and aspiration thrombectomy in the setting of STEMI. EPDs have a proven advantage in reducing the incidence of PMI in SVG PCI; these devices are discussed in detail in the following section. Manual thrombectomy with aspiration of the occluding thrombus has been shown to reduce embolization, no-reflow phenomenon, infarct size, and mortality during primary PCI for acute STEMI.[116] Whether that can be considered under the category of PMI remains unclear. Further evidence in support of manual aspiration thrombectomy comes from a 2013 meta-analysis that incorporated 18 trials ($N = 3936$) to compare aspiration thrombectomy/PCI to PCI alone in STEMI patients. Risks of all-cause mortality (the primary end point) and MACE—a composite of death, MI, and target-vessel revascularization—were significantly lower with aspiration thrombectomy (RR 0.71 [95% CI, 0.51 to 0.99] and 0.76 [95% CI, 0.63 to 0.92]). However, these results were refuted by a larger multicenter, prospective, randomized trial on a very similar patient population in the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial.[117] This trial randomly assigned 7244 STEMI patients to either manual thrombus aspiration followed by PCI or PCI alone. The primary end point of death from any cause at 30 days was similar in both groups (2.8% vs. 3.0%, respectively; HR 0.61; 95% CI, 0.34 to 1.07).

CONCLUSIONS

PMI is not uncommon after PCI. The reported incidence varies according to the biomarker used and the threshold for diagnosis. Side-branch occlusion and/or distal embolization of atherosclerotic debris and platelet aggregates are the most common mechanisms underlying PMI. Overall data suggest that PMI is associated with late mortality, although a cause-effect relationship has been debated. The larger the PMI, the more robust is the association with future mortality and major adverse outcomes. Use of coronary stents has dramatically reduced incidence of abrupt vessel closure, which was a major cause of large PMI in the early balloon angioplasty experience. Potent platelet inhibitor therapy (IV or oral), statins (as antiinflammatory agents), and EPDs (in SVG PCI) had the most success in reducing the incidence of PMI. Cardiac biomarkers should be serially assayed in patients who have signs or symptoms suggestive of MI during or after PCI or in asymptomatic patients with significant persistent angiographic complications (e.g., large SBO, flow-limiting dissection, no-reflow phenomenon, or coronary thrombosis).

EMBOLIC PROTECTION DEVICES

With the wider acceptance of the significance of distal embolization during PCI, efforts to reduce the incidence and impact of this phenomenon have been underway. As discussed earlier, effective antiplatelet therapy with GP IIb/IIIa inhibitors and $P2Y_{12}$ inhibitors significantly reduces procedure-related myonecrosis. Despite routine use of these pharmacologic agents, a small PMI is not uncommon even after uncomplicated procedures. This is of particular concern in the setting of SVG interventions, which have a high propensity for distal embolization, no-reflow phenomenon, and PMI. Lesions with high thrombus burden are another subgroup of procedures with a higher risk of distal embolization with any interventional device. The prototype of such procedures is PCI in the setting of acute MI. Over the last few years, several innovative designs for EPDs have been developed to improve outcomes in these subsets of patients, as well as in those in other clinical settings.

The three basic designs of EPD are (1) distal filters, (2) distal occlusion balloons, and (3) proximal occlusion devices (Fig. 29-9; see also Fig. 29-14 later). Table 29-3 summarizes the differences between the various concepts for EPDs.

Distal Filter Devices

Distal filter devices consist of a filter bag or basket attached to the terminal portion of an angioplasty guidewire. The Angioguard filter wire (Cordis, Hialeah, FL) and the FilterWire (Boston Scientific, Natick, MA) are the prototypes of the filter devices. Generally, these devices consist of a 0.014-inch wire that has a filter basket near its distal end (see Fig. 29-9). Beyond the filter protrudes a short portion of guidewire that can be shaped. The currently used version has pores that are approximately 100 μm in diameter. The smallest nominal filter basket size is currently 3.5 mm, which would be used for vessels larger than 3.0 mm but not more than 3.5 mm, whereas the largest basket size is 8 mm. As a general principle, the filter should be oversized by about 0.5 to 1.0 mm compared with the vessel reference diameter. Once the wire crosses the lesion and the filter basket is in a relatively disease-free portion of the artery, the sheath is retracted and the basket is released to deploy in the artery. It should be positioned about 2.5 to 3 cm distal to the lesion. The sheath is removed over the wire, which then serves as a standard angioplasty wire. During the intervention, blood flow through the pores of the filter is preserved, and injecting contrast for visualization is not affected by the deployed filter. When the interventional procedure is complete, a retrieval sheath is advanced over the wire and is used to collapse the filter basket securely. The retrieval sheath and the collapsed filter trapping the embolic debris inside it are then removed as one unit.

The Spider (Covidien, Plymouth, MN), the Accunet (Abbott Vascular, Santa Clara, CA), and the Interceptor Plus Coronary Filter (Medtronic Vascular, Minneapolis, MN) are additional examples of devices that work similarly. The chief advantage of this type of device is the ability to maintain antegrade perfusion throughout the

TABLE 29-3 Characteristics of Different Concepts in Embolic Protection Devices

	Distal Filter	Distal Balloon Occlusion	Proximal Occlusion
Antegrade perfusion	Uninterrupted	Temporarily interrupted*	Temporarily interrupted*
Visualization of the distal vessel	Unhindered	Not possible during inflation	Possible via the inner sheath
Efficacy of emboli protection	May allow passage of emboli smaller than the pore size (100 μm)†	Once inflated, traps all emboli	All particles can be aspirated
Vasoactive substances	Pass unimpeded	Can be aspirated completely	Can be aspirated completely
Crossing profile	0.04 0″ to 0.050″	0.026″ to 0.033″	No crossing, deployed proximal to the lesion
Embolization during device positioning	Likely to occur	Less likely to occur	None because device does not cross the lesion
Retrieval profile	Occasionally difficult if filter is full of debris	Not a problem after balloon deflation	Not a problem; device is proximal to the lesion
Flexibility of guidewire use	None because the filter is attached to wire	None because the balloon is attached to wire	Excellent; device can be used with any wire
Effect of distal disease on device	May not be feasible if no disease-free segment is present	May not be feasible if no disease-free segment is present	Device is proximal, distal disease irrelevant

*Transient ischemia can occur while the embolism protection system is being used unless adequate retrograde collaterals are present.
†In reality, the filter can trap particles smaller than its pore size due to clumping of particles. Numerous trials have demonstrated no clinically significant differences between distal balloon occlusion and distal filter concepts.

procedure; the chief disadvantage is the inability to capture smaller microparticulate debris and vasoactive mediators.

Distal Occlusion Devices

The PercuSurge GuardWire System (6 Fr; Medtronic), the prototype of the balloon occlusion devices, consists of a 0.014-inch hollow hydrotube with an occlusion balloon toward the distal end and a 2.5-cm steerable tip beyond the balloon (see Fig. 29-9, *A*). The wire is used to cross the lesion, and the balloon is positioned distal to the lesion in a relatively disease-free segment. The balloon is inflated at a low atmospheric pressure to create a seal; the occlusion diameter ranges from 3 to 6 mm. Angioplasty, stenting, and postdilation are all performed as necessary over the hydrotube. The aspiration catheter is then advanced over the wire, and any dislodged debris is removed with a slow distal-to-proximal pullback. The balloon is deflated, the GuardWire is withdrawn, and angiography is performed to confirm distal flow. Provided the balloon is inflated at low pressure, the risk of restenosis is not increased. Although this is the first EPD approved by the FDA in the United States, this device is no longer available for commercial use.

A theoretic advantage of distal occlusion includes capture of unlimited debris (regardless of size) and aspiration of inflammatory vasomediators released with angioplasty. However, crossing the lesion with the device may potentiate embolism, and some debris may be shunted into side branches during aspiration of the target artery. Also, antegrade flow is aborted with inflation of the occlusion balloon, allowing for distal ischemia.

Proximal Occlusion Devices

The Proxis Embolic Protection System (St. Jude Medical) was the best example of a proximal occlusion device in SVG interventions, but it is no longer available for use in the United States. The system contains an inner working sheath about 6 Fr in diameter, which is advanced through a 7- or 8-Fr guiding catheter. An inflatable balloon is attached to the end and to the external surface of the inner sheath. Inflation of this balloon in the target artery proximal to the lesion provides a seal that prevents antegrade flow through the target artery. After the system is in place, the intervention can be performed through the inner working sheath using the wire, balloon, and stent of choice. Small contrast injections for visualization are feasible. At the end of the procedure, the interventional devices are removed, and the stagnant blood in the target artery is aspirated via the working sheath. The final step is to deflate the balloon and remove the working sheath, leaving the guiding catheter in the artery after aspiration of debris and vasoactive substances.

Similar devices are now available for use in carotid stenting procedures. These include the Mo.Ma Ultra Cerebral Protection Device (Medtronic Vascular, Minneapolis, MN) and the Gore Flow Reversal System (W.L. Gore and Associates, Flagstaff, AZ). Both devices contain an inflatable balloon around the main guiding catheter that occludes the common carotid artery during internal carotid angioplasty. They also have a secondary extension balloon that is inflated in the external carotid artery to isolate flow from collaterals that may propel atherothrombotic debris toward the cerebral circulation. After inflation of both common and external carotid balloons, the internal carotid artery is crossed with the angioplasty wire of choice. Balloon dilation and stenting are performed in the usual manner with no internal carotid flow permitted. After stenting and postdilation are complete, the blood and debris trapped distal to the common carotid occlusion balloon are then aspirated manually in the case of the Mo.Ma device. With the Gore Flow Reversal System, the guiding catheter contains an additional channel connected to flow-reversal tubing attached to the femoral vein. As the distal common carotid and internal carotid arteries are isolated by inflation of both balloons, the static blood that includes the debris from the treated lesion is continuously drained by the flow-reversal channel and tubing connected to the lower-pressure femoral vein. The tubing is fitted with a filtering chamber to prevent the atherothrombotic debris from reaching the femoral vein. The Gore Flow Reversal System is no longer commercially available for sale in the United States.

SAPHENOUS VEIN GRAFT PERCUTANEOUS CORONARY INTERVENTION

Traditionally, vein graft PCI is considered a high-risk procedure because of the increased risk of distal macroembolization and microembolization with subsequent slow flow or no reflow and PMI. Degenerated vein grafts contain more diffuse, friable, lipid-rich, concentric plaques than native coronary arteries, which makes them particularly prone to distal embolization.[64,118] Of note, one of the most potent interventions to reduce the risk of PMI in native coronary PCI—namely, GP IIb/IIIa inhibitors—appears to be ineffective in the setting of vein graft PCI. A pooled analysis of several of GP IIb/IIIa inhibitor trials, as well as large registry data, demonstrated that addition of IV GP IIb/IIIa inhibitors to standard anticoagulation regimens was not associated with any significant reduction in ischemic complications, including PMI, in patients undergoing vein graft PCI.[119,120]

Several small studies tested the efficacy of EPDs (particularly, the PercuSurge GuardWire) and demonstrated that particulate matter can be aspirated in the majority of cases with an associated reduction in the incidence and magnitude of CK-MB elevation expected with such

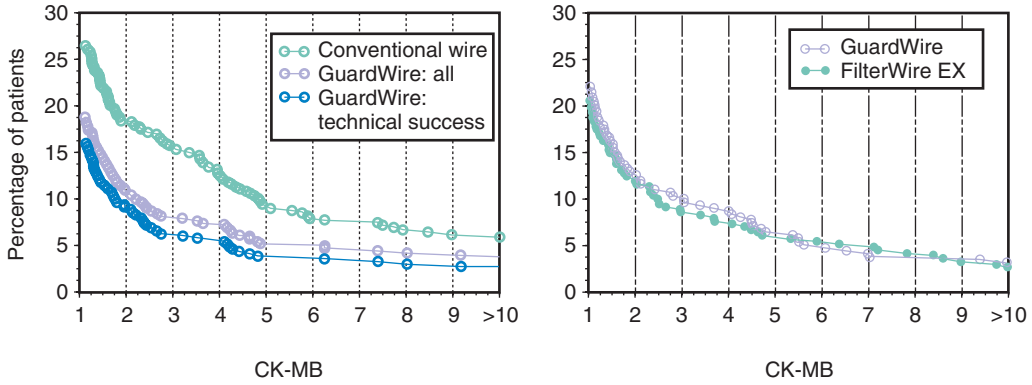


FIGURE 29-10 Impact of embolic protection devices on periprocedural myocardial infarction (PMI) in vein graft percutaneous coronary intervention. *Left:* From the SAFER trial, cumulative distribution-function curve of peak cardiac enzyme values after assignment to placebo or GuardWire and the per-protocol subgroup with technically successful GuardWire use. CK-MB is represented as multiples of the upper limit of normal. The incidence of PMI of any size is significantly lower with GuardWire use. *Right:* From the FilterWire EX Randomized Evaluation (FIRE), a similar plot for patients randomized to distal protection with the FilterWire EX versus the GuardWire, showing noninferiority of the FilterWire. (From Baim DS, Wahr D, George B, et al: Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. *Circulation* 105:1285-1290, 2002; and Stone GW, Rogers C, Hermiller J, et al: Randomized comparison of distal protection with a filter-based catheter and a balloon occlusion and aspiration system during percutaneous intervention of diseased saphenous vein aorto-coronary bypass grafts. *Circulation* 108:548-553, 2003.)

procedures.[121] Based on these findings, 801 patients from 47 centers were randomized to undergo vein graft PCI with GuardWire protection versus no EPD in the SVG Angioplasty Free of Emboli Randomized (SAFER) trial.[35] The primary end point was death, Q-wave MI, non–Q-wave MI (CK-MB > 3× ULN), emergent bypass surgery, or target-vessel revascularization within 30 days. Almost 40% of patients had angiography that revealed thrombus. Technical success was achieved with the device in 90.1% of the cases. The primary end point was significantly reduced with use of the PercuSurge GuardWire (from 16.5% to 9.6%, $P = .004$), primarily driven by the approximate 50% reduction in non–Q-wave MI, from 13.7% to 7.4% (Fig. 29-10). A number of important secondary end points were also favorably influenced; most important, no-reflow phenomenon was reduced dramatically (9.0% vs. 3.0%; $P = .02$).[35] Moreover, a cost-effectiveness analysis of the SAFER trial demonstrated that the reduction in ischemic complications leads to a shorter hospital stay and reduction in early costs, thus compensating for most of the added expense of the EPD. The projected improved survival on the basis of reduced early complications—namely, reduced PMI—was calculated to cost less than $4000 per year of life saved, which makes the use of EPD in vein graft PCI a very cost-effective strategy.[122]

This significant improvement in outcome with the use of the GuardWire occlusion device ushered in a new era in which EPD use has become the standard of care with vein graft PCI. Thus the randomized controlled trials leading to FDA approval of other EPDs for use in vein graft PCI were designed as noninferiority trials, with the GuardWire used in the "active" control arm. In a controlled trial, 651 patients undergoing vein graft PCI were randomized to receive the FilterWire EX versus the GuardWire. Use of GP IIb/IIIa inhibitors was left to the discretion of the operators. The primary end point was a composite similar to that used in the SAFER trial. At 30 days, no difference was seen in the incidence of any MI, with a trend toward a reduction in the primary endpoint in the FilterWire arm (9.9% vs. 11.6%, $P = .53$ for superiority, $P = .0008$ for noninferiority; see Fig. 29-10).[37] Currently, the FilterWire is the most commonly used EPD in SVG PCI.

A more complex study design was used to demonstrate noninferiority of the Proxis system. A total of 639 target vein grafts in 594 patients were prospectively randomized to a test group (use proximal protection when possible, distal protection when not) or a control group (use distal protection when possible). The 30-day composite end point was similar to that used in the SAFER trial. The study demonstrated noninferiority of proximal protection when the analysis was performed by intention to treat or by actual device use.[123]

Noninferiority trials were similarly designed to test the efficacy of other devices. In those trials, the 30-day primary end point was reached in 8% to 11% of patients, achieving the preset standard for noninferiority in comparison to the GuardWire or FilterWire in all studies.[124,125]

The use of EPDs during SVG intervention is a class 1 recommendation per the ACC/AHA/SCAI guidelines.[2] Exceptions might include in-stent restenosis or aortoostial stenosis because the former are typically composed of smooth muscle cells, whereas the latter are fibrotic; neither are necessarily prone to cause embolization. Unfortunately, adoption of EPD use for SVG interventions in the United States has been sluggish. Data from the National Cardiovascular Data Registry (NCDR) on more than 19,000 vein graft interventions between 2004 and 2006 demonstrate that EPD was used in 22% of cases; 19% of centers were not using EPDs, and 41% used them in fewer than 10% of cases.[126] More recently, analysis of the Stenting of Saphenous Vein Grafts (SOS) trial demonstrated that EPDs were used in 54% of cases. Although some of the lack of use was dictated by anatomic considerations, evidence shows that operator preference still contributes to this underutilization of EPDs.[127] Operators may also reserve the use of EPDs for SVG lesions presumed to be associated with the highest risk of embolism. In a pooled analysis of 3958 patients included in five randomized trials and one registry, a prediction model was developed to estimate the risk of major adverse events after SVG PCI. Angiographic scoring of the severity of degeneration, volume of plaque, and presence of thrombus were among the strongest predictors of adverse events. However, the value of EPD use in reducing PMI (by ~40%) was demonstrated across all categories of angiographically estimated risk.[128] These findings suggest a clear need for continuing education and training of interventional operators on the value of these devices in reducing morbidity and mortality and for intensifying efforts to develop more affordable and easy-to-use devices (Fig. 29-11).

Percutaneous Coronary Intervention for Acute Myocardial Infarction

The concept of EPD use in primary PCI is both attractive and intuitive. These are the prototypical thrombotic lesions with a very high likelihood of distal embolization. The success of EPD in vein graft PCI led to clinical trials to examine the feasibility of the concept. In a small

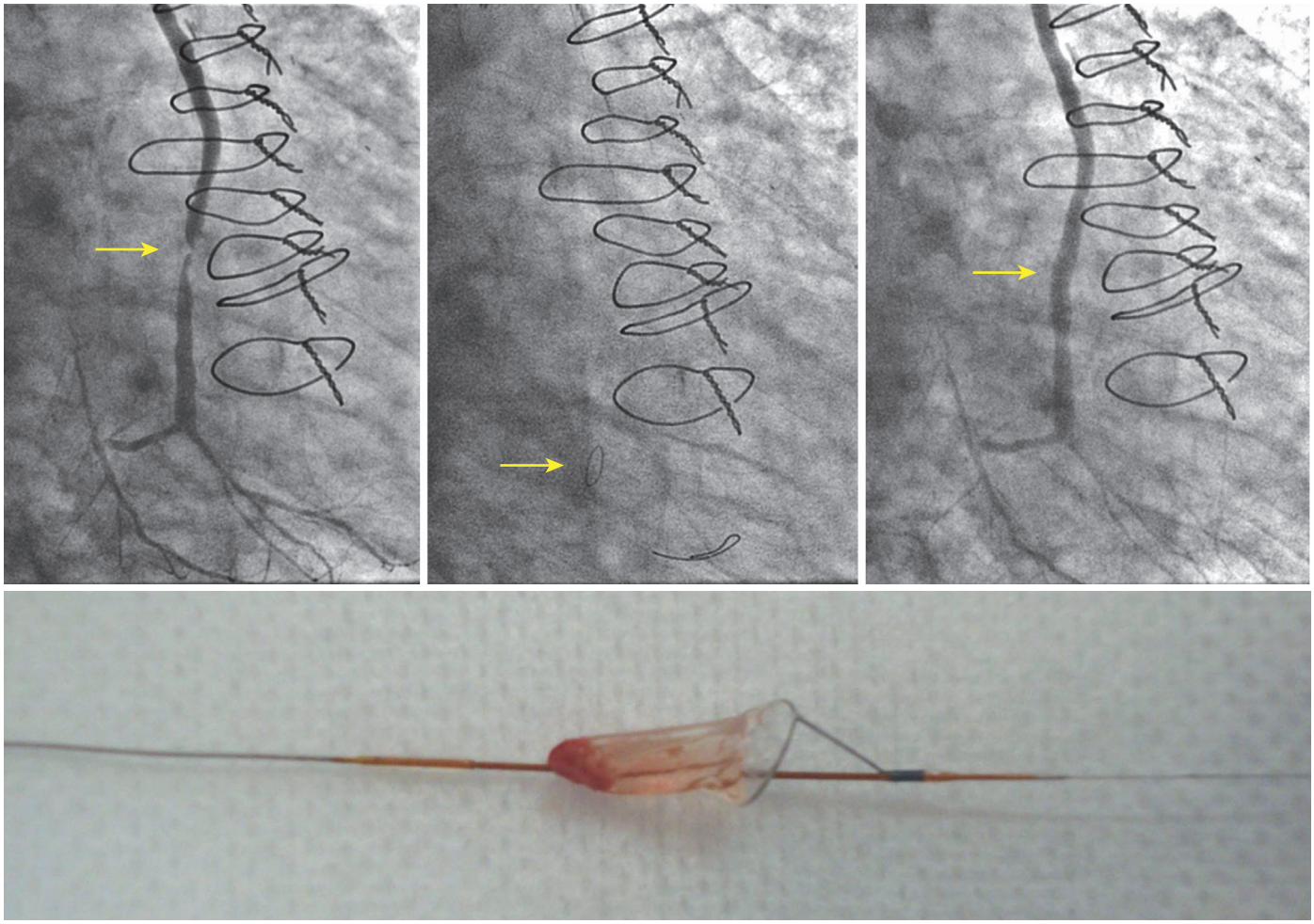


FIGURE 29-11 Use of the FilterWire in contemporary saphenous vein graft (SVG) percutaneous coronary intervention. Angiograms of an SVG to an obtuse marginal branch in a patient presenting with non–ST-segment–elevation myocardial infarction (MI). *Left:* A subtotal lesion is noted in the body of the SVG (*arrow*). *Middle:* The lesion is crossed with a FilterWire EZ, which is then deployed in the distal graft, as noted by the radiopaque nitinol ring at the base of the filter basket (*arrow*). The radioopaque spring coil tip is folded in the native vessel beyond the anastomosis. *Right:* The final angiogram after stent deployment and removal of the FilterWire with no residual stenosis within the stented segment (*arrow*) and good runoff into the distal obtuse marginal branch. *Bottom:* The FilterWire contains macroscopic evidence of thrombotic material and fatty debris from the degenerated lesion. (From Foley JD, Ziada KM: Embolic protection devices for saphenous vein graft percutaneous coronary interventions. *Interv Cardiol Clin* 2(2):259-271, 2013.)

study, use of the PercuSurge GuardWire during primary stenting of infarct-related artery resulted in improved flow and subsequently improved ventricular function when compared with procedures performed without EPD use.[129]

However, the larger randomized trials did not confirm the initial favorable impression regarding EPD use in primary PCI. The Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris (EMERALD) trial[130] was an international multicenter, prospective, randomized trial that enrolled 501 patients with STEMI undergoing primary or rescue PCI. Patients were randomized to PCI with the PercuSurge GuardWire distal protection device versus PCI without an EPD. Among 252 patients assigned to the GuardWire, debris was retrieved in 73%. Disappointingly, no difference was found between the two groups in any of the primary or secondary end points (ST resolution in 63% vs. 62%; infarct size 12% vs. 9.5%; P = nonsignificant [NS] for both). The Protection Devices in PCI Treatment of Myocardial Infarction for Salvage of Endangered Myocardium (PROMISE) trial tested the efficacy of the FilterWire in the setting of PCI for acute MI. This study included patients with NSTEMI and used different surrogate end points: coronary flow velocity measured by an intravascular Doppler wire and the size of the infarction measured by hyperenhancement on MRI scans 3 days after the procedure. Similar to the results of the EMERALD trial, FilterWire protection provided no additional benefit.[131] Other trials to examine filter-based EPD in the setting of primary angioplasty have not demonstrated any clinical benefit to this approach.[132]

Use of proximal protection combined with thrombus aspiration was examined in the Proximal Embolic Protection in Acute Myocardial Infarction and Resolution of ST-Elevation (PREPARE) trial. In this prospective randomized trial, 284 patients were randomized to primary PCI with the Proxis system versus primary PCI alone after angiography. The primary end point was the occurrence of complete (≥70%) ST-segment resolution at 60 minutes. The results demonstrated an earlier resolution of the ST segment in the proximal protection arm, but no difference was found between the groups in the primary end point, infarct size by MR or clinical adverse outcomes.[133,134]

Several potential explanations exist for the disappointing results of EPD use in primary angioplasty. Using EPD may delay restoration of epicardial flow, and the devices may cause further embolization while crossing the lesion, thus negating any favorable effects of subsequent

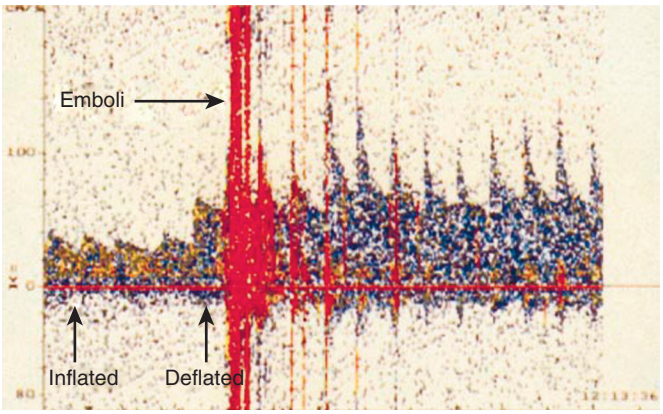


FIGURE 29-12 Transcranial Doppler monitoring of middle cerebral artery flow during elective carotid artery stenting. The high-intensity transients observed at the time of balloon deflation represent a surge of microemboli from the extracranial site of angioplasty to the intracranial circulation. (From Topol EJ, Yadav JS: Recognition of the importance of embolization in atherosclerotic vascular disease, *Circulation* 101: 570-580, 2000.)

protection. The incomplete aspiration of liberated debris or leaking of vasoactive substances released from the ruptured plaques may lead to further downstream damage at the time of EPD removal. Embolization into side branches may play a role, particularly in cases with acute thrombotic occlusion, leading to initial TIMI flow grade 0 and absence of visualization of the distal artery at the time of EPD positioning. Notably, these results also indicate a relative underestimation of the degree of existing damage and the role of reperfusion injury in determining the final infarct size after primary PCI.[135]

Carotid Stenting

Although the clinical implications of embolization were first elucidated for coronary interventions, the paradigm is applicable and relevant in angioplasty procedures in other arterial beds. Interventional procedures in the carotid and renal arteries are two areas where embolization may be particularly significant; embolization appears to occur more frequently after carotid stenting than after carotid endarterectomy (CEA). Using transcranial Doppler (TCD) monitoring, microscopic embolization occurs at least eight times more frequently with carotid angioplasty and stenting than with CEA.[136] Indeed, the vast majority of patients who undergo carotid stenting have TCD evidence of microembolization (Fig. 29-12). Similar to embolization related to coronary interventions, it appears that evidence of systemic inflammatory response can lead to more embolization. In a small study of 43 patients who underwent carotid stenting with TCD monitoring of the ipsilateral middle cerebral artery, a positive correlation was found between TCD-identified microembolism and preprocedural leukocyte count (a marker of systemic inflammation). This correlation remained significant even after adjusting for age, sex, comorbidities, medical therapy, and use of an EPD.[137]

Potentially, even small embolic particles are poorly tolerated by the cerebral microcirculation.[138] In an ex-vivo model of carotid angioplasty, particles generated from human carotid plaques were injected into the cerebral circulation of rats. Of interest, stenting produced almost twice as much embolization as balloon angioplasty in this model; passage of the guidewire also produced embolization, although only about a quarter as many emboli were produced than with balloon angioplasty. Particles smaller than 200 µm in size did not cause cerebral ischemia during the first 3 days after the procedure, whereas particles of 200 to 500 µm did cause neuronal death. However, at 7 days, injury was detected by fragments of both sizes. Thus if smaller sizes of emboli are relevant in humans, an occlusion device may be better than a filter device. Although filters can be designed with smaller pore sizes, the disadvantage is that this can increase the risk of thrombosis by the filter itself and can decrease distal flow.

Thus several EPDs were designed for use in conjunction with carotid angioplasty and stenting in the hope of reducing the incidence of procedure-related strokes. The earlier and more extensive experience thus far is with distal filter devices (balloon occlusion and filter types). More recently, proximal occlusion devices have become available, and early experience has shown significant promise that these devices might be associated with further reduction in stroke rates.

Distal Embolism Protection Devices in Carotid Stenting

Reimers and colleagues[139] reported their initial experience with three different filter designs (Angioguard, NeuroShield [MedNova, Galway, Ireland], and FilterWire) in 84 patients undergoing carotid stenting. Macroscopic debris was collected in 53% of filters, and histologic analysis of the debris revealed lipid-rich macrophages, fibrin, and cholesterol clefts. The early experience with the balloon-occlusion variety of EPD (PercuSurge GuardWire) was reported in a series of 75 patients. In this series, macroscopic debris was collected from all patients (100%), and histologic analysis was very similar to particles obtained from filter devices.[140]

In addition to retrieval of macroscopic and microscopic debris, additional evidence suggests that the use of EPD during carotid stenting effectively reduces embolism to the cerebral microcirculation. These data have been gleaned from studies using MR diffusion-weighted imaging (DWI), the most sensitive imaging modality for detection of early cerebral ischemia.[141,142] Comparison of DWI scans before and after carotid stenting reveals that use of an EPD significantly reduces both the incidence and number of new lesions identified on the postprocedure scan. Most new lesions were small (<10 mm) and asymptomatic (Fig. 29-13). In a study of 206 patients, no difference was reported in the incidence of stroke between patients who did and did not receive EPD protection, but the number of DWI-visualized new lesions was significantly higher in patients who did develop a stroke.[142]

Although no randomized trial has been done to compare outcomes of carotid stenting with and without EPD protection, evidence from large multicenter registries demonstrate that EPD use has resulted in a significant reduction in neurologic adverse events. In a systematic review of published reports, Kastrup and coworkers[143] compared outcomes of 2357 patients undergoing carotid stenting without an EPD with outcomes of 839 patients in whom stenting was performed with an EPD in place. A significant reduction was seen in 30-day death/stroke rate with EPD use (1.8% vs. 5.5%, $P < .001$). Both minor and major strokes were significantly reduced in patients who received EPDs (minor stroke 0.5% vs. 3.7%, $P < .001$; major stroke 0.3% vs. 1.1%, $P < .05$). The larger Global Carotid Artery Stent Registry surveys the major interventional centers worldwide and collects self-reported data on technical details and outcomes. In the most recent update, 6753 patients had undergone stenting without EPD protection, and 4221 patients did receive EPD protection. The 30-day incidence of stroke and procedure-related death was reduced by more than 50%, from 5.3% to 2.2%. Despite EPD use, symptomatic patients remained at higher risk for developing stroke or procedure-related death compared with the asymptomatic subgroup (2.7% vs. 1.75%).[144]

Few randomized trials have compared contemporary carotid artery stenting with CEA. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial randomized patients to either endarterectomy or carotid stenting with the Angioguard filter device. Both symptomatic and asymptomatic patients were included if they had a coexisting condition that placed them at a higher risk of complications during a CEA. The primary composite end point was death, stroke, or MI at 30 days plus death due to neurologic causes or ipsilateral stroke between day 31 and 1 year. Because of slowing recruitment, the trial was terminated after randomizing

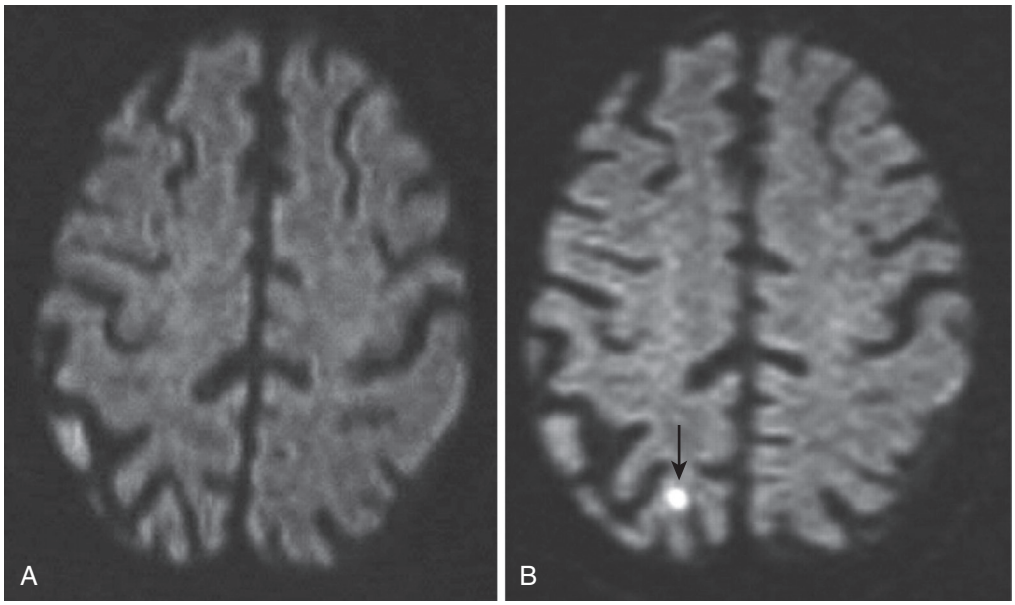


FIGURE 29-13 Axial diffusion-weighted imaging of the brain. **A,** Preprocedure. **B,** Postprocedure. Despite carotid stenting with an embolic protection device in place, an ipsilateral hyperintense lesion (*arrow*) related to silent cerebral embolism is appreciable at the cortical-subcortical junction of the right parietal lobe. (From Cosottini M, Michelassi MC, Puglioli M, et al: Silent cerebral ischemia detected with diffusion-weighted imaging in patients treated with protected and unprotected carotid artery stenting, *Stroke* 36:2389-2393, 2005.)

334 patients. In this high-risk population, the primary composite end point was reduced in the stent group compared with the surgical group (12.2% vs. 20.1%, $P = .004$ for noninferiority, $P = .053$ for superiority). At 30 days, the incidence of stroke was 3.6% and 3.1% in the stent and CEA arms, respectively. This reduction in primary end point was driven primarily by a reduction in MI in the stent arm rather than by differences in cerebral events.[145]

To gain FDA approval, several manufacturers of EPDs and stents initiated a number of large patient registries to demonstrate safety and efficacy of their novel devices. Most of these enrolled patients at high risk of complications, similar to the SAPPHIRE design. The low incidence of death or stroke compared with historic adverse event rates in CEA resulted in the eventual FDA approval of many of these devices.[146,147]

Two European-based randomized trials attempted to demonstrate noninferiority of carotid stenting compared with CEA, the Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE) trial and the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S). Both studies included patients with symptomatic carotid stenosis and attempted to demonstrate the noninferiority of stenting.[148,149] The end points were relatively similar: death or stroke at 30 days. Both studies did not emphasize EPD use; only 25% of patients in SPACE had EPDs. In EVA-3S, EPD use was mandated only after evidence of excess stroke in the first 80 patients.[150] Both studies failed to demonstrate noninferiority, and excess stroke (mostly minor) was evident in the stenting arm.

The two larger randomized trials to compare carotid stenting with endarterectomy, the International Carotid Stenting Study (ICSS) and the Carotid Endarterectomy Versus Stenting Trial (CREST) have been completed. ICSS enrolled 1713 symptomatic patients, emphasized EPD use (80%), and had a primary end point of fatal or disabling stroke at 3 years. At 120 days, the investigators reported an excess of minor strokes in the stenting arm (7.6% vs. 4.1% in the endarterectomy group) and an excess of laryngeal nerve palsy in the endarterectomy arm.[151] Alternatively, CREST randomized 2502 patients with both symptomatic and asymptomatic disease, making it the largest study to date to address this question. The primary composite end point was periprocedural stroke, death, or infarction plus ipsilateral stroke within 4 years. All stenting procedures included EPD use. At 30 days, the stroke rate was 4.1% for stenting and 2.3% for endarterectomy, and the rate of major stroke was less than 1% in both groups. The study showed no difference between the groups in the composite end point and no difference between symptomatic and asymptomatic patients. An excess of minor strokes occurred with stenting, balanced by an excess of MIs in the endarterectomy group.[152]

Based on the totality of evidence, several factors can be seen to have a significant impact on outcomes of carotid stenting: symptomatic status, EPD use, and operator experience. In the two trials that mandated use of an EPD and restricted enrollment to experienced operators (SAPPHIRE and CREST), there is more evidence of equipoise between stenting and endarterectomy. Of note, both studies included asymptomatic patients, who are considered to be at lower risk for events. On the other hand, trials that did not mandate EPD use on a large scale and/or that included interventional operators with minimal or no experience (SPACE, EVA-3S, and ICSS) had a higher event rate with stenting, albeit these trials focused on symptomatic patients.

Proximal Embolism Protection Devices in Carotid Stenting

The single-center experience using the Mo.Ma Ultra Proximal Cerebral Protection Device (Fig. 29-14) generated significant promise in this approach. In a series of 1300 patients who underwent carotid stenting using this device, the incidence of all strokes was 0.84%, with a surprisingly low 1.38% incidence of death and stroke at 30 days.[153] The Proximal Protection With the Mo.Ma Device During Carotid Stenting (ARMOUR) prospective registry was intended to provide U.S. data for FDA approval. Among 225 pivotal patients, primarily asymptomatic, device success exceeded 98%. The 30-day incidence of stroke was 0.9% and the combined death and stroke rate was 2.7%, emphasizing both the safety and efficacy of the device.[154] A similar prospective single-arm study examined the outcome of carotid stenting using the Gore Flow Reversal System in 245 pivotal high-surgical-risk patients. The primary end point was a major adverse event—stroke, death, MI, or transient ischemic attack—within 30 days of stenting. The adverse event rate was

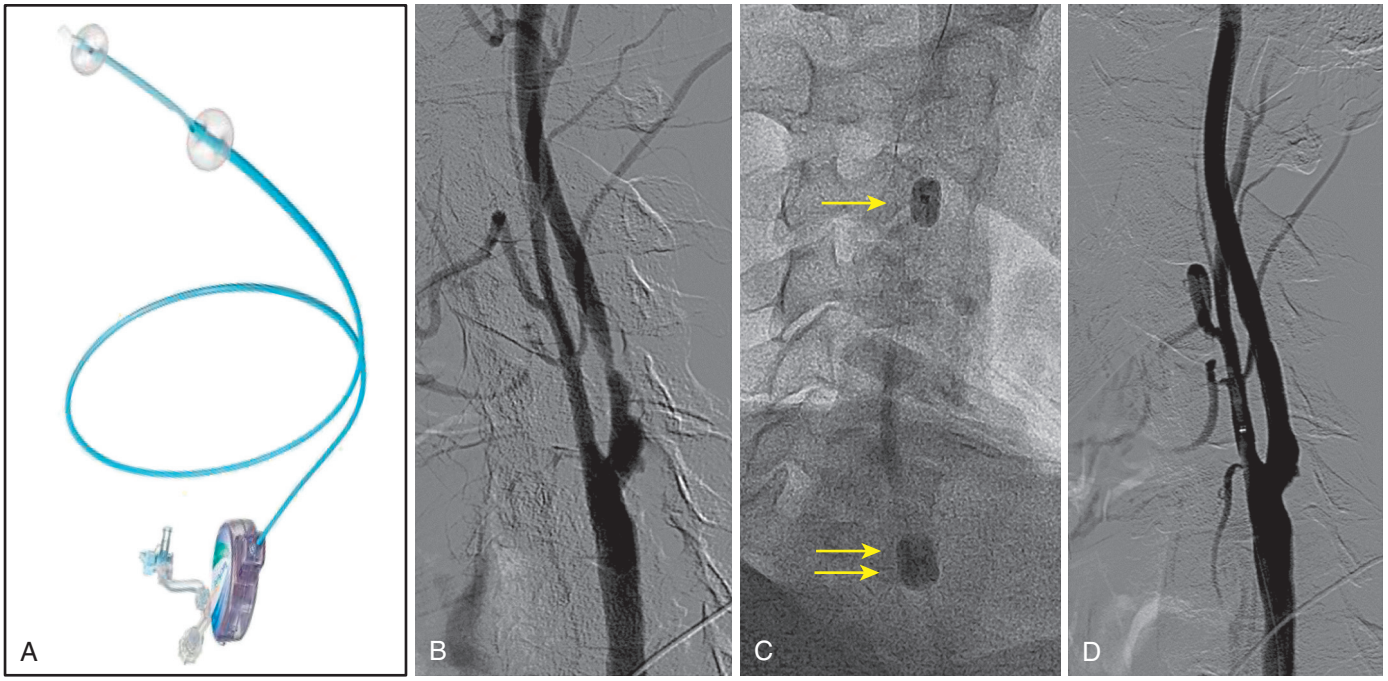


FIGURE 29-14 Example of carotid stenting using Medtronic's Mo.Ma proximal protection system. This embolic protection device is based on preventing antegrade flow and potential retrograde flow through the internal carotid artery during carotid angioplasty by use of common carotid and external carotid occlusive balloons. **A,** The catheter with its two occlusive balloons. **B,** The lesion in the left internal carotid artery is severe. **C,** The external carotid balloon (*yellow arrow*) and the common carotid balloon (*double arrows*) are inflated to occlude flow. Contrast stain is seen indicating absence of antegrade flow. After stenting and dilation, debris in the isolated segment is aspirated before occlusive balloons are deflated. **D,** Final angiographic result.

compared with an objective performance criterion derived from studies that included carotid stenting with embolic protection. At 30 days, the composite end point was reached in 11 patients (4.5%), which statistically was significantly better than the objective criterion (P = .002). The stroke and death rate was 2.9%, and no patient had a major ischemic stroke.[155]

A subsequent meta-analysis of 2397 patients from six independent databases of the two proximal occlusion devices examined the incidence and predictors of 30-day major adverse clinical events including stroke, MI, and death using random effects models. The incidence rates were 1.71% for stroke, 0.02% for MI, and 0.40% for death. The composite primary end point at 30 days was 2.25%. Age and diabetic status were the only significant independent risk predictors; however, total stroke rates remained below 2.6% in all subgroups, including symptomatic octogenarians. The authors concluded that carotid stenting with proximal occlusion devices yields a very low incidence of adverse events at 30 days.[156]

The improved outcomes noted with proximal protection devices in carotid stenting raise the question of whether another large randomized trial to compare stenting with endarterectomy is warranted. This may be of particular importance because the stroke risk of procedures performed with these devices was not affected by symptomatic status and old age, the two important predictors of adverse outcome with stenting in the CREST trial.

Renal and Peripheral Interventions

Although fewer data demonstrate the importance of atheroembolism in the renal vasculature, it appears that emboli are also detrimental in this arterial bed. A study by Krishnamurthi and colleagues[157] examined the impact of embolization after surgical revascularization for renal artery stenosis. In this series, evidence of atheroembolism was detected in 16 of 44 patients. In another series of 56 patients, 65 renal arteries were successfully stented with EPD protection (GuardWire, FilterWire, and Angioguard devices). Visible debris was aspirated with 100% of the patients with GuardWire protection and in 80% of those in whom filter devices were used.[158]

Although difficult to prove, there is little doubt that embolization also occurs in the setting of percutaneous renal revascularization and is likely also associated with worse patient outcomes. It is estimated that 25% of patients have worse renal function after renal intervention. Although the reason for this decrease in renal function is probably multifactorial, embolization is likely part of the problem.

Early experiences with EPD in lower extremity percutaneous revascularization procedures have been reported as well.[159,160] In most cases, filter devices were deployed and retrieved successfully. Macroscopic and microscopic debris were present in all cases, which suggests a potential benefit of these devices in lower extremity procedures, particularly in cases of acute or subacute ischemia with large thrombus burden and high risk of distal showering.

CONCLUSIONS

EPDs have gained widespread acceptance in the interventional cardiology and vascular community over the last decade. Solid evidence shows that they are safe to use and effective in reducing distal embolism during interventional procedures. Clinical outcomes have been excellent in vein graft PCI, and EPD protection is now considered the standard of care. For various reasons, results of EPD use in the setting of primary and rescue PCI have been disappointing, and at this point in time, there does not seem to be a future for those devices in acute MI intervention. However, solid evidence shows that carotid stenting with EPD protection is associated with reduced risk of stroke. Carotid stenting with proximal EPD protection seems to be even more protective against risk of stroke, although randomized comparative trials are lacking. With more innovation in EPD design, and as the ongoing clinical trials are completed, the potential exists for future application of EPDs in other settings of coronary and peripheral interventions.

REFERENCES

1. Togni M, Balmer F, Pfiffner D, et al: Percutaneous coronary interventions in Europe 1992-2001. *Eur Heart J* 25:1208–1213, 2004.
2. Levine GN, Bates ER, Blankenship JC, et al: 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 124:2574–2609, 2011.
3. Thygesen K, Alpert JS, Jaffe AS, et al: Third universal definition of myocardial infarction. *J Am Coll Cardiol* 60:1581–1598, 2012.
4. Moussa ID, Klein LW, Shah B, et al: Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol* 62:1563–1570, 2013.
5. Cutlip DE, Kuntz RE: Does creatinine kinase-MB elevation after percutaneous coronary intervention predict outcomes in 2005? Cardiac enzyme elevation after successful percutaneous coronary intervention is not an independent predictor of adverse outcomes. *Circulation* 112:916–922, discussion 922, 2005.
6. Harrington RA, Lincoff AM, Califf RM, et al: Characteristics and consequences of myocardial infarction after percutaneous coronary intervention: insights from the coronary angioplasty versus excisional atherectomy trial (caveat). *J Am Coll Cardiol* 25:1693–1699, 1995.
7. Abdelmeguid AE, Topol EJ, Whitlow PL, et al: Significance of mild transient release of creatine kinase-MB fraction after percutaneous coronary interventions. *Circulation* 94:1528–1536, 1996.
8. Ellis SG, Chew D, Chan A, et al: Death following creatine kinase-MB elevation after coronary intervention: identification of an early risk period: importance of creatine kinase-MB level, completeness of revascularization, ventricular function, and probable benefit of statin therapy. *Circulation* 106:1205–1210, 2002.
9. Ghazzal Z, Ashfaq S, Morris DC, et al: Prognostic implication of creatine kinase release after elective percutaneous coronary intervention in the pre-IIb/IIIa antagonist era. *Am Heart J* 145: 1006–1012, 2003.
10. Simoons ML, van den Brand M, Lincoff M, et al: Minimal myocardial damage during coronary intervention is associated with impaired outcome. *Eur Heart J* 20:1112–1119, 1999.
11. Ioannidis JP, Karvouni E, Katritsis DG: Mortality risk conferred by small elevations of creatine kinase-MB isoenzyme after percutaneous coronary intervention. *J Am Coll Cardiol* 42:1406–1411, 2003.
12. Roe MT, Mahaffey KW, Kilaru R, et al: Creatine kinase-MB elevation after percutaneous coronary intervention predicts adverse outcomes in patients with acute coronary syndromes. *Eur Heart J* 25:313–321, 2004.
13. Thygesen K, Alpert JS, White HD: Universal definition of myocardial infarction. *J Am Coll Cardiol* 50:2173–2195, 2007.
14. Ricciardi MJ, Wu E, Davidson CJ, et al: Visualization of discrete microinfarction after percutaneous coronary intervention associated with mild creatine kinase-MB elevation. *Circulation* 103:2780–2783, 2001.
15. Selvanayagam JB, Porto I, Channon K, et al: Troponin elevation after percutaneous coronary intervention directly represents the extent of irreversible myocardial injury: insights from cardiovascular magnetic resonance imaging. *Circulation* 111:1027–1032, 2005.
16. Herrmann J: Peri-procedural myocardial injury: 2005 update. *Eur Heart J* 26:2493–2519, 2005.
17. van Gaal WJ, Arnold JR, Testa L, et al: Myocardial injury following coronary artery surgery versus angioplasty (MICASA): A randomised trial using biochemical markers and cardiac magnetic resonance imaging. *EuroIntervention* 6:703–710, 2011.
18. Cavallini C, Savonitto S, Violini R, et al: Impact of the elevation of biochemical markers of myocardial damage on long-term mortality after percutaneous coronary intervention: results of the CK-MB and PCI study. *Eur Heart J* 26:1494–1498, 2005.
19. Testa L, Van Gaal WJ, Biondi Zoccai GG, et al: Myocardial infarction after percutaneous coronary intervention: a meta-analysis of troponin elevation applying the new universal definition. *QJM* 102:369–378, 2009.
20. Nallamothu BK, Chetcuti S, Mukherjee D, et al: Prognostic implication of troponin I elevation after percutaneous coronary intervention. *Am J Cardiol* 91:1272–1274, 2003.
21. Srinivas VS, Brooks MM, Detre KM, et al: Contemporary percutaneous coronary intervention versus balloon angioplasty for multivessel coronary artery disease: a comparison of the National Heart, Lung and Blood Institute Dynamic Registry and the Bypass Angioplasty Revascularization Investigation (BARI) study. *Circulation* 106:1627–1633, 2002.
22. The EPISTENT Investigators: Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Evaluation of platelet IIb/IIIa inhibitor for stenting. *Lancet* 352:87–92, 1998.
23. Porto I, Selvanayagam JB, Van Gaal WJ, et al: Plaque volume and occurrence and location of periprocedural myocardial necrosis after percutaneous coronary intervention: insights from delayed-enhancement magnetic resonance imaging, thrombolysis in myocardial infarction myocardial perfusion grade analysis, and intravascular ultrasound. *Circulation* 114: 662–669, 2006.
24. Topol EJ, Yadav JS: Recognition of the importance of embolization in atherosclerotic vascular disease. *Circulation* 101:570–580, 2000.
25. Prati F, Pawlowski T, Gil R, et al: Stenting of culprit lesions in unstable angina leads to a marked reduction in plaque burden: a major role of plaque embolization? A serial intravascular ultrasound study. *Circulation* 107:2320–2325, 2003.
26. Rogers C, Huynh R, Seifert PA, et al: Embolic protection with filtering or occlusion balloons during saphenous vein graft stenting retrieves identical volumes and sizes of particulate debris. *Circulation* 109:1735–1740, 2004.
27. Angelini A, Rubartelli P, Mistrorigo F, et al: Distal protection with a filter device during coronary stenting in patients with stable and unstable angina. *Circulation* 110:515–521, 2004.
28. Chen WH, Lee PY, Ng W, et al: Aspirin resistance is associated with a high incidence of myonecrosis after non-urgent percutaneous coronary intervention despite clopidogrel pretreatment. *J Am Coll Cardiol* 43:1122–1126, 2004.
29. Bonz AW, Lengenfelder B, Jacobs M, et al: Cytokine response after percutaneous coronary intervention in stable angina: effect of selective glycoprotein IIb/IIIa receptor antagonism. *Am Heart J* 145:693–699, 2003.
30. Iuliano L, Pratico D, Greco C, et al: Angioplasty increases coronary sinus F2-isoprostane formation: evidence for in vivo oxidative stress during PTCA. *J Am Coll Cardiol* 37:76–80, 2001.
31. Kini A, Marmur JD, Kini S, et al: Creatine kinase-MB elevation after coronary intervention correlates with diffuse atherosclerosis, and low-to-medium level elevation has a benign clinical course: implications for early discharge after coronary intervention. *J Am Coll Cardiol* 34:663–671, 1999.
32. Zairis MN, Ambrose JA, Ampartzidou O, et al: Preprocedural plasma C-reactive protein levels, postprocedural creatine kinase-MB release, and long-term prognosis after successful coronary stenting (four-year results from the generation study). *Am J Cardiol* 95:386–390, 2005.
33. Saadeddin SM, Habbab MA, Sobki SH, Ferns GA: Association of systemic inflammatory state with troponin I elevation after elective uncomplicated percutaneous coronary intervention. *Am J Cardiol* 89:981–983, 2002.
34. Chew DP, Bhatt DL, Robbins MA, et al: Incremental prognostic value of elevated baseline C-reactive protein among established markers of risk in percutaneous coronary intervention. *Circulation* 104:992–997, 2001.
35. Baim DS, Wahr D, George B, et al: Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. *Circulation* 105: 1285–1290, 2002.
36. Naidu SS, Turco MA, Mauri L, et al: Contemporary incidence and predictors of major adverse cardiac events after saphenous vein graft intervention with embolic protection (an AMETHYST trial substudy). *Am J Cardiol* 105:1060–1064, 2010.
37. Stone GW, Rogers C, Hermiller J, et al: Randomized comparison of distal protection with a filter-based catheter and a balloon occlusion and aspiration system during percutaneous intervention of diseased saphenous vein aorto-coronary bypass grafts. *Circulation* 108:548–553, 2003.
38. Abdelmeguid AE, Ellis SG, Sapp SK, et al: Defining the appropriate threshold of creatine kinase elevation after percutaneous coronary interventions. *Am Heart J* 131:1097–1105, 1996.
39. van Gaal WJ, Ponnuthurai FA, Selvanayagam J, et al: The SYNTAX score predicts peri-procedural myocardial necrosis during percutaneous coronary intervention. *Int J Cardiol* 135: 60–65, 2009.
40. Kawamoto T, Okura H, Koyama Y, et al: The relationship between coronary plaque characteristics and small embolic particles during coronary stent implantation. *J Am Coll Cardiol* 50:1635–1640, 2007.
41. Tanaka A, Imanishi T, Kitabata H, et al: Lipid-rich plaque and myocardial perfusion after successful stenting in patients with non-ST-segment elevation acute coronary syndrome: an optical coherence tomography study. *Eur Heart J* 30:1348–1355, 2009.
42. Abdelmeguid AE, Whitlow PL, Sapp SK, et al: Long-term outcome of transient, uncomplicated in-laboratory coronary artery closure. *Circulation* 91:2733–2741, 1995.
43. Yang EH, Gumina RJ, Lennon RJ, et al: Emergency coronary artery bypass surgery for percutaneous coronary interventions: changes in the incidence, clinical characteristics, and indications from 1979 to 2003. *J Am Coll Cardiol* 46:2004–2009, 2005.
44. Almeda FQ, Nathan S, Calvin JE, et al: Frequency of abrupt vessel closure and side branch occlusion after percutaneous coronary intervention in a 6.5-year period (1994 to 2000) at a single medical center. *Am J Cardiol* 89:1151–1155, 2002.
45. Aliabadi D, Tilli FV, Bowers TR, et al: Incidence and angiographic predictors of side branch occlusion following high-pressure intracoronary stenting. *Am J Cardiol* 80:994–997, 1997.
46. Stone GW, Ellis SG, Cannon L, et al: Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. *JAMA* 294:1215–1223, 2005.
47. Applegate R: Evaluation of the effects of everolimus-eluting and paclitaxel-eluting stents on target lesions with jailed side branches: 2-year results from the SPIRIT III randomized trial. *Catheter Cardiovasc Interv* 76:644–651, 2010.
48. Topol EJ, Leya F, Pinkerton CA, et al: A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease. The CAVEAT Study Group. *N Engl J Med* 329:221–227, 1993.
49. Baim DS, Cutlip DE, Sharma SK, et al: Final results of the balloon vs optimal atherectomy trial (BOAT). *Circulation* 97:322–331, 1998.
50. Lefkovits J, Holmes DR, Califf RM, et al: Predictors and sequelae of distal embolization during saphenous vein graft intervention from the CAVEAT-II trial. Coronary angioplasty versus excisional atherectomy trial. *Circulation* 92:734–740, 1995.
51. Dehmer GJ, Nichols TC, Bode AP, et al: Assessment of platelet activation by coronary sinus blood sampling during balloon angioplasty and directional coronary atherectomy. *Am J Cardiol* 80:871–877, 1997.
52. Kini A, Reich D, Marmur JD, et al: Reduction in periprocedural enzyme elevation by abciximab after rotational atherectomy of type b2 lesions: results of the ROTA REOPRO randomized trial. *Am Heart J* 142:965–969, 2001.
53. Bhatt DL, Topol EJ: Does creatinine kinase-MB elevation after percutaneous coronary intervention predict outcomes in 2005? Periprocedural cardiac enzyme elevation predicts adverse outcomes. *Circulation* 112:906–915, discussion 923, 2005.
54. Inoue T, Sohma R, Miyazaki T, et al: Comparison of activation process of platelets and neutrophils after coronary stent implantation versus balloon angioplasty for stable angina pectoris. *Am J Cardiol* 86:1057–1062, 2000.
55. Iakovou I, Mintz GS, Dangas G, et al: Increased CK-MB release is a "trade-off" for optimal stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol* 42:1900–1905, 2003.
56. Hoole SP, Heck PM, Sharples L, et al: Coronary stent length predicts PCI-induced cardiac myonecrosis. *Coron Artery Dis* 21:312–317, 2010.
57. Topol EJ, Ferguson JJ, Weisman HF, et al: Long-term protection from myocardial ischemic events in a randomized trial of brief integrin beta3 blockade with percutaneous coronary intervention. EPIC Investigator Group. Evaluation of Platelet IIb/IIIa Inhibition for Prevention of Ischemic Complication. *JAMA* 278: 479–484, 1997.
58. Tardiff BE, Califf RM, Tcheng JE, et al: Clinical outcomes after detection of elevated cardiac enzymes in patients undergoing percutaneous intervention. IMPACT-II Investigators. Integrilin (eptifibatide) to Minimize Platelet Aggregation and Coronary Thrombosis-II. *J Am Coll Cardiol* 33:88–96, 1999.
59. Smith SC, Jr, Feldman TE, Hirshfeld JW, Jr, et al: ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (ACC/AHA/SCAI writing committee to update 2001 guidelines for percutaneous coronary intervention). *Circulation* 113:e166–e286, 2006.
60. Brener SJ, Lytle BW, Schneider JP, et al: Association between CK-MB elevation after percutaneous or surgical revascularization and three-year mortality. *J Am Coll Cardiol* 40:1961–1967, 2002.
61. Herrmann J, Lennon RJ, Jaffe AS, et al: Defining the optimal cardiac troponin T threshold for predicting death caused by periprocedural myocardial infarction after percutaneous coronary intervention. *Circ Cardiovasc Interv* 7:533–542, 2014.
62. Jeremias A, Baim DS, Ho KK, et al: Differential mortality risk of postprocedural creatine kinase-MB elevation following successful versus unsuccessful stent procedures. *J Am Coll Cardiol* 44:1210–1214, 2004.
63. Prasad A, Gersh BJ, Bertrand ME, et al: Prognostic significance of periprocedural versus spontaneously occurring myocardial infarction after percutaneous coronary intervention in patients with acute coronary syndromes: an analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *J Am Coll Cardiol* 54:477–486, 2009.
64. Brilakis ES, Lee M, Mehilli J, et al: Saphenous vein graft interventions. *Curr Treat Options Cardiovasc Med* 16:301, 2014.
65. Parikh KH, Chag MC, Shah KJ, et al: Intracoronary boluses of adenosine and sodium nitroprusside in combination reverses slow/no-reflow during angioplasty: a clinical scenario of ischemic preconditioning. *Can J Physiol Pharmacol* 85:476–482, 2007.
66. Jaffe R, Dick A, Strauss BH: Prevention and treatment of microvascular obstruction-related myocardial injury and coronary no-reflow following percutaneous coronary intervention: a systematic approach. *JACC Cardiovasc Interv* 3:695–704, 2010.
67. Stone GW, Mehran R, Dangas G, et al: Differential impact on survival of electrocardiographic Q-wave versus enzymatic myocardial infarction after percutaneous intervention: a device-specific analysis of 7147 patients. *Circulation* 104:642–647, 2001.
68. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 349:1429–1435, 1997.
69. The PURSUIT trial investigators: Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary

syndromes. Platelet glycoprotein IIb/IIIa in unstable angina: receptor suppression using integrilin therapy. *N Engl J Med* 339:436–443, 1998.
70. ESPRIT Investigators. Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy: Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): A randomised, placebo-controlled trial. *Lancet* 356:2037–2044, 2000.
71. The RESTORE Investigators: Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. Randomized efficacy study of tirofiban for outcomes and restenosis. *Circulation* 96:1445–1453, 1997.
72. Valgimigli M, Percoco G, Barbieri D, et al: The additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high-risk coronary angioplasty: the ADVANCE trial. *J Am Coll Cardiol* 44:14–19, 2004.
73. Ndrepepa G, Berger PB, Mehilli J, et al: Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. *J Am Coll Cardiol* 51:690–697, 2008.
74. Lincoff AM, Bittl JA, Harrington RA, et al: Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 289:853–863, 2003.
75. Kastrati A, Neumann FJ, Mehilli J, et al: Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N Engl J Med* 359:688–696, 2008.
76. Stone GW, McLaurin BT, Cox DA, et al: Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 355:2203–2216, 2006.
77. Lincoff AM, Steinhubl SR, Manoukian SV, et al: Influence of timing of clopidogrel treatment on the efficacy and safety of bivalirudin in patients with non-ST-segment elevation acute coronary syndromes undergoing percutaneous coronary intervention: an analysis of the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *JACC Cardiovasc Interv* 1:639–648, 2008.
78. Steinhubl SR, Lauer MS, Mukherjee DP, et al: The duration of pretreatment with ticlopidine prior to stenting is associated with the risk of procedure-related non-Q-wave myocardial infarctions. *J Am Coll Cardiol* 32:1366–1370, 1998.
79. Steinhubl SR, Berger PB, Mann JT, 3rd, et al: Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 288:2411–2420, 2002.
80. Mehta SR, Yusuf S, Peters RJ, et al: Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 358:527–533, 2001.
81. Muller I, Besta F, Schulz C, et al: Prevalence of clopidogrel nonresponders among patients with stable angina pectoris scheduled for elective coronary stent placement. *Thromb Haemost* 89:783–787, 2003.
82. Patti G, Colonna G, Pasceri V, et al: Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty) study. *Circulation* 111:2099–2106, 2005.
83. von Beckerath N, Taubert D, Pogatsa-Murray G, et al: Absorption, metabolization, and antiplatelet effects of 300-, 600-, and 900-mg loading doses of clopidogrel: results of the ISAR-CHOICE (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) Trial. *Circulation* 112:2946–2950, 2005.
84. Montalescot G, Sideris G, Meuleman C, et al: A randomized comparison of high clopidogrel loading doses in patients with non-ST-segment elevation acute coronary syndromes: the ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) trial. *J Am Coll Cardiol* 48:931–938, 2006.
85. Di Sciascio G, Patti G, Pasceri V, et al: Effectiveness of in-laboratory high-dose clopidogrel loading versus routine preload in patients undergoing percutaneous coronary intervention: results of the ARMYDA-5 PRELOAD (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) randomized trial. *J Am Coll Cardiol* 56:550–557, 2010.
86. Stankovic G, Zivkovic M: In-laboratory high-dose clopidogrel loading: do we need a mirror of diamond for "Armida's garden"? *J Am Coll Cardiol* 56:558–560, 2010.
87. Kastrati A, Mehilli J, Schuhlen H, et al: A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med* 350:232–238, 2004.
88. Lincoff AM, Kereiakes DJ, Mascelli MA, et al: Abciximab suppresses the rise in levels of circulating inflammatory markers after percutaneous coronary revascularization. *Circulation* 104: 163–167, 2001.
89. Wiviott SD, Braunwald E, McCabe CH, et al: Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. *Lancet* 371:1353–1363, 2008.
90. Wallentin L, Becker RC, Budaj A, et al: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 361:1045–1057, 2009.
91. Cannon CP, Harrington RA, James S, et al: Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet* 375:283–293, 2010.
92. Harrington RA, Stone GW, McNulty S, et al: Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med* 361: 2318–2329, 2009.
93. CHAMPION PLATFORM Investigators: Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med* 361:2330–2341, 2009.
94. Bhatt DL, Harrington RA, Committee CHAMPION PHOENIX Executive Committee and Investigators: Platelet inhibition with cangrelor during PCI. *N Engl J Med* 369:393–394, 2013.
95. CHAMPION Investigators: Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. *Lancet* 382:1981–1992, 2013.
96. Chang SM, Yazbek N, Lakkis NM: Use of statins prior to percutaneous coronary intervention reduces myonecrosis and improves clinical outcome. *Catheter Cardiovasc Interv* 62:193–197, 2004.
97. Jones SP, Gibson MF, Rimmer DM, 3rd, et al: Direct vascular and cardioprotective effects of rosuvastatin, a new HMG-CoA reductase inhibitor. *J Am Coll Cardiol* 40:1172–1178, 2002.
98. Gurm HS, Breitbart Y, Vivekanathan D, et al: Preprocedural statin use is associated with a reduced hazard of postprocedural myonecrosis in patients undergoing rotational atherectomy–a propensity-adjusted analysis. *Am Heart J* 151(1031):e1031–e1036, 2006.
99. Briguori C, Colombo A, Airoldi F, et al: Statin administration before percutaneous coronary intervention: impact on periprocedural myocardial infarction. *Eur Heart J* 25:1822–1828, 2004.
100. ARMYDA Investigators: Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: results from the ARMYDA (Atorvastatin for Reduction of MYocardial Damage during Angioplasty) study. *Circulation* 110:674–678, 2004.
101. Patti G, Chello M, Pasceri V, et al: Protection from procedural myocardial injury by atorvastatin is associated with lower levels of adhesion molecules after percutaneous coronary interventions: results from the ARMYDA-CAMS (Atorvastatin for Reduction of Myocardial Damage During Angioplasty–Cell Adhesion Molecules) substudy. *J Am Coll Cardiol* 48:1560–1566, 2006.
102. Briguori C, Visconti G, Focaccio A, et al: Novel approaches for preventing or limiting events (NAPLES) II trial: Impact of a single high loading dose of atorvastatin on periprocedural myocardial infarction. *J Am Coll Cardiol* 54:2157–2163, 2009.
103. Di Sciascio G, Patti G, Pasceri V, et al: Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention: results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) Randomized Trial. *J Am Coll Cardiol* 54:558–565, 2009.
104. Benjo AM, El-Hayek GE, Messerli F, et al: High dose statin loading prior to percutaneous coronary intervention decreases cardiovascular events: a meta-analysis of randomized controlled trials. *Catheter Cardiovasc Interv* 85:53–60, 2015.
105. Ellis SG, Brener SJ, Lincoff AM, et al: Beta-blockers before percutaneous coronary intervention do not attenuate postprocedural creatine kinase isoenzyme rise. *Circulation* 104:2685–2688, 2001.
106. Lee CH, Low A, Tai BC, et al: Pretreatment with intracoronary adenosine reduces the incidence of myonecrosis after nonurgent percutaneous coronary intervention: a prospective randomized study. *Eur Heart J* 28:19–25, 2007.
107. Bonello L, Sbragia P, Amabile N, et al: Protective effect of an acute oral loading dose of trimetazidine on myocardial injury following percutaneous coronary intervention. *Heart* 93:703–707, 2007.
108. Ballarino MA, Moreyra E, Jr, Damonte A, et al: Multicenter randomized comparison of direct vs. Conventional stenting: the DIRECTO trial. *Catheter Cardiovasc Interv* 58:434–440, 2003.
109. Nageh T, Thomas MR, Sherwood RA, et al: Direct stenting may limit myocardial injury during percutaneous coronary intervention. *J Invasive Cardiol* 15:115–118, 2003.
110. IJsselmuiden AJ, Serruys PW, Scholte A, et al: Direct coronary stent implantation does not reduce the incidence of in-stent restenosis or major adverse cardiac events: six month results of a randomized trial. *Eur Heart J* 24:421–429, 2003.
111. Nordic PCI Study Group: Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. *Circulation* 114:1955–1961, 2006.
112. Hausenloy DJ, Mwamure PK, Venugopal V, et al: Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. *Lancet* 370:575–579, 2007.
113. Hoole SP, Heck PM, Sharples L, et al: Cardiac remote ischemic preconditioning in coronary stenting (CRISP STENT) study: a prospective, randomized control trial. *Circulation* 119:820–827, 2009.
114. Loukogeorgakis SP, Williams R, Panagiotidou AT, et al: Transient limb ischemia induces remote preconditioning and remote postconditioning in humans by a K(ATP)-channel dependent mechanism. *Circulation* 116:1386–1395, 2007.
115. Konstantinov IE, Arab S, Kharbanda RK, et al: The remote ischemic preconditioning stimulus modifies inflammatory gene expression in humans. *Physiol Genomics* 19:143–150, 2004.
116. Svilaas T, Vlaar PJ, van der Horst IC, et al: Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med* 358:557–567, 2008.
117. Fröbert O, Lagerqvist B, Olivecrona GK, et al: Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 369:1587–1597, 2013.
118. Lee MS, Park SJ, Kandzari DE, et al: Saphenous vein graft intervention. *JACC Cardiovasc Interv* 4:831–843, 2011.
119. Roffi M, Mukherjee D, Chew DP, et al: Lack of benefit from intravenous platelet glycoprotein IIb/IIIa receptor inhibition as adjunctive treatment for percutaneous interventions of aorto-coronary bypass grafts: a pooled analysis of five randomized clinical trials. *Circulation* 106:3063–3067, 2002.
120. Karha J, Gurm HS, Rajagopal V, et al: Use of platelet glycoprotein IIb/IIIa inhibitors in saphenous vein graft percutaneous coronary intervention and clinical outcomes. *Am J Cardiol* 98:906–910, 2006.
121. Webb JG, Carere RG, Virmani R, et al: Retrieval and analysis of particulate debris after saphenous vein graft intervention. *J Am Coll Cardiol* 34:468–475, 1999.
122. Cohen DJ, Murphy SA, Baim DS, et al: Cost-effectiveness of distal embolic protection for patients undergoing percutaneous intervention of saphenous vein bypass grafts: results from the SAFER trial. *J Am Coll Cardiol* 44:1801–1808, 2004.
123. Mauri L, Cox D, Hermiller J, et al: The PROXIMAL trial: Proximal Protection During Saphenous Vein Graft Intervention Using The Proxis Embolic Protection System: a randomized, prospective, multicenter clinical trial. *J Am Coll Cardiol* 50:1442–1449, 2007.
124. Mauri L, Rogers C, Baim DS: Devices for distal protection during percutaneous coronary revascularization. *Circulation* 113:2651–2656, 2006.
125. Kereiakes DJ, Turco MA, Breall J, et al: A novel filter-based distal embolic protection device for percutaneous intervention of saphenous vein graft lesions: results of the AMETHYST randomized controlled trial. *JACC Cardiovasc Interv* 1:248–257, 2008.
126. Mehta SK, Frutkin AD, Milford-Beland S, et al: Utilization of distal embolic protection in saphenous vein graft interventions (an analysis of 19,546 patients in the American College of Cardiology-National Cardiovascular Data Registry). *Am J Cardiol* 100:1114–1118, 2007.
127. Badhey N, Lichtenwalter C, de Lemos JA, et al: Contemporary use of embolic protection devices in saphenous vein graft interventions: insights from the stenting of saphenous vein grafts trial. *Catheter Cardiovasc Interv* 76:263–269, 2010.
128. Coolong A, Baim DS, Kuntz RE, et al: Saphenous vein graft stenting and major adverse cardiac events: a predictive model derived from a pooled analysis of 3958 patients. *Circulation* 117:790–797, 2008.
129. Nakamura T, Kubo N, Seki Y, et al: Effects of a distal protection device during primary stenting in patients with acute anterior myocardial infarction. *Circ J* 68:763–768, 2004.
130. Stone GW, Webb J, Cox DA, et al: Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. *JAMA* 293:1063–1072, 2005.
131. Gick M, Jander N, Bestehorn HP, et al: Randomized evaluation of the effects of filter-based distal protection on myocardial perfusion and infarct size after primary percutaneous catheter intervention in myocardial infarction with and without ST-segment elevation. *Circulation* 112:1462–1469, 2005.
132. Cura FA, Escudero AG, Berrocal D, et al: Protection of distal embolization in high-risk patients with acute ST-segment elevation myocardial infarction (PREMIAR). *Am J Cardiol* 99:357–363, 2007.
133. Haeck JD, Koch KT, Bilodeau L, et al: Randomized comparison of primary percutaneous coronary intervention with combined proximal embolic protection and thrombus aspiration versus primary percutaneous coronary intervention alone in ST-segment elevation myocardial infarction: the PREPARE (Proximal Embolic Protection in Acute Myocardial Infarction and Resolution of ST-Elevation) study. *JACC Cardiovasc Interv* 2:934–943, 2009.
134. Haeck JD, Kuijt WJ, Koch KT, et al: Infarct size and left ventricular function in the proximal embolic protection in acute myocardial infarction and resolution of ST-segment elevation (PREPARE) trial: ancillary cardiovascular magnetic resonance study. *Heart* 96:190–195, 2010.
135. Ali OA, Bhindi R, McMahon AC, et al: Distal protection in cardiovascular medicine: current status. *Am Heart J* 152:207–216, 2006.
136. Jordan WD, Jr, Voellinger DC, Doblar DD, et al: Microemboli detected by transcranial Doppler monitoring in patients during carotid angioplasty versus carotid endarterectomy. *Cardiovasc Surg* 7:33–38, 1999.
137. Aronow HD, Shishehbor M, Davis DA, et al: Leukocyte count predicts microembolic Doppler signals during carotid stenting: a link between inflammation and embolization. *Stroke* 36:1910–1914, 2005.
138. Rapp JH, Pan XM, Sharp FR, et al: Atheroemboli to the brain: size threshold for causing acute neuronal cell death. *J Vasc Surg* 32:68–76, 2000.

139. Reimers B, Corvaja N, Moshiri S, et al: Cerebral protection with filter devices during carotid artery stenting. *Circulation* 104:12–15, 2001.
140. Whitlow PL, Lylyk P, Londero H, et al: Carotid artery stenting protected with an emboli containment system. *Stroke* 33:1308–1314, 2002.
141. Cosottini M, Michelassi MC, Puglioli M, et al: Silent cerebral ischemia detected with diffusion-weighted imaging in patients treated with protected and unprotected carotid artery stenting. *Stroke* 36:2389–2393, 2005.
142. Kastrup A, Nagele T, Groschel K, et al: Incidence of new brain lesions after carotid stenting with and without cerebral protection. *Stroke* 37:2312–2316, 2006.
143. Kastrup A, Gröschel K, Krapf H, et al: Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. *Stroke* 34(3):813–819, 2003.
144. Wholey MH, Al-Mubarek N, Wholey MH: Updated review of the global carotid artery stent registry. *Catheter Cardiovasc Interv* 60:259–266, 2003.
145. Yadav JS, Wholey MH, Kuntz RE, et al: Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 351:1493–1501, 2004.
146. Gray WA, Hopkins LN, Yadav S, et al: Protected carotid stenting in high-surgical-risk patients: the ARCHeR results. *J Vasc Surg* 44:258–268, 2006.
147. White CJ, Iyer SS, Hopkins LN, et al: Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30 day results. *Catheter Cardiovasc Interv* 67:503–512, 2006.
148. Ringleb PA, Allenberg J, Bruckmann H, et al: 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 368:1239–1247, 2006.
149. Mas JL, Chatellier G, Beyssen B, et al: Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med* 355:1660–1671, 2006.
150. Mas JL, Chatellier G, Beyssen B: Carotid angioplasty and stenting with and without cerebral protection: clinical alert from the Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial. *Stroke* 35:e18–e20, 2004.
151. Ederle J, Dobson J, Featherstone RL, et al: Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet* 375: 985–997, 2010.
152. Brott TG, Hobson RW, 2nd, Howard G, et al: Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 363:11–23, 2010.
153. Stabile E, Salemme L, Sorropago G, et al: Proximal endovascular occlusion for carotid artery stenting: results from a prospective registry of 1,300 patients. *J Am Coll Cardiol* 55:1661–1667, 2010.
154. Investigators for the ARMOUR Pivotal Trial: Safety and effectiveness of the INVATEC MO.MA proximal cerebral protection device during carotid artery stenting: results from the ARMOUR pivotal trial. *Catheter Cardiovasc Interv* 76:1–8, 2010.
155. EMPiRE Clinical Study Investigators: Neuroprotection during carotid artery stenting using the GORE flow reversal system: 30-day outcomes in the EMPiRE Clinical Study. *Catheter Cardiovasc Interv* 77:420–429, 2011.
156. Bersin RM, Stabile E, Ansel GM, et al: A meta-analysis of proximal occlusion device outcomes in carotid artery stenting. *Catheter Cardiovasc Interv* 80:1072–1078, 2012.
157. Krishnamurthi V, Novick AC, Myles JL: Atheroembolic renal disease: effect on morbidity and survival after revascularization for atherosclerotic renal artery stenosis. *J Urol* 161:1093–1096, 1999.
158. Henry M, Henry I, Klonaris C, et al: Renal angioplasty and stenting under protection: The way for the future? *Catheter Cardiovasc Interv* 60:299–312, 2003.
159. Wholey MH, Toursarkissian B, Postoak D, et al: Early experience in the application of distal protection devices in treatment of peripheral vascular disease of the lower extremities. *Catheter Cardiovasc Interv* 64:227–235, 2005.
160. Siablis D, Karnabatidis D, Katsanos K, et al: Outflow protection filters during percutaneous recanalization of lower extremities' arterial occlusions: a pilot study. *Eur J Radiol* 55:243–249, 2005.
161. Natarajan MK, Kreatsoulas C, Velianou JL, et al: Incidence, predictors, and clinical significance of troponin-I elevation without creatine kinase elevation following percutaneous coronary interventions. *Am J Cardiol* 93:750–753, 2004.
162. Testa L, Van Gaal WJ, Biondi Zoccai GG, et al: Myocardial infarction after percutaneous coronary intervention: a meta-analysis of troponin elevation applying the new universal definition. *QJM* 102:369–378, 2009.

Access Management and Closure Devices

30

FERNANDO CURA

KEY POINTS

- Access-site complications continue to be the most common adverse events after cardiovascular interventions, extending the patient's hospital stay and increasing the associated procedural costs.
- Selection of the appropriate access site is frequently a key issue for the successful completion of coronary, peripheral vascular, or structural procedures. Selection depends on the target vessel or structural intervention, the operator's skills, and the patient's preferences.
- Several femoral access closure technologies are on the interventional field that offer equivalent or even better patient outcomes compared with manual compression.
- The most commonly used femoral closure devices provide two types of mechanisms for percutaneously controlling bleeding: deploying sutures or staples to close the femoral puncture site or using resorbable plugs to temporarily seal the arteriotomy.
- When using closure devices, the operator should be careful in choosing the site of cannulation of the femoral artery.
- Hemostasis accelerators are based on the electrical attractive forces between the patch and the erythrocytes, and they produce more rapid clot formation.
- Vascular closure devices have improved patient comfort by enabling early ambulation, and their use has decreased the burden on the medical staff with a potential reduction in groin complication rates.

The exponential increase in percutaneous interventional procedures for the treatment of cardiovascular diseases in a variety of vascular and nonvascular territories is associated with closer attention to access-site management. The aggressive level of anticoagulation used during therapeutic procedures requires the achievement of safe and reliable hemostasis of the access site. Coronary interventions have been usually performed by the femoral approach; however, to reduce complications and increase patient comfort, radial access is increasingly used and is becoming the preferred access site by many interventionalists.[1] Moreover, the use of a radial approach has demonstrated a reduction not only in major bleeding events but also in hospital stay when compared with femoral access using manual compression for hemostasis.[2-4] Patients undergoing a femoral approach are usually immobilized overnight, which may result in significant discomfort because of increased back pain and the need for analgesics. Noncompliance of patients in regard to strict bed rest after the procedure has been reported to be a substantial factor for femoral complications.

During the last decade, a rapid increase was seen in the percutaneous treatment of aortic aneurysms, dissections, and valve replacements using much larger sheaths that require special attention to the access site. In general, the most common catheterization adverse event is related to the vascular access site.[5,6] Additionally, major access-site complications increase the length of hospital stay and increase medical costs. Vascular complications are also associated with an increased risk of nonfatal myocardial infarction (MI) or death in the year following the procedure, in particular when accompanied by significant bleeding.[7]

The use of manual or mechanical compression was until recently the only way to control bleeding by allowing clot formation at the arteriotomy site. The clinical use of vascular closure devices for rapid hemostasis after femoral access started 25 years ago. Since then, these devices have improved patient comfort by enabling early ambulation, and their use has decreased the burden of the medical staff.

Initially, their use has not resulted in a reduction in groin complication rates. However, during the last decade, large observational studies demonstrated that the use of vascular closure devices—whether suture or collagen based or patches—is associated with a reduction of bleeding and vascular complications compared with manual compression. The introduction of newer femoral closure devices and better patient selection, as well as the learning curve, has probably improved the safety of this intervention.[8,9]

This chapter summarizes the concepts of femoral access puncture, the use of arterial closure devices, and postprocedural management.

PLANNING ACCESS

The selection of an appropriate access site is frequently a key issue for the successful completion of coronary or peripheral vascular procedures. Proficiency with all available vascular puncture techniques is therefore a basic requirement for the interventionalist. The selection of a vascular access site is related to the interventional target, sheath diameter, access to the target lesion length, atheromatosis burden of the route, and patient clinical characteristics.

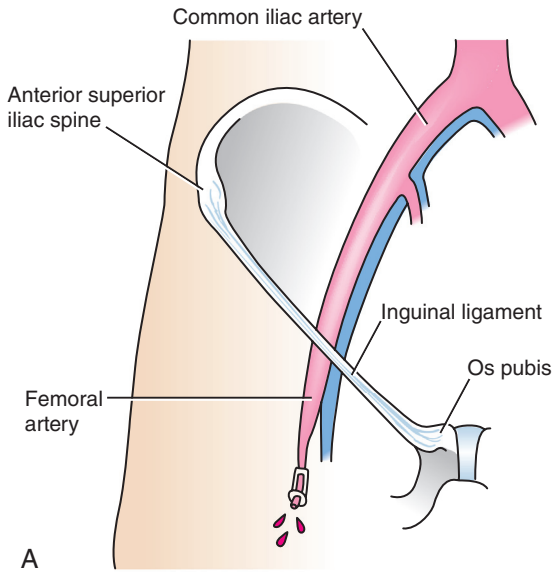
It is important to review clinical reports and to perform preprocedural vascular assessment of the quality of all peripheral pulses, presence of bruits, blood pressure difference between arms, and other pertinent findings such as skin color, trophic changes, ulcerations, or the presence of intermittent claudication. Body habitus, such as extreme obesity, may dictate the use of the radial artery instead of the femoral approach. This important decision deserves full analysis of the target vessel for treatment, consideration of the patient's preference, and assessment of the interventionalist's skills. Some aspects of the vascular access are crucial to the safety and success of the procedure.

The retrograde femoral access and radial access, with the choice based on the patient's limitations or the operator's preferences, are the two preferred approaches for coronary interventions. Ulnar and brachial accesses are seldom utilized anymore. Several techniques are possible for endovascular peripheral therapies based on the target treatment vessel: the crossover femoral approach for contralateral iliofemoral treatment; antegrade femoral puncture for ipsilateral treatment of below-the-knee arteries; femoral retrograde access for aortic, carotid, iliac, and renal vessels; local puncture for dialysis access treatment; and direct retrograde access from below-the-knee arteries. Moreover, the common femoral artery is the preferred access for percutaneous aortic artery and aortic valve interventions.

Retrograde Puncture Technique for the Femoral Artery

The common femoral artery is preferred for percutaneous arterial cannulation because it is large, accessible, and easily compressible. However, strict adherence to meticulous vascular access technique is necessary to avoid vascular complications while using manual compression or femoral closure devices, in particular when larger sheaths are being used.

The mean luminal diameter of the common femoral artery is between 6 and 7 mm. This is theoretically large enough to comfortably accommodate the typical range of femoral sheath sizes for most diagnostic and interventional procedures. Women and patients with diabetes have disproportionately smaller common femoral arteries. The vascular access is generally the only painful part of the procedure, but patient sedation and generous local anesthesia are needed, as well as adequate pressure and rhythm monitoring. The operator should be careful in choosing the site of cannulation of the common femoral artery. When drawing an imaginary line between the anterior superior iliac supine and the pubis, the arterial pulsation is near or at the midpoint of the line (Fig. 30-1). It is important not to rely on the inguinal crease for selection of the puncture site because the distance from the inguinal ligament to the inguinal crease varies, particularly in overweight and elderly patients. Puncture of the skin below is particularly important, so as to enter the artery at the center of the femoral head. Fluoroscopy should be used to ascertain the relative location of the femoral head and pelvic brim in this subgroup of patients.[10,11] Moreover, accessing the common femoral artery using fluoroscopy, compared with traditional anatomic landmark guidance, has improved the arterial puncture site.[10]



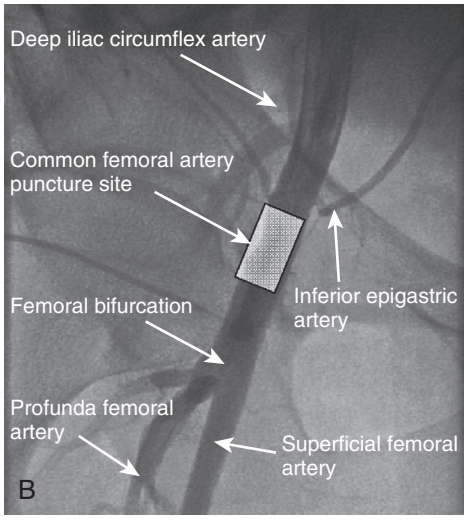


FIGURE 30-1 Accessing the femoral artery. **A,** An imaginary line between the superior anterior crest and the pubis is constructed; this line usually corresponds to the location of the inguinal ligament. The needle should enter approximately 1 cm below the imaginary line while advancing at a 30- to 45-degree angle. **B,** An excellent method for localizing the puncture site is to use fluoroscopy of the femoral head. The needle point should be over the lower inner quadrant (see also Video 30-1).

Ideally, the femoral artery is entered about 1 or 2 cm below the inguinal ligament (see Fig. 30-1). Cannulation of the artery too low increases the chance of entering the superficial femoral artery rather than the common femoral artery. This entry site may predispose to dissection, arterial occlusion, pseudoaneurysm, bleeding, and arteriovenous fistula formation. Entering the artery above the inguinal ligament may lead to problems in compressing the artery against the inguinal ligament, increasing the risk of hematoma formation and favoring retroperitoneal hemorrhage. Some use vascular ultrasound to guide needle entry into the femoral artery. The use of femoral closure devices is contraindicated in higher or lower femoral punctures. The other important aspect is careful puncture of only the anterior wall of the femoral artery with open-bore needles, which have the advantage of demonstrating blood return immediately (Fig. 30-2). Appropriate vascular hemostasis can be achieved with the use of manual compression or femoral closure devices.

The reduction in the sheath size was presumed to result in fewer access complications, but this has not been proven. Retrograde femoral access can be considered the standard technique for coronary, renal, and iliac procedures and as a crossover for contralateral femoral interventions (Fig. 30-3). Endovascular repair of abdominal and thoracic aortic aneurysms has become the standard of care for anatomically appropriate patients. All the devices developed to date are deployed through relatively large (12 to 24 Fr) sheaths. Moreover, transcatheter aortic valve implantation is a rapidly emerging treatment option for patients with aortic valve stenosis and high surgical risk. Different access routes have been proposed that include transapical, transsubclavian, and transfemoral, with percutaneous transfemoral being preferred because it is least invasive and potentially nonsurgical. However, vascular access-site complications due to the large-bore delivery catheters remain an important clinical issue, particularly with respect to elderly patients. Traditionally, this access has required arterial exposure with open cutdown, but with the development of suture-mediated arterial closure devices, the trend toward percutaneous endovascular repair is increasing.[12] This is an effective and safe approach in a select group of patients. The need of larger sheaths for these interventions requires a meticulous puncture technique in the anterior wall of the common femoral artery.

Puncture Technique for the Radial Artery

Miniaturization of the procedural equipment led to a revival of the transradial approach. Despite the considerable training needed, this approach remarkably improves patient comfort and decreases bleeding complications, particularly among patients with aggressive anticoagulation regimens. This approach provides an alternative for coronary angiography and angioplasty and for peripheral arterial angiography. A radial artery access site is associated with far lower rates of bleeding or vascular complications compared with a femoral access site (odds ratio [OR], 0.33; 95% confidence interval [CI], 0.29 to 0.39; $P < .001$)[9]; however, a small proportion of patients present technical challenges that obligate a switch to femoral access (Fig. 30-4, *A* and *B*). This technique is addressed in Chapter 31.

Puncture Technique for the Brachial Artery

Brachial access is an alternative technique that can be used for coronary, renal, and lower limb interventions. However, radial access is usually preferred because of a higher rate of brachial access-site complications compared with femoral access, such as artery occlusion or hematoma (OR, 2.41; 95% CI, 2.15 to 2.69; $P < .001$).[9] Puncture of the brachial artery should be performed in its distal part above the

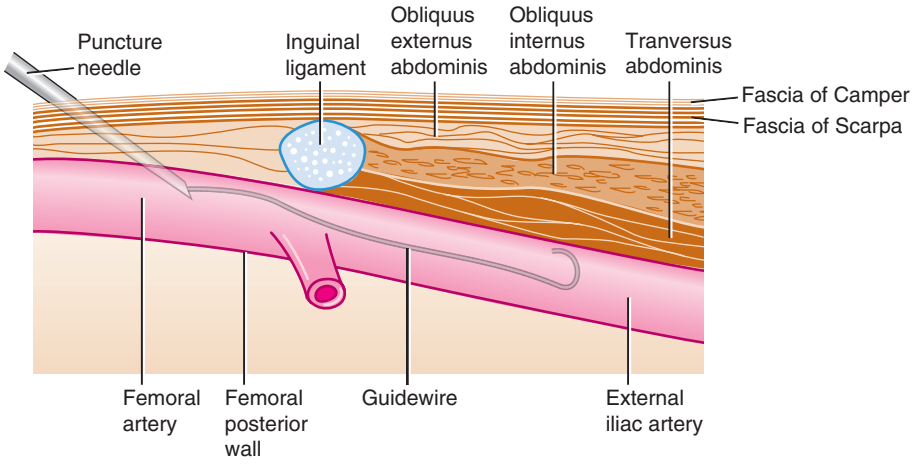


FIGURE 30-2 The femoral artery must be entered using a large-bore needle with backflow of blood. As soon as the needle passes into the vessel through the anterior wall, flow is brisk and pulsatile. The guidewire is advanced and prevents occult bleeding through the posterior wall.

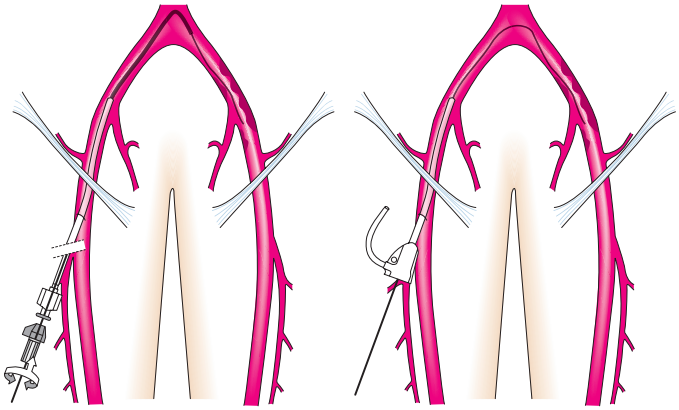


FIGURE 30-3 Retrograde femoral access for a contralateral approach.

antecubital fossa, where the artery is relatively superficial. At this level, after sheath removal, the artery can be compressed against the humerus to obtain hemostasis (Fig. 30-5). Direct puncture of the axillary artery, which has been performed in the past, has largely been abandoned.

Antegrade Puncture Technique for the Femoral Artery

The antegrade puncture technique provides more direct access to many lesions in the femoropopliteal segment and the infraglenoidal arteries. It allows reduction of the volume of contrast and provides stronger support for superficial femoral artery chronic occlusions. However, antegrade puncture is technically far more challenging. Although a high puncture of the common femoral artery is required to have enough space for navigation of the guidewire into the superficial femoral artery, suprainguinal puncture should be avoided because of the higher risk for retroperitoneal bleeding (Fig. 30-6). Injection of contrast through the needle usually helps to identify the femoral bifurcation anatomy.

Puncture Technique for the Popliteal Artery

Transpopliteal retrograde access becomes useful when the superficial femoral artery cannot be crossed using other antegrade techniques. Patients are placed in a prone position, and the puncture is performed with the assistance of roadmap fluoroscopy after the injection of contrast from an ipsilateral femoral catheter or sheath (Fig. 30-7). Particular attention should be paid to achieving complete hemostasis after intervention by careful manual compression. The incidence of access-site complications is potentially higher with transpopliteal access than with conventional techniques.[13]

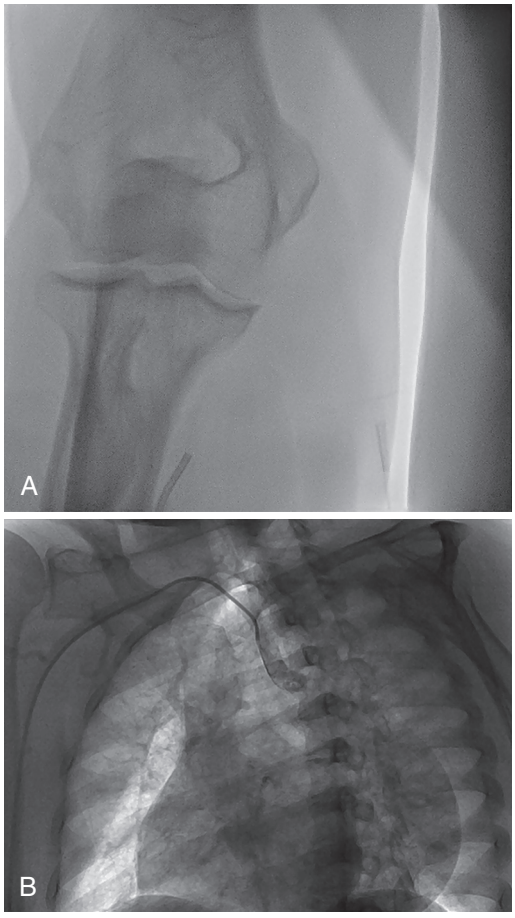


FIGURE 30-4 **A,** Complex radial access due to tortuosity. **B,** Right subclavian artery arising from aortic arch (see also Video 30-2).

Transapical Left Ventricular Puncture

Percutaneous interventions are becoming increasingly complex, but in some instances the target lesion may be difficult to reach using conventional transvenous or transarterial access. Transapical left ventricular (LV) puncture gives direct access to the left ventricle, and although it was frequently used in the past for diagnostic reasons, it has largely been abandoned. Nevertheless, many clinical circumstances exist in which direct transapical access is required for interventional indications, including access to the left ventricle for inaccessible

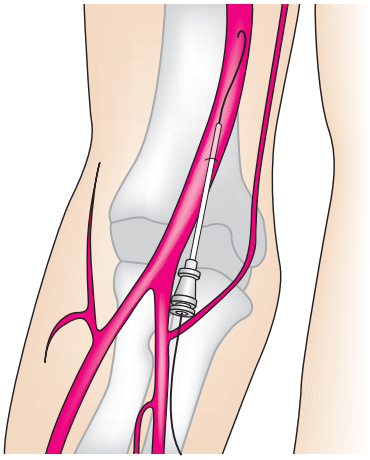


FIGURE 30-5 Puncture technique for the brachial artery.

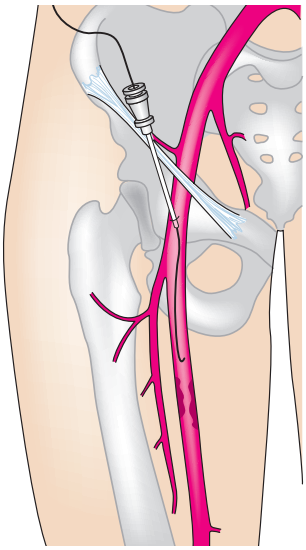


FIGURE 30-6 Anterograde puncture technique for the femoral artery.

percutaneous mitral paravalvular leak repair, percutaneous aortic valve implantation, and many other procedures.[14,15]

Percutaneous transthoracic puncture is appealing for an interventional cardiologist but can be complicated with lung puncture, resulting in pneumothorax or hemothorax as a result of damage to the internal mammary and subcostal arteries or a persistent leak after sheath withdrawal. Damage to the coronary artery can be avoided by doing selective coronary angiography before puncture. However, most of these complications can be diminished by puncturing under direct vision after a mini thoracotomy. Computed tomography (CT) scan is useful to guide the access site either for direct puncture or to perform the mini thoracotomy.

HEMOSTATIC METHODS AFTER PERCUTANEOUS CARDIOVASCULAR PROCEDURES

Proper technique is essential for achieving successful femoral artery hemostasis without complications. Methods used to achieve hemostasis after percutaneous procedures include manual or mechanical compression, vascular plugs, percutaneous vascular sutures or staples, and topical hemostasis accelerators.

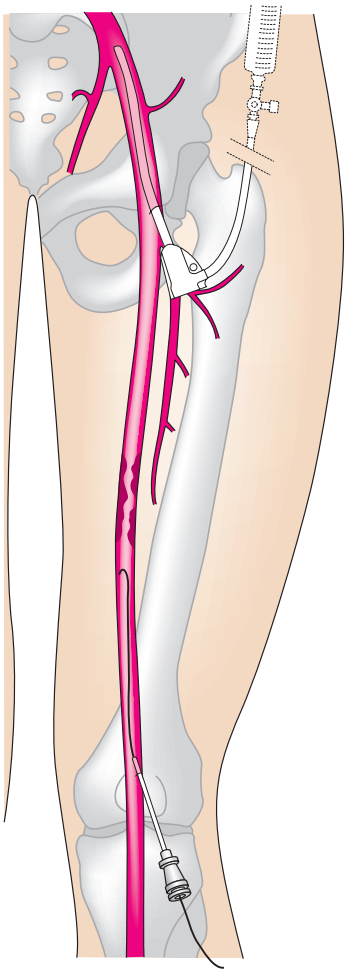


FIGURE 30-7 Puncture technique for the popliteal artery.

Manual and Mechanical Compression

Digital compression should be considered the gold standard for compressive methods. Performed properly, it can prevent bleeding and maintain distal perfusion. This procedure may be performed by a physician, nurse, or technician who has received formal training.

Before sheath removal, the distal pulses and the access site are assessed for signs of an existing hematoma. The duration of manual compression and the time of immobilization are proportional to the size of the introducer sheath and the level of anticoagulation. Although a manual compression technique is effective with smaller sheath sizes, it becomes more challenging and hazardous with increasing sheath sizes. The recommended compression time should be 10 minutes of "firm" pressure, 2 to 5 minutes of "less firm" pressure, and 2 minutes of "light" pressure while doing the pressure dressing. If bleeding continues, another 15 minutes of manual pressure should be applied.

Risk factors for prolonged bleeding include severe atherosclerosis at the puncture site and a loss of elasticity without adequate approximation of the vessel edges after removing the sheath. Other risk factors for bleeding include the sheath size, anticoagulation level at the time of sheath removal, aortic regurgitation, elevated blood pressure, obesity, and older age. The use of manual compression has the advantage of continuous observation and modulation of vascular compression. However, it has the disadvantages of requiring staff member availability, prolonged immobilization, and bed rest, and it increases patient discomfort and length of hospital stay. Advanced Vascular Dynamics (Vancouver, WA) has developed a mechanical compression-assist device, called the Compass, to enhance comfort for

FIGURE 30-8 Compass compression-assist device is placed over the femoral sheath before pulling it. Then, more comfortable manual pressure is applied. (Photo courtesy Advanced Vascular Dynamics, Vancouver, WA.)

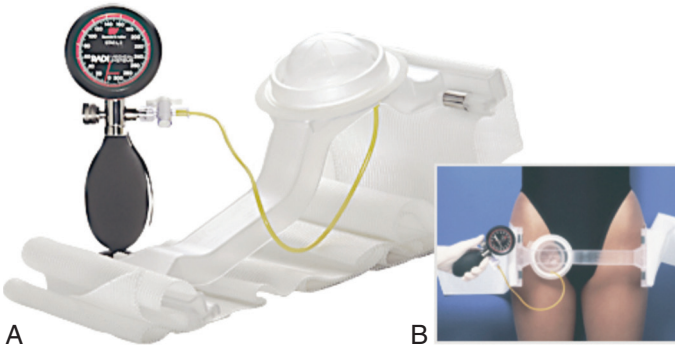


FIGURE 30-9 **A,** The FemoStop pressure system with sphygmomanometer. **B,** The belt should be aligned with the puncture site equally across both hips.

patients and practitioners. It includes a handle and a detachable sterile and disposable disk; practitioners apply external pressure, using the system in much the same way that they would apply manual pressure (Fig. 30-8).

The FemoStop (St. Jude Medical, St. Paul, MN) is a pneumatic pressure device that uses a clear plastic compression bag that molds to skin contours (Fig. 30-9). It is composed of a plastic arch, an inflatable transparent dome, connection tubing, a stopcock, an elastic or adjustable belt, and a handheld manometer. It is held in place by straps that pass around the hip. The amount of applied pressure may be modulated and observed with a sphygmomanometer, and the device allows visualization of the puncture site. The FemoStop is frequently indicated for compression to repair pseudoaneurysms.

In conjunction with manual compression, the Catalyst II (Cardiva Medical, Sunnyvale, CA) provides temporary hemostasis at a femoral access site after femoral arterial catheterization while allowing continuous distal perfusion. After completion of the catheterization procedure, the device is inserted into the artery through the existing introducer sheath. The distal tip of the Catalyst II wire is deployed, which opens the biconvex, low-profile Catalyst disc within the lumen of the femoral artery distal to the introducer sheath tip. After removing the introducer sheath, gentle upward tension is applied to promote hemostasis at an arteriotomy site as an adjunct to manual compression.[16]

Femoral Closure Devices

The most commonly used hemostasis devices provide two types of mechanisms for percutaneously controlling bleeding: deploying sutures or staples to close the femoral puncture site or using resorbable plugs to temporarily seal the arteriotomy. A third group of devices are hemostasis accelerators whose mechanism of action is based on the electrical attractive forces between the closure device and the erythrocytes, leading to more rapid clot formation. Arteriotomy closure devices have emerged as an alternative to traditional mechanical compression after percutaneous cardiovascular intervention. These devices have the potential to reduce the time to hemostasis, facilitate patient mobilization, decrease length of hospital stay, and improve patient satisfaction.

Among endovascular interventions, bleeding and vascular complications are the most common noncardiac, procedure-related adverse outcomes, and these occur in 1% to 2% of cases regardless of whether a vascular closure device is utilized.[9] Although older, single-center studies and randomized trials have shown mixed results regarding the safety of arterial closure devices compared with manual compression, later data show decreased complications with closure devices.[9] This difference may result from increased operator experience with arterial closure devices and improved device technology. A large observational registry from the National Cardiovascular Data Registry (NCDR) showed evidence that vascular closure devices are associated with safety profiles that are not significantly different than manual compression (Table 30-1).[9] However, mechanical compression devices have showed significantly higher odds of "bleeding or vascular complications" than manual compression (OR, 1.15; 95% CI, 1.10 to 1.20; $P < .001$).[9] Several recent studies have presented evidence that closure devices are even associated with decreased risk of bleeding and vascular complications.[17] However, vascular closure device are associated with a higher rate of retroperitoneal bleeding (see Table 30-1).[9] All closure devices have been reported to be safe in patients receiving glycoprotein (GP) IIb/IIIa inhibitors.[18] However, some reports have raised concerns about an increased risk of bleeding complications with the use of vascular closure devices compared with manual compression among patients treated with a combination of anticoagulation drugs, oral antiplatelets, and GP IIb/IIIa inhibitors.[9]

Several studies comparing the benefits and cost-effectiveness of closure devices and manual compression found that the use of closure devices is not only safe but also cost saving.[19,20] Although the use of vascular closure devices has a cost implication, it allows a reduction in hospitalization time that leads to significant cost savings due to decreased personnel and infrastructure demands.

Despite the advances in techniques and the introduction of new products, vessel closure technologies have failed to become commonplace most diagnostic and interventional cases.[21]

Suture-Based Closure Devices

The percutaneous suture-mediated closure device is a method to achieve arteriotomy hemostasis in a safe and timely manner. Several

TABLE 30-1 Risk of Adverse Events After Cardiac Catheterizations by Hemostasis Device

	TYPE OF HEMOSTASIS STRATEGY								
Complication	Manual (%)	Mechanical (%)	AngioSeal (%)	PerClose (%)	BCW (%)	StarClose (%)	Mynx (%)	Patches (%)	Total (%)
Entry-site bleed	0.95	1.10	0.61	0.62	0.70	0.80	0.71	0.82	0.82
Retroperitoneal bleed	0.26	0.26	0.38	0.22	0.11	0.36	0.39	0.18	0.29
Occlusion	0.04	0.03	0.04	0.05	0.00	0.03	0.02	0.03	0.04
Embolization	0.05	0.04	0.04	0.03	0.00	0.02	0.02	0.04	0.04
Dissection	0.25	0.45	0.19	0.15	0.15	0.14	0.09	0.29	0.24
Pseudoaneurysm	0.59	0.63	0.19	0.12	0.40	0.14	0.37	0.51	0.41
Arteriovenous fistula	0.08	0.09	0.03	0.03	0.07	0.02	0.01	0.07	0.06
All bleeding	1.18	1.32	0.95	0.80	0.80	1.12	1.07	0.98	1.08
All vascular	0.97	1.20	0.47	0.35	0.60	0.35	0.49	0.92	0.76
Bleeding or vascular	1.99	2.34	1.36	1.10	1.27	1.42	1.48	1.77	1.72

From Tavris DR, Wang Y, Jacobs S, et al: Bleeding and vascular complications at the femoral access site following percutaneous coronary intervention (PCI): an evaluation of hemostasis strategies. *J Invasive Cardiol* 24:328-334, 2012.
BCW, Boomerang Closure Wire.

studies have shown the efficacy of percutaneous suture-mediated closure devices in decreasing time to hemostasis and time to ambulation without increasing the rate of access-site complications. However, experience suggests that such devices may result in infrequent but challenging vascular complications of the groin, such as retroperitoneal hemorrhage, arterial thromboses, infections, dissections, and large pseudoaneurysms. Proper training and operator skills are necessary for the successful use of these suture-based closure devices. The use of standard aseptic techniques in all cases, along with a single dose of prophylactic intravenous antibiotics during placement of the percutaneous suture-mediated closure device in high-risk patients, appears to prevent infectious complications.

The PerClose (Abbott Vascular, Redwood City, CA) was the first suture-based closure device on the market, and it is based solely on sutures. The main advantage of the PerClose compared with other closure devices is that no material is left at the puncture site except for the sutures. Needles are used to guide the sutures through the vessel wall. Also from Abbott Vascular, the ProStar XL devices use four needles and two sutures and the ProGlide devices use two needles and one suture; both device types can be used with 6- to 10-Fr sheaths. PerClose consists of multiple components that include an automatic knot-pushing tool and the suture-containing device. The tool consists of a sheath connected to a handle by a guide that is introduced into the vessel by means of the 0.035-inch guidewire after the angioplasty sheath has been removed. When the intravascular position has been achieved, the device is secured by pulling the lever and releasing the anchor. Using the needle plunger, needles are inserted through the vessel wall and grip the sutures. The needles are then retracted until they are outside of the skin with the sutures. Each of the two suture ends can be retrieved and pulled down to the surface of the artery with the help of a knot pusher. This improved device has shortened the time of deployment and has improved handling. After it is apparent that hemostasis will be achieved, the guidewire is removed with further sequential tightening of the suture pairs. This device is being used for even larger sheaths with the "preclosing" technique,[22] which allows off-label use of the ProStar or two ProGlide devices to achieve hemostasis for larger sheaths. After accessing the common femoral artery with a 6 to 10 Fr sheath, a ProStar suture-mediated closure device is deployed without tying it. As an alternative, two sequential and perpendicular ProGlides can be implanted. After the intervention is finalized, the preloaded sutures are tied over the large sheath while it is removed. A modified preclosure technique is a feasible alternative for hemostasis after using larger sheaths (12 to 18 Fr) to avoid the open surgical cutdown and diminishing the need for general anesthesia.[12] However, there is still an unmet need for dedicated percutaneous femoral closure devices for these large arteriotomies.

The StarClose (Abbott Vascular) represents the novel concept of an extravascular, clip-based femoral closure device (Fig. 30-10).[23-25] The clips are made of nitinol alloy and are deployed through the existing procedural sheath. The extravascular approach closes by apposing the tissue at and above the arteriotomy site, leaving nothing in the arterial lumen. The artery may be accessed again shortly after hemostasis has been achieved.

Plug-Based Sealing Devices

Collagen is considered one of the most thrombogenic components of the vascular wall. It attracts and binds platelets. Collagen also plays an important role in healing wounds by carrying growth factors and by providing a matrix for cellular proliferation. Because it is highly compatible and easily manufactured in many different forms, collagen is an ideal component for hemostasis products. Collagen can be used alone to plug the vessel wall or tissue tract, or it can be combined with thrombin or Gelfoam (Pharmacia and Upjohn, Kalamazoo, MI). Thrombin converts fibrinogen to fibrin, accelerating and strengthening clot formation. Moreover, substances other than collagen can be used as sealants.

The AngioSeal device (St. Jude Medical)[26] mechanically closes the site by sandwiching the arteriotomy site between a bioabsorbable polymer anchor inside the vessel and an extravascular collagen sponge covering the arterial surface within the skin tract (Fig. 30-11).[26] It consists of four components within a delivery device: (1) an anchor, (2) a collagen plug, (3) a connecting suture, and (4) a tamper. All three components that are deployed into the patient are completely resorbable. The small plug contains only about 15 mg of collagen, and the anchor is made from polyglycolic and polylactic acids. Before AngioSeal deployment, the access site should be assessed by injecting contrast through the sheath under fluoroscopy. If the introducer enters the femoral artery above the inguinal ligament, at the bifurcation, at a branch vessel, or at an atherosclerotic vessel, the risk of device failure or embolization is increased, and an alternative method for hemostasis should be used. Proper technique must be followed to avoid bleeding complications, anchor embolization, thrombosis, and infection.

The ExoSeal (Cordis Endovascular, Hialeah, FL) consists of a feltlike plug made of polyglycolic acid (PGA) that completely dissolves into carbon dioxide and water over about 3 months. It can be used following diagnostic angiography or interventional procedures and is anchored in place on top of the puncture in the femoral artery, after the catheter is removed. The device uses an indicator nitinol wire to locate the arterial anterior wall to ensure extravascular plug placement; the wire is removed before the plug is delivered. Because none of the plug is inserted into the artery itself, it does not interfere with blood flow.[27,28]

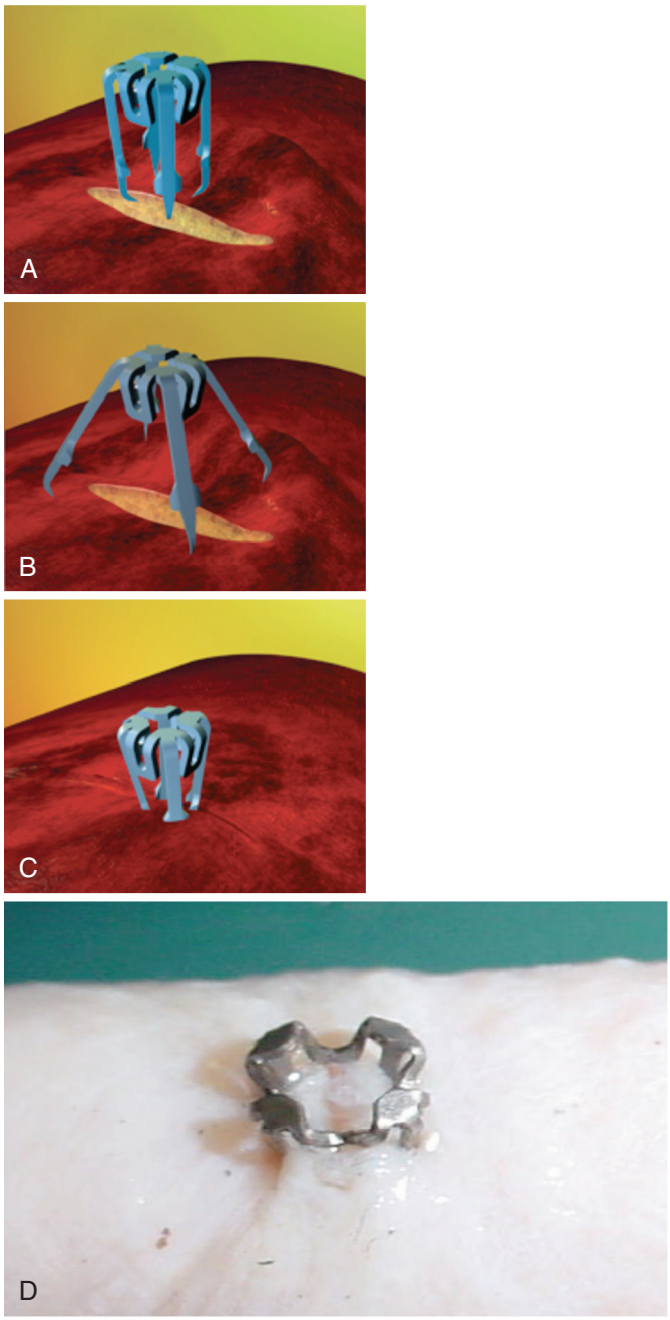


FIGURE 30-10 Expanding staple-based closure device. **A,** Staple tracks are small and deployed through a sterile delivery system, reducing the chance of touch contamination. **B,** The device expands wide above the arteriotomy to close the arteriotomy. **C,** It purses the arteriotomy closed to promote healing, does not remodel the vessel, and has no intraluminal components to impede flow. **D,** The staple gathers the full thickness of the vessel media and adventitia for a secure mechanical closure. (Photograph courtesy Medtronic, Minneapolis, MN.)

The Mynx Vascular Closure Device (Cardinal Health, Dublin, OH) uses an extravascular, biologically inert sealant to provide immediate hemostasis of the puncture site.[24,29] The device met the challenge of simultaneously sealing the puncture hole in the artery and in the tissue tract by generating a thrombus (Fig. 30-12). It incorporates a unique, low-profile, balloon-positioning catheter in combination with a biologic procoagulant compound.[24]

The Cardiva Catalyst is intended to promote hemostasis at an arteriotomy site as an adjunct to manual compression in heparinized patients. It consists of a sterile disposable wire and a sterile disposable clip. After completion of the catheterization procedure, the Catalyst wire is inserted into the artery through the existing introducer sheath. The distal tip of the wire is deployed, which opens the biconvex, low-profile disc within the lumen of the femoral artery distal to the introducer sheath tip.[30] Tension between the disc and the clip creates a site-specific compression of the arteriotomy and establishes temporary hemostasis.

Electrical-Based Sealing Pads

The use of noninvasive closure devices for interventional procedures has rapidly increased in the past few years.[31] The patch technologies are a new form of biologically active, superficially applied therapies that accelerate local hemostasis at the puncture site.[32] One of the substances used in these pads is chitosan, derived from the deacetylation of chitin, a substance obtained from the shells of lobsters, crab, and shrimp that has a slightly positive charge; chitosan has a strong positive charge, whereas erythrocytes and platelets are negatively charged. Because of their positive charges, chitin and chitosan attract negatively charged platelets and red blood cells to the applied area. Other hemostatic pads are impregnated with chemicals such as bovine thrombin or potato starch. These agents, combined with effective manual compression, may result in a shorter time to hemostasis and a stronger blood clot at the puncture site. These devices are effectively used for adjunctive closure devices or as hemostatic accelerators for manual compression of the access site. The simple application and the low cost make this system attractive. The reliability of these devices, however, still needs to be evaluated in a larger number of patients.

Chito-Seal Topical Hemostasis Pad (Abbott Vascular) is intended for use in the management of bleeding wounds such as vascular access sites. The pad is coated with chitosan gel, which is a powerful hemostatic agent twice as chemically active as chitin. The Clo-Sur P.A.D. (Scion Cardio-Vascular, Miami, FL) is a pad that consists of the hydrophilic, naturally occurring biopolymer polyprolate acetate. It also activates electrical interference between erythrocytes and the pad, leading to red blood cell agglutination and clot formation. The SyvekPatch (Marine Polymer Technologies, Danvers, MA), an external device used to control bleeding from vascular access sites, consists of a poly-*N*-acetyl glucosamine polymer isolated from a microalga. The mechanism of action involves clot formation and local vasoconstriction as part of its hemostatic effect. Neptune Pad, a noninvasive hemostasis device from Biotronik (Berlin, Germany), is made of calcium alginate derived from seaweed with antimicrobial and wound-healing properties.

ACCESS-SITE COMPLICATIONS

Local bleeding or vascular complications at the site of catheter insertion constitute the most common adverse events after cardiovascular intervention. Access-site complications can extend the patient's length of hospitalization and increases the associated procedural costs.

An access-site *bleeding complication* is defined as blood loss at the site of arterial or venous access, or due to perforation of an artery or vein, that requires transfusion and prolongs the hospital stay or that causes a drop in hemoglobin of more than 3.0 g/dL. Bleeding attributable to the vascular site could be retroperitoneal, a local hematoma (defined as >10 cm with femoral access, >2 cm with radial access, or >5 cm with brachial access), or external at the entry site. However, the term *vascular complication* includes the presence of any one of the following: occlusion (defined as total obstruction of the artery by thrombus or dissection), embolization, dissection, pseudoaneurysm (defined as the occurrence of a disruption and dilation of the arterial wall without identification of the arterial wall layers at the site of the catheter entry), or arteriovenous (AV) fistula. Other rare complications are neural damage and vascular infection.

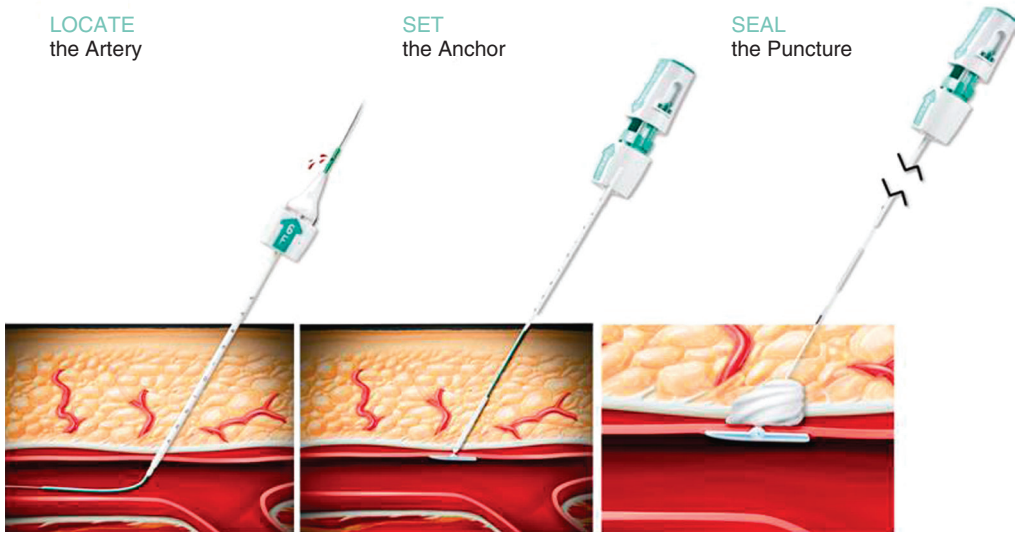


FIGURE 30-11 AngioSeal hemostasis system. The anchor is deployed, and retraction of the system secures the anchor against the anterior vessel wall. The collagen plug is deployed outside of the artery, and the suture is cut at the skin line, leaving the subcutaneous vascular closure components hidden. (Image courtesy St. Jude Medical, St. Paul, MN.)

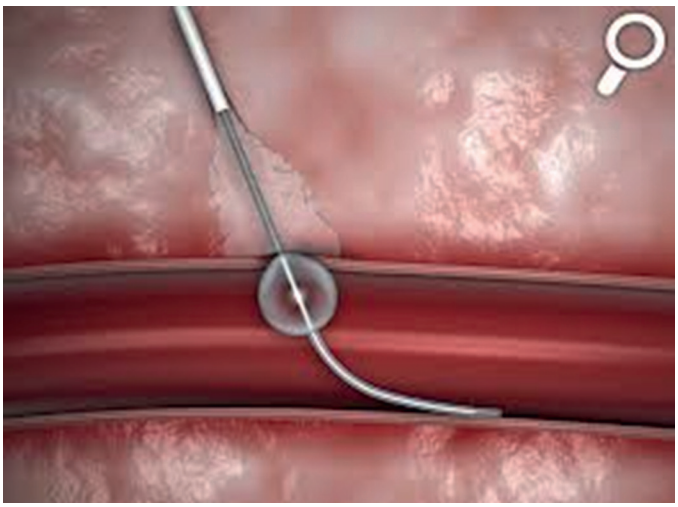


FIGURE 30-12 The Mynx hemostatic device uses a low-profile, balloon-positioning catheter in combination with a biologic, procoagulant-containing bovine collagen and thrombin solution.

Patient characteristics associated with an increased risk of bleeding or vascular complications include advanced age, female sex, high body mass index, renal failure, peripheral vascular disease, hypertension, congestive heart failure, acute MI, recent angioplasty, use of an intraaortic balloon pump during the procedure, an emergency procedure, and use of GP IIb/IIIa inhibitors, thrombolytics, low-molecular-weight heparin, or unfractionated heparin during the procedure.[9]

The American College of Cardiology–National Cardiovascular Data Registry (ACC-NCDR) reported an overall in-hospital serious adverse event rate related to vascular access of 1.72% among 1,819,611 percutaneous coronary intervention (PCI) procedures performed via a femoral access site of 1089 American sites that submitted data to the CathPCI Registry from 2005 through 2009.

Before vascular closure device placement, a femoral artery angiogram through the sheath should be obtained to assess the puncture site, vessel diameter, and presence and severity of atherosclerosis. It can help to identify patients at higher risk for groin complications. Some femoral closure devices should be avoided when the artery diameter is less than 5 mm and in cases of higher or lower femoral punctures.

Bleeding complications occur more frequently while obtaining access and positioning sheaths or early after removal, when local pressure is not properly achieved. Several comorbid conditions have been associated with groin complications.

Hematoma

Hematoma is considered a significant complication when it has a diameter of more than 10 cm. The incidence of local hematoma varies from 1% to 5%, and most hematomas require only observation and no further intervention. Occasionally, hematoma-mediated femoral nerve compression and accompanying limb weakness may occur; it resolves spontaneously within 2 to 3 weeks.

Retroperitoneal Hemorrhage

Retroperitoneal hemorrhage remains an infrequent but occasionally devastating consequence of percutaneous cardiovascular intervention. The incidence of retroperitoneal hemorrhage is 0.29%, 73% of these patients require blood transfusions, and 10% die during hospitalization.[33] Retroperitoneal hemorrhage is independently associated with several factors: "high femoral artery stick," when femoral artery sheaths are placed superior to the inferior epigastric artery; female sex; use of an AngioSeal device; use of a GP IIb/IIIa inhibitor; presentation of acute MI; and inversely with the patient's weight.[33] Other studies have confirmed three factors to be predictive for retroperitoneal hemorrhage—female sex, low body weight, and high femoral puncture—whereas the use of GP IIb/IIIa inhibitors, sheath size, and the use of a closure device did not correlate with bleeding complications.[34] Bleeding complications should be considered when a patient has a new onset of hypotension, flank pain, or decreased hematocrit level. Strict adherence to meticulous vascular access technique, judicious use of closure devices, and appropriate and rapid management when this complication is suspected should lessen the occasionally serious consequences related to this problem.

A major cause of retroperitoneal bleeding is a puncture above the inguinal ligament. When the posterior arterial wall is punctured, blood can spread into the retroperitoneal space. The location of the inferior epigastric artery may be helpful in judging the location of the puncture with regard to the inguinal ligament; the inferior border of this vessel

defines the border of the inguinal ligament and represents a marker by which femoral punctures can be assessed for possible risk of retroperitoneal bleeding. The inferior epigastric artery arises from the distal external iliac artery just before it crosses under the inguinal ligament to enter the thigh and become the femoral artery. It typically originates opposite the deep iliac circumflex branch and bears a direct relation to the inferior extent of the peritoneal transversalis fascia (see Fig. 30-12). When the entry site of the sheath is superior to the origin of the inferior epigastric artery, the sheath passes through various layers of the anterior abdominal wall, including superficial fascia and muscles, before entering the artery (Fig. 30-13). The collagen plug–based closure devices may not reach the wall of the artery in some cases; therefore the operator should be careful in choosing the site of cannulation of the femoral artery. Fluoroscopy can be used to ascertain the relative location of the femoral head and pelvic brim in that endeavor (see Fig. 30-1). The retroperitoneal space appears to be able to sequester large amounts of blood. Volume and blood-product support and correction of thrombin and platelet inhibition are central to management when this complication is suspected. Although computed tomography or other forms of imaging are occasionally useful in diagnosing retroperitoneal hemorrhage, this modality is usually not required and may delay treatment. Peripheral vascular surgery or endovascular treatment is appropriate if blood-product transfusion does not result in hemodynamic stabilization or if there is clinically significant organ or nerve compression.

Pseudoaneurysm

The incidence of iatrogenic femoral pseudoaneurysms after percutaneous procedures is approximately 0.4%. A pseudoaneurysm is a hematoma that remains in continuity with the artery, allowing flow in and out of the hematoma. It can be differentiated from a simple hematoma by the presence of a bruit and a palpable pulsatile mass. Pseudoaneurysms are normally detected by ultrasound (Fig. 30-14). Older age, obesity, female sex, larger sheath size, peripheral vascular disease, a low arterial puncture site (below the common femoral bifurcation), and the level of anticoagulation are associated with this complication. A pseudoaneurysm larger than 3 cm in diameter is usually treated by mechanical compression, thrombin injection, or surgery. Smaller pseudoaneurysms can be followed by serial ultrasound. Ultrasound-guided manual or mechanical compression is often used to convert the pseudoaneurysm to a thrombosed hematoma by compressing the neck that connects it to the artery. Ultrasound-guided, low-dose thrombin injection appears to be more effective in reducing the need for surgical repair, is better tolerated by the patients, and requires a shorter hospital stay.[35]

Arteriovenous Fistula

Arteriovenous fistula is defined as an abnormal connection between an artery and a vein (Fig. 30-15 and Video 30-3). This may be caused by trauma, improper removal of adjacent arterial and venous sheaths, or inadvertent puncture of a vein while accessing an artery. It is an uncommon and low-risk groin complication that is suspected by the detection of a continuous bruit at the access site, and it is diagnosed

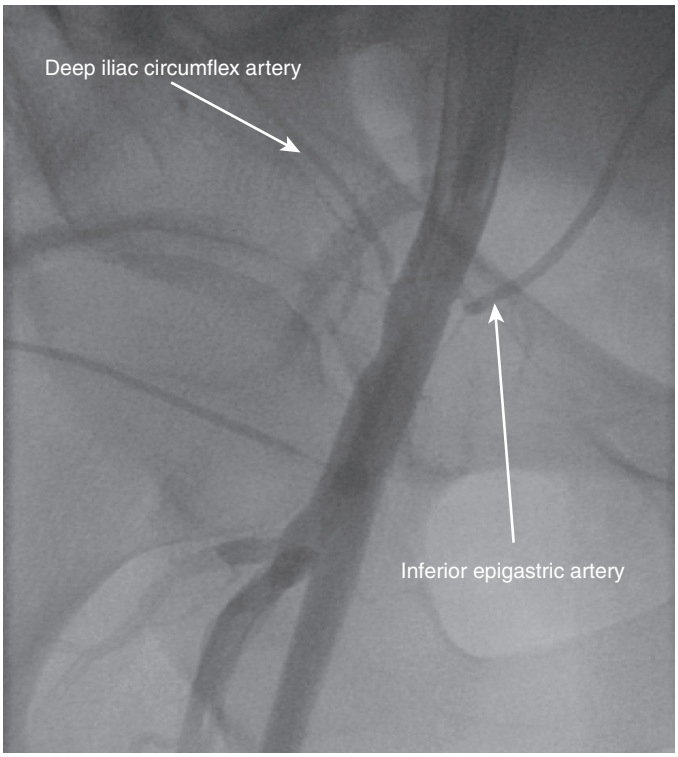


FIGURE 30-13 Angiogram through the sheath to assess the femoral artery and puncture location. The right anterior oblique, 30-degree projection of a typical femoral artery access site shows the inferior epigastric entry in relation to its surrounding anatomy. The inferior epigastric artery arises from the distal external iliac artery just before it crosses under the inguinal ligament; the inferior border of this vessel defines the border of the inguinal ligament.

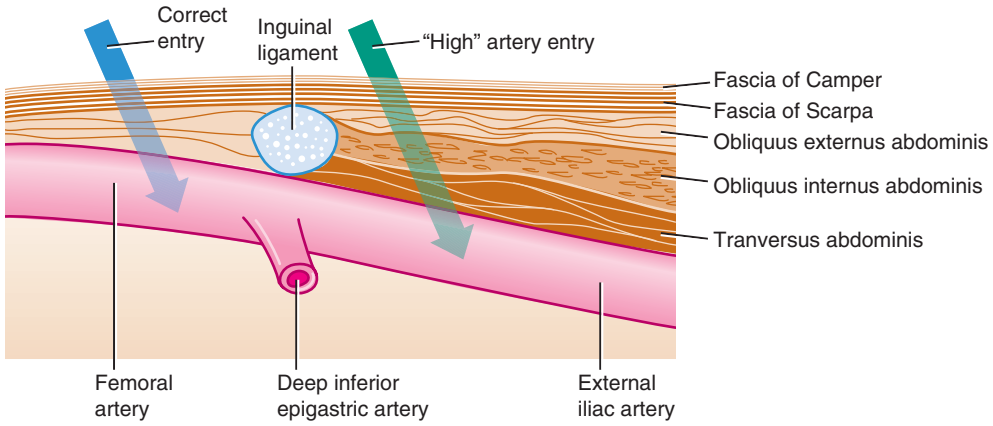


FIGURE 30-14 The diagram depicts the relation between the high entry and the correct puncture site related to the inguinal ligament and inferior epigastric artery. The placement of sheath in a high puncture site crosses over the fascia of Camper, fascia of Scarpa, obliquus externus, obliquus internus, and the transverses abdominis muscles.

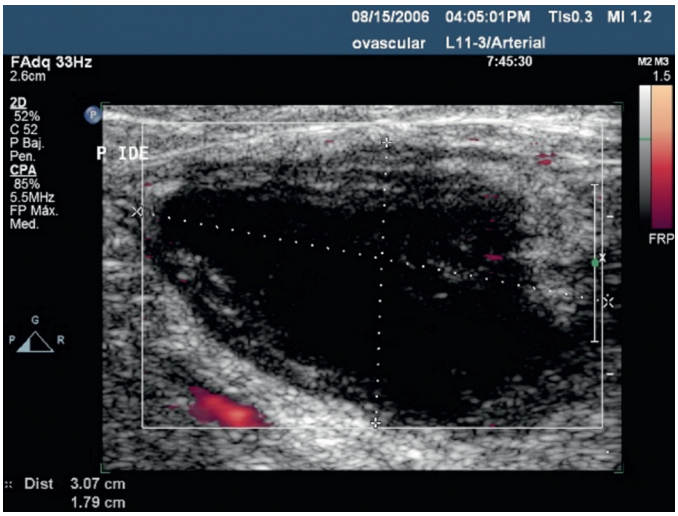


FIGURE 30-15 Pseudoaneurysm arising from the common femoral artery is assessed by duplex ultrasound (see also Video 30-3).

by ultrasound. In cases of arterial insufficiency, the fistula can be treated with ultrasound-guided compression, endovascular stenting, or surgical repair.

Vessel Occlusion

Vessel occlusion associated with manual compression may occur because of excessive occlusive pressure during the compression process. Patients with diabetes, female patients, or those with peripheral vascular disease have arteries with reduced lumen diameters and may be more susceptible to this complication. Vessel occlusion is characterized by a sudden onset of pain and possible paresthesia. The affected limb is cyanotic, cool, and has diminished or absent pulses. Treatment methods for vessel occlusion include administration of heparin or lytic agents or an endovascular or surgical thrombectomy procedure.

Access-Site Infections

Although relatively uncommon, vascular closure device–related infection is an emerging and serious phenomenon with a high morbidity rate. It requires aggressive medical and surgical intervention to achieve cure.[36] Access-site infections manifest with high fever, femoral abscess, septic thrombosis, and mycotic aneurysm. The predominant source of pathogens is the endogenous flora of the patient's skin, so attention to skin preparation is part of the infection-prevention strategy. Diabetes mellitus and obesity are the most common associated comorbidities, and infectious groin complications are significantly increased with suture-based closure devices. Surgical removal of the percutaneous closure device and debridement to normal arterial wall are recommended for all patients with suspected femoral endarteritis. Before inserting a closure device, it is recommended to again prepare the skin insertion site and remove any pooled blood before beginning the arterial closure, especially in the case of a prolonged procedure. If compromise of sterile technique is suspected, the operator should consider a change of gloves before beginning the arterial closure and a change of towels around the skin insertion site, especially if the drape has become saturated with blood. Some interventionalists routinely administer one or more doses of intravenous antibiotics when using a vascular closure device. Although some differences may exist regarding local complications with the use of femoral closure systems, neither device has been shown to reduce major local complications.

CONCLUSIONS AND FUTURE TRENDS

Access-site complications continue to be the most common adverse events after cardiovascular interventions that extend the length of hospitalization and increase the associated procedural costs. Several femoral access closure technologies offer equivalent or even better patient outcomes compared with manual compression, and improvement of the safety profile of vascular closure devices has been consistent over time. The ease of use is continuing to improve, patients are being more carefully selected, and operators are gaining more experience with such devices. Sealing and suturing closure devices have been shown to shorten hemostasis time, reduce the discomfort of manual and mechanical compression, and allow earlier ambulation after cardiovascular procedures compared with conventional compression techniques. Patch technologies are a new form of biologically active, superficially applied therapies that have found acceptance in many practices. Ultimately, the further expansion of femoral closure devices will depend on which device provides a simple approach with reliable hemostasis at a cost that can justify their incorporation into routine practice. A need still exists for dedicated femoral closure devices for larger arteriotomies for aortic endovascular repair and aortic valve replacement.

REFERENCES

1. Jolly SS, Amlani S, Hamon M, et al: Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. *Am Heart J* 157:132–140, 2009.
2. Bernat I, Horak D, Stasek J, et al: ST-elevation myocardial infarction treated by radial or femoral approach in a multicenter randomized clinical trial: the STEMI-RADIAL trial. *J Am Coll Cardiol* 63:964–972, 2013.
3. Brewster S, Khimdas K, Cleary N, et al: Impact of a dedicated "radial lounge" for percutaneous coronary procedures on same-day discharge rates and bed utilization. *Am Heart J* 165:299–302, 2013.
4. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al: Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (radial versus femoral randomized investigation in ST-elevation acute coronary syndrome) study. *J Am Coll Cardiol* 60:2481–2489, 2012.
5. Applegate RJ, Sacrinty MT, Kutcher MA, et al: Propensity score analysis of vascular complications after diagnostic cardiac catheterization and percutaneous coronary intervention 1998-2003. *Catheter Cardiovasc Interv* 67:556–562, 2006.
6. Nikolsky E, Mehran R, Dangas G, et al: Development and validation of a prognostic risk score for major bleeding in patients undergoing percutaneous coronary intervention via the femoral approach. *Eur Heart J* 28:1936–1945, 2007.
7. Applegate R, Sacrinty M, Little W, et al: Prognostic implications of vascular complications following PCI. *Catheter Cardiovasc Interv* 74:64–73, 2009.
8. Tavris DR, Dey S, Albrecht-Gallauresi B, et al: Risk of local adverse events following cardiac catheterization by hemostasis device use—phase II. *J Invasive Cardiol* 17:644–650, 2005.
9. Tavris DR, Wang Y, Jacobs S, et al: Bleeding and vascular complications at the femoral access site following percutaneous coronary intervention (PCI): an evaluation of hemostasis strategies. *J Invasive Cardiol* 24:328–334, 2012.
10. Abu-Fadel MS, Sparling JM, Zacharias SJ, et al: Fluoroscopy vs. traditional guided femoral arterial access and the use of closure devices: a randomized controlled trial. *Catheter Cardiovasc Interv* 74:533–539, 2009.
11. Huggins CE, Gillespie MJ, Tan WA, et al: A prospective randomized clinical trial of the use of fluoroscopy in obtaining femoral arterial access. *J Invasive Cardiol* 21:105–109, 2009.
12. Nelson PR, Kracjer Z, Kansal N, et al: A multicenter, randomized, controlled trial of totally percutaneous access versus open femoral exposure for endovascular aortic aneurysm repair (the PEVAR trial). *J Vasc Surg* 59:1181–1193, 2014.
13. Kluge A, Rauber K, Breithecker A, et al: Puncture of the popliteal artery using a Doppler-equipped (smart) needle in transpopliteal interventions. *Eur Radiol* 13:1972–1978, 2003.
14. Nietlispach F, Johnson M, Moss RR, et al: Transcatheter closure of paravalvular defects using a purpose-specific occluder. *JACC Cardiovasc Interv* 3:759–765, 2010.
15. Brown SC, Boshoff DE, Rega F, et al: Transapical left ventricular access for difficult to reach interventional targets in the left heart. *Catheter Cardiovasc Interv* 74:137–142, 2009.
16. Cirillo P, Petrillo G, D'Ascoli GL, et al: Successful use of the Cardiva Boomerang vascular closure device to close a brachial artery puncture site after emergency PTCA. *Heart Vessels* 25:565–568, 2010.
17. Marso SP, Amin AP, House JA, et al: Association between use of bleeding avoidance strategies and risk of periprocedural bleeding among patients undergoing percutaneous coronary intervention. *JAMA* 303:2156–2164, 2010.
18. Exaire JE, Tcheng JE, Kereiakes DJ, et al: Closure devices and vascular complications among percutaneous coronary intervention patients receiving enoxaparin, glycoprotein IIb/IIIa inhibitors, and clopidogrel. *Catheter Cardiovasc Interv* 64:369–372, 2005.
19. Resnic FS, Arora N, Matheny M, Reynolds MR: A cost-minimization analysis of the Angio-seal vascular closure device following percutaneous coronary intervention. *Am J Cardiol* 99:766–770, 2007.
20. Rickli H, Unterweger M, Sutsch G, et al: Comparison of costs and safety of a suture-mediated closure device with conventional manual compression after coronary artery interventions. *Catheter Cardiovasc Interv* 57:297–302, 2002.
21. Bangalore S, Arora N, Resnic FS: Vascular closure device failure: frequency and implications: a propensity-matched analysis. *Circ Cardiovasc Interv* 2:549–556, 2009.
22. Kahlert P, Eggebrecht H, Erbel R, Sack S: A modified "preclosure" technique after percutaneous aortic valve replacement. *Catheter Cardiovasc Interv* 72:877–884, 2008.
23. McTaggart RA, Raghavan D, Haas RA, Jayaraman MV: StarClose vascular closure device: safety and efficacy of deployment and reaccess in a neurointerventional radiology service. *AJNR Am J Neuroradiol* 31:1148–1150, 2010.

24. Scheinert D, Sievert H, Turco MA, et al: The safety and efficacy of an extravascular, water-soluble sealant for vascular closure: initial clinical results for Mynx. *Catheter Cardiovasc Interv* 70:627–633, 2007.
25. Tay EL, Co M, Tai BC, et al: Clinical experience of StarClose vascular closure device in patients with first and recurrent femoral punctures. *J Interv Cardiol* 21:67–73, 2008.
26. Applegate RJ, Sacrinty M, Kutcher MA, et al: Vascular complications with newer generations of Angioseal vascular closure devices. *J Interv Cardiol* 19:67–74, 2006.
27. Pieper CC, Wilhelm KE, Schild HH, Meyer C: Feasibility of vascular access closure in arteries other than the common femoral artery using the ExoSeal vascular closure device. *Cardiovasc Intervent Radiol* 37:1352–1357, 2014.
28. Wiemer M, Langer C, Fichtlscherer S, et al: First-in-man experience with a new 7F vascular closure device (Exoseal): the 7F ECLIPSE study. *J Interv Cardiol* 25:518–525, 2012.
29. Grandhi R, Kanaan H, Shah A, et al: Safety and efficacy of percutaneous femoral artery access followed by Mynx closure in cerebral neurovascular procedures: a single center analysis. *J Neurointerv Surg* 6:445–450, 2013.
30. Doyle BJ, Godfrey MJ, Lennon RJ, et al: Initial experience with the Cardiva Boomerang vascular closure device in diagnostic catheterization. *Catheter Cardiovasc Interv* 69:203–208, 2007.
31. Applegate RJ, Sacrinty MT, Kutcher MA, et al: Propensity score analysis of vascular complications after diagnostic cardiac catheterization and percutaneous coronary intervention using thrombin hemostatic patch-facilitated manual compression. *J Invasive Cardiol* 19:164–170, 2007.
32. Hirsch JA, Reddy SA, Capasso WE, Linfante I: Non-invasive hemostatic closure devices: "Patches and pads,". *Tech Vasc Interv Radiol* 6:92–95, 2003.
33. Ellis SG, Bhatt D, Kapadia S, et al: Correlates and outcomes of retroperitoneal hemorrhage complicating percutaneous coronary intervention. *Catheter Cardiovasc Interv* 67:541–545, 2006.
34. Farouque HM, Tremmel JA, Raissi Shabari F, et al: Risk factors for the development of retroperitoneal hematoma after percutaneous coronary intervention in the era of glycoprotein IIb/IIIa inhibitors and vascular closure devices. *J Am Coll Cardiol* 45:363–368, 2005.
35. Olsen DM, Rodriguez JA, Vranic M, et al: A prospective study of ultrasound scan-guided thrombin injection of femoral pseudoaneurysm: a trend toward minimal medication. *J Vasc Surg* 36:779–782, 2002.
36. Geary K, Landers JT, Fiore W, Riggs P: Management of infected femoral closure devices. *Cardiovasc Surg* 10:161–163, 2002.

31 Transradial Approach for Diagnostic Coronary Angiography and Intervention

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KEY POINTS

- Access-site and non–access-site bleeding complications after percutaneous coronary intervention (PCI) are associated with poor outcome, including mortality.
- A transradial approach to PCI is associated with virtually no major access-site bleeding with subsequent increase of net clinical benefit.
- After an initial short learning curve, the procedural success rates of the transradial approach become similar to those of the transfemoral approach.
- A transradial approach can be used in any clinical condition for all procedures and devices compatible with 5-, 6-, or 7-Fr guiding catheters.
- A transradial approach is associated with a reduction of mortality rates in the setting of PCI for ST-elevation myocardial infarction (STEMI).

Both diagnostic coronary angiography and PCI are still most commonly performed via transfemoral access in a majority of catheterization laboratories, although initial reports in the late 1980s demonstrated the feasibility and safety of diagnostic coronary angiography via a transradial approach.[1] The development of highly active antithrombotic regimens associated with a major reduction in thrombotic complications of PCI, but also an increase in femoral access-site–related bleeding complications, have led to the development of a transradial approach for PCI during the past decade. The use of 6-Fr and more recently 5-Fr guiding catheters with the generalization of 6- and 5-Fr compatible balloons, coronary stents, and other devices such as rotational atherectomy, thrombectomy, or distal protection devices allows treatment of complex lesions—such as with multivessel PCI, bifurcation lesions, and so on—in complex situations (PCI for acute coronary syndromes [ACSs]), including primary or rescue PCI via a transradial approach, following a relatively short and easy learning curve. Used rarely in the United States until 2007 (1.3% of procedures),[2] its place is growing exponentially with rates around 16% in the last trimester of 2012,[3] although the U.S. still lags far behind Asian and European countries, where current rates are more than 80%.[4] Similarly, primary PCI is more and more frequently performed with a radial access, as recently shown in the international randomized Acute STEMI Treated With Primary Angioplasty and Intravenous Enoxaparin or UFH to Lower Ischemic and Bleeding Events at Short- and Long-Term Follow-Up (ATOLL) study, in which 66% of procedures used the radial artery.[5] The growing interest in the transradial approach is also apparent in the medical literature, and half of the medical publications concerning the subject have been published within the past 4 years. Since the initial description of the transradial approach, more than 1000 articles have been published.

RATIONALE FOR TRANSRADIAL APPROACH TO PERCUTANEOUS CORONARY INTERVENTION

Anatomic Considerations

The radial artery, as well as the ulnar artery, is usually a terminal branch of the brachial artery, originating below the elbow. In some cases the radial artery originates from the upper brachial artery or even directly from the axillary artery. It follows the external margin of the forearm to reach the wrist, where it divides most of the time into two branches, joining branches of the ulnar artery through superficial and deep palmar arches. The palmar arches may also be irrigated by branches of the common interosseous artery, a high-originating branch of the ulnar artery. Quite superficial all along, the radial artery is covered by the brachioradialis muscle proximally. It becomes very superficial and accessible in its 3- to 5-cm distal portion before the wrist, considered the puncture site. Moreover the satellite radial nerve changes direction at this final portion, making puncture-related nerve injury almost impossible. The absence of major veins around the radial artery also reduces the risk of arteriovenous fistula. Because of such anatomy, the transradial approach to PCI appears to be very safe.

Feasibility

The feasibility and security of a transradial approach to coronary diagnostic or interventional procedures have been widely demonstrated. The historical data from such studies are summarized in Table 31-1. The transradial approach requires a variable learning curve, leading to higher rates of procedural success and lower x-ray exposure among experienced operators.[6] The importance of the learning curve was recently highlighted by the American National Cardiovascular Data Registry (NCDR), based on a study population of 54,561 patients. It showed that as the operator's transradial intervention volume increases, more high-risk patients are treated on the one hand, whereas on the other, fluoroscopy time, contrast volume, and bleeding risk are reduced. The threshold to overcome the learning curve is still debated but is around 30 to 50 cases.[7]

Overall the feasibility of a transradial approach for diagnostic or interventional coronary procedures is high (>90%), especially in experienced centers (>95%). In a series of 1119 consecutive South Korean patients, the mean radial artery diameter measured by ultrasound was 2.6 (± 0.41) mm in men and 2.43 (± 0.38) mm in women.[8] In another series of 250 Japanese patients, the radial artery diameter was larger than 7- and 8-Fr catheters in 71.5% and 44.9% of male patients and 40.3% and 24% of female patients, respectively.[9] Although such data may not be totally generalized to all other populations, it underlies the fact that the transradial approach could potentially be used in a vast majority of patients with 5-, 6-, and even 7-Fr catheters. In some patients with sufficiently large artery diameter, 8-Fr catheters may also be used if needed. Yet it must be remembered that catheter–radial artery diameter mismatch is associated with a higher risk of radial artery occlusion.

The transradial approach has been used for different types of procedures with various devices and methods such as intravascular ultrasound (IVUS)–guided stenting, coronary brachytherapy, distal protection, embolectomy, rotational atherectomy, bifurcated stents, and so on. However, this approach is still incompatible with the intraaortic balloon pump (IABP) and all other devices or procedures needing 8-Fr or greater access.

Recently, the use of sheathless guiding catheters with smaller outer diameters—6.5- and 7.5-Fr catheters, equivalent to 5- and 6-Fr introducer diameters respectively—has been reported to be feasible and safe.[10] Although their use remains somewhat confidential, such

TABLE 31-1 Historical Transradial Percutaneous Coronary Intervention Feasibility Studies

Author	Type of Procedure	*N*	Catheter Size	Success Rate (%)	Access-Site Complication (%)
Saito[9]	Unselected patient PCI	1360	6F/7F/8F	92	0.2
Kim[37]	Primary PCI	30	6F	90	0
Valsecchi[38]	Primary PCI	163	6F	97	0
Valsecchi[39]	Unselected				
	≥70 years old	323	6F	98.8	0.4
	<70 years old	80	6F	99	0
Kiemeneij[40]	POBA (?)	100	6F	94	2
Kiemeneij[67]	Stenting	20	6F	100	0
Kiemeneij[68]	Stenting	100	6F	96	3
Louvard[69]	Primary PCI	277	6F	95	0
Mulukutla[70]	Primary PCI (GP IIb/IIIa inhibitors in 75%)	41	6F	100	0

GP, Glycoprotein; *PCI,* percutaneous coronary intervention; *POBA,* plain old balloon angioplasty.

catheters may allow more complex procedures, such as simultaneous "kissing" stenting, in patients with small radial arteries.

A transradial approach may be somewhat limited in patients who have previously undergone coronary artery bypass grafting (CABG). A recently published small ($N = 128$) monocentric randomized study in this setting (58% diagnostic angiography alone) reported higher crossover rates, contrast volume, procedure time, and patient and operator exposure in the global group associated with a left transradial compared with a transfemoral approach. Nevertheless, as acknowledged by authors, with the first operator being always a trainee, the study may have been biased for the radiation exposure and contrast volume parameters. Furthermore, in the subgroup of patients who underwent PCI, procedural success was similar between the two groups.[11] In patients with a left mammary graft, it is usually easier to cannulate the ostium selectively by using a left radial approach. However, selective catheterization of left or right internal thoracic bypasses is often possible via the contralateral approach, such as by using a Judkins left or other dedicated catheter. In patients with bilateral left internal thoracic bypasses, technical difficulties can be overcome easily by a bilateral radial access.

In a recent publication from a high radial volume center with a radial-first strategy, based on a consecutive series of more than 1600 patients, a transfemoral approach was directly used in 2.7% of patients, and in another 1.8%, it was used after a failed attempt at a transradial approach.[12] Female sex, previous CABG, and cardiogenic shock were independent predictors of a transradial approach failure.

TRANSRADIAL VERSUS TRANSFEMORAL APPROACH FOR PERCUTANEOUS CORONARY INTERVENTION

The transfemoral approach represents an easily accessible superficial arterial access point, through which large catheters delivering all types of devices could be introduced. Compared with the transfemoral approach, transradial access is associated with fewer vascular complications, more comfort for patients, and the possibility of rapid ambulation, lower procedure cost, and reduced hospital stay and cost. Several randomized trials comparing advantages and disadvantages of each method are summarized in Table 31-2.

The major study comparing the transradial and transfemoral approaches is the Radial Versus Femoral Access for Coronary Intervention (RIVAL) trial,[13] which included 7021 ACS patients randomly assigned to each of the approaches for angiography and/or PCI. Indications for angiography were STEMI in 27.2% and 28.5% and non-STEMI (NSTEMI) in 28.5% and 25.8% in transradial and transfemoral groups, respectively. Angiography was performed in 99.8% and PCI was performed in approximately 66% of patients in both groups. PCI success rates were comparable between the two groups (95.4% vs. 95.2%), with higher access-site crossover rates in the transradial group (7.6% vs. 2%, $P < .0001$). The rates of the primary end point—the composite of death, myocardial infarction (MI), stroke, or non-CABG bleeding at 30 days—were comparable between the transradial and transfemoral groups (3.7% and 4%) as were each of the individual components. However, the secondary end point of major vascular complications occurred more often in the transfemoral group (1.4% vs. 3.7%, $P < .0001$). Moreover, all post-hoc exploratory outcomes including Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY)–defined major bleeding, the composite of death or MI or ACUITY-defined major bleeding and the composite of major non-CABG bleeding and vascular complications were met more often in the transfemoral group.

Although RIVAL failed to show a significant difference between the two groups regarding the primary end point used in the protocol, two major findings in the subgroup analysis should be underlined: first, in the STEMI subgroup of the study, the transradial approach was not only associated with a significant reduction of the primary end point but also a reduction in mortality; second, the primary end point was also significantly reduced by the transradial approach in the centers with the highest radial PCI volume (hazard ratio [HR] 0.49; 95% confidence interval [CI], 0.28 to 0.87), which highlights the importance of the learning curve and operator experience for the transradial approach.

The overall advantages of the transradial approach have been advanced by three meta-analyses. First, a meta-analysis of 11 randomized controlled trials that included 3224 patients showed that overall, the rates of postprocedure major ischemic coronary events were comparable between methods, the procedural success rate was higher with the transfemoral approach (98% vs. 93%, $P = .0009$), and analysis showed a significant advantage of the transradial approach in terms of bleeding complications, mainly an 89% risk reduction for entry-site complications (0.3% vs. 3%, $P < .0001$).[14] The study also showed a clear trend toward equalization of procedural success rates between the two approaches through the years. Such a finding is probably explained by the technologic improvements of the materials and the improvement in operators' skills and experience following the learning curve. The average length of exposure to x-rays was nevertheless longer for the transradial approach (8.9 vs. 7.8 min, $P < .001$).

Another meta-analysis[15] of 23 randomized trials that included 7020 patients undergoing coronary angiography or PCI concordantly showed a significant ($P < .001$) 73% reduction in rates of major bleeding among those undergoing PCI, as well as trends toward lower rates of the combined end point of death/MI/stroke (odds ratio [OR] 0.71, $P = .058$) and death (OR 0.74, $P = .29$). Although access-site crossover was higher with the transradial approach, the procedure failure rate was not significantly lower and was similar among operators experienced with the that approach, whereas a trend ($P = .07$) toward higher failure rates was observed among less-experienced operators.

TABLE 31-2 Randomized Trials Comparing Transradial and Transfemoral Approaches for Percutaneous Coronary Intervention

Author	Type of Procedure	*N*	Technical Success (%)		Access-Site Complication (%)		Other End Points
			TR	TF	TR	TF	
RIVAL trial[13]	Diagnostic and/or PCI for ACS	7021	92.4	98	1.4	3.7	Comparable rates of the primary end point—death, MI, stroke, and major bleeding at 30 days—significantly higher rates of femoral access-site complications
Agostoni meta-analysis[14]	Diagnostic or PCI	2845	93	98	0.3	2.8	Shorter hospital stay, lower hospital costs, longer fluoroscopy times with TR
Jolly meta-analysis[15]	PCI	7020	95	97	0.05	2.3	Significant (73%) reduction of major bleeding, trends toward less 30-day mortality and fewer MACEs, significantly shorter hospital stay with TR
Louvard[19]	PCI in pts. >80 yr	371	89	91	1.6	6.6	Trend to longer TR procedure duration
Cantor[23]	Primary or rescue PCI	50	99.6	100	0.4	0.4	Similar fluoroscopy time and contrast media quantity
STEMI-RADIAL trial[28]	Primary PCI	707	96	97	0.3	0.8	Significant superiority of the TR approach for net adverse clinical events, bleeding, and duration of ICU stay
RIFLE-STEACS trial[29]	Primary or rescue PCI	1001	94	99	2.6	6.8	Significant superiority of TR approach for the 30-day primary end point of net adverse clinical events, death, bleeding, and duration of hospital stay
Kiemeneij[31]	POBA	600	92	91	0	2	Similar procedure, hospital stay, and x-ray exposure length
Benit[32]	Elective stenting	112	89	98	0	10	Similar procedure, hospital stay, and x-ray exposure length
Mann[71]	POBA	152	91	96	0	5	TR reduced length of stay and total cost
Mann[72]	Stenting in ACS	152	96	96	0	4	TR reduced length of stay and total cost
Mann[73]	Stenting TR versus TF with PerClose	218			0	3.4	TR reduced length of procedure, hospital stay, and total cost PerClose: Inadequate in 18%, failure of hemostasis in 10%
Louvard[74]	Diagnostic±ad-hoc PCI in ~43%	210	100	100	2	6	TR reduced length of stay, total cost, and was patient preferred, but it increased x-ray exposure length
Saito[75]	Primary stenting	149	96	97	0	3	Comparable in-hospital MACE rates
Slagboom[76]	Outpatient PCI	644	96	97	0	6	Similar rates of major bleeding, higher rates of same-day discharge, and lower rates of minor bleeding with TRA
Brasselet[77]	Primary PCI with abciximab	114	91.6	96.5	3.5	19.3	Similar rates of bleeding, transfusion, and MACE; higher fluoroscopy time and earlier ambulation with TRA
Li[78]	Primary PCI	370	98.4	98.9	2	7	Similar procedure times
Achenbach[79]	PCI in patients aged >75	307	91	100	1.3	9	Higher examination time with TR but similar fluoroscopy time, number of catheters, and amount of contrast media
RADIAMI[80]	Primary PCI	100	94	98	2	12	Similar procedure times, clinical event rates, and bleeding rates
RADIAMI II[81]	Primary PCI, femoral access closure device	109	96	98	0	3	Longer door-to-balloon time in transradial approach, similar clinical adverse event and bleeding rates, successful closure of femoral access 93%

ACS, Acute coronary syndrome; *ICU,* intensive care unit; *PCI,* percutaneous coronary intervention; *POBA,* plain old balloon angioplasty; *MACE,* major acute coronary events; *MI,* myocardial infarction; *TF,* transfemoral; *TR,* transradial; *TRA,* transradial approach.

TABLE 31-3 Recent Randomized Trials Comparing Transradial and Femoral Approaches in ST-Elevation Myocardial Infarction

30-Day End Point	TRANSRADIAL N/Total	TRANSRADIAL %	TRANSFEMORAL N	TRANSFEMORAL %	OR (95% CI) Radial vs. Femoral Approach	P
Death						
RIVAL	12/955	2.7	32/1003	3.2	0.39 (0.20-0.76)	.026
RIFLE-STEACS*	26/500	5.2	46/501	9.2	—	.020
STEMI-RADIAL	8/348	2.3	11/359	3.1	—	.64
Death/MI/stroke						
RIVAL	26/955	2.7	46/1003	4.6	0.59 (0.36-0.95)	.032
RIFLE-STEACS†	36/500	7.2	57/501	11.4	—	.029
STEMI-RADIAL	12/348	3.5	15/359	4.2		.7
Major bleeding						
RIVAL	8/955	0.8	9/1003	0.9	0.92 (0.0.36-2.39)	.87
RIFLE-STEACS	39/500	7.8	61/501	12.2	—	.026
STEMI-RADIAL	5/348	1.4	26/359	7.2	—	.0001
Access-site crossover						
RIVAL	51/955	5.3	16/1003	1.6	3.32 (1.89-5.82)	< .0001
RIFLE-STEACS	47/500	9.4	14/501	2.8	—	—
STEMI-RADIAL	13/348	3.7	2/359	0.6		.003

*Cardiac death.
†Death/myocardial infarction/target-lesion revascularization/stroke.
CI, Confidence interval; *MI,* myocardial infarction; *OR,* odds ratio.

Finally, the most recent meta-analysis of 76 randomized and nonrandomized PCI trials using a hierarchical bayesian analysis showed that compared with the transfemoral approach, transradial access was associated with significant, dramatic reductions in the risk of major bleeding (78%), transfusion (80%), death or MI (31%), and even death (44%).[16] Such advantages make the transradial approach the access of choice for same-day PCI, which has been reported to be highly feasible and safe.[17]

The transradial approach is also of particular interest in patients at high risk for bleeding (older adults, women, patients with renal failure, the obese, or patients on multiple antithrombotic agents, especially glycoprotein [GP] IIb/IIIa inhibitors). The transradial approach has been reported to be associated with fewer vascular complications in obese patients (multivariate OR 0.12; 95% CI, 0.02 to 0.94, $P = .043$) in a retrospective series of 5234 diagnostic or interventional (56.6%) procedures,[18] as well as in older adults (1.6% vs. 6.5%, $P = .03$).[19] Other patients with obvious advantages for a radial, rather than a femoral, approach are patients with severe and/or proximal peripheral artery disease (PAD), patients with bilateral aortofemoral bypass grafts, those with aortic aneurysms, and patients with a prior history of femoral complication after catheterization.

Compared with radial access, in patients with chronic kidney disease—as in the British Columbia cohort of 69,214 patients undergoing catheterization—femoral access was associated with an adjusted odds ratio of 4.36 (95% CI, 2.48 to 7.66) for the development of the composite end point of new dialysis or new chronic kidney disease.[20] The potential of the transradial approach to improve preservation of renal function was reported more recently in a large ($N = 82,225$) multicenter cohort of patients for whom such an approach was associated with lower rates of PCI-related acute kidney injury both on covariable adjusted (OR 0.74; 95% CI, 0.62 to 0.92) and propensity score–matched (OR 0.74; 95% CI, 0.58 to 0.96) analyses, independent of the associated reduction in the risk of bleeding.[21] Such findings may be related to the reduced atheroembolic potential of the transradial access.

Finally, when considering PCI registries such as the RIVIERA registry,[22] which prospectively included 7962 unselected patients, the transradial approach appears as an independent predictor of better in-hospital outcome (OR for death or MI, 0.16; 95% CI, 0.05 to 0.50), as well as the only variable correlated to less bleeding. Similar results were also reported by the Canadian MORTAL registry of 38,872 procedures, among which 20.5% were done by a transradial approach, showing a significant reduction in 30 day (adjusted OR 0.71; 95% CI, 0.61 to 0.82) and 1 year (adjusted OR 0.83; 95% CI, 0.71 to 0.98) mortality by the latter approach. The superiority of the transradial approach appears to be entirely linked to the reduced rates of transfusion in the prior study. The recently published report of the NCDR for 2007 through 2012 ($N = 2,820,874$ procedures) comparing transradial and transfemoral approaches confirms the prior findings with overall higher success rates (94.7% vs. 93.8%, adjusted OR 1.13, $P < .001$) and fewer vascular (0.16% vs. 0.45%, adjusted OR 0.51, $P < .001$) and bleeding complications (2.67% vs. 6.08%, adjusted OR 0.39, $P < .001$) with the transradial approach.[3]

TRANSRADIAL APPROACH IN ST-ELEVATION MYOCARDIAL INFARCTION

The transradial approach is of particular interest in the setting of primary PCI for STEMI (Tables 31-1 through 31-3) performed by experienced operators in patients treated by aggressive antithrombotic regimens, in which life-threatening access-site bleeding complications and the subsequent major cardiovascular events may be avoided by such an approach. In this setting, growing evidence suggests that the transradial approach is associated with overall similar door-to-balloon times, lower rates of vascular complication and bleeding in presence of triple antithrombotic therapy,[23-26] and even reduced 30-day mortality as compared with a femoral approach.[27] As mentioned above, in the STEMI subgroup of the RIVAL trial,[13] the transradial approach was not only associated with a significant reduction of the primary end point (HR 0.6; 95% CI, 0.38 to 0.94) but also mortality (HR 0.39; 95% CI, 0.20 to 0.76).

A meta-analysis of 21 randomized trials, which included the RIVAL trial STEMI subgroup, and nonrandomized studies recently reported consistent and significant reductions in mortality (OR 0.55; 95% CI, 0.42 to 0.72), major adverse cardiac events (MACEs; OR 0.56; 95% CI, 0.44 to 0.72), and major bleeding (OR 0.32; 95% CI, 0.22 to 0.48) by the transradial compared with the transfemoral approach.

Two recently published studies in the specific setting of PCI for STEMI confirmed overall the superiority of the transradial versus the transfemoral approach in terms of net adverse clinical events (NACEs), combining bleeding and thrombotic events.[28,29] Moreover, the Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE-STEACS) trial[29] reported a significant reduction of 30-day mortality and bleeding associated with a transradial approach (5.2% vs. 9.2%, $P = .02$, and 7.8% vs. 12.2%, $P = .03$). The clinical results of the RIVAL study STEMI subgroup and the two latter studies are summarized in Table 31-3. Considering such data,

the last European Society of Cardiology (ESC) guidelines for the management of STEMI[30] recommended a transradial over a transfemoral approach in the setting of primary PCI (level of recommendation IIb).

TRANSRADIAL VERSUS TRANSBRACHIAL APPROACHES

Two of the previous randomized trials also had a transbrachial approach subgroup of patients. The Radial Versus Femoral Access for Coronary Angiography of Intervention and the Impact on Major Bleeding and Ischemic Events (ACCESS) study[31] reported comparable procedural success rates, equipment consumption, and procedural and fluoroscopy time among the three approaches for PCI. The transbrachial approach was nevertheless associated with higher rates of vascular complications compared with the transradial approach (2% vs. 0%, $P = .035$). The Brachial, Radial, or Femoral Approach for Elective Palmaz-Schatz Stent Implantation (BRAFE) stent study compared transradial and transfemoral approaches with a transbrachial cutdown approach, reporting no local vascular complication with the latter.[32] Such a brachial approach is not commonly used anymore and still bears a higher risk of vascular complications. The brachial access does not need a cutdown and can be done with a classic percutaneous approach but is usually preferred when neither femoral nor radial approaches are possible.

TRANSRADIAL VERSUS TRANSULNAR APPROACH

The ulnar artery is usually less superficial than the radial artery, and both its puncture and compression may be technically more difficult. The Transulnar Versus Transradial Artery Approach for Coronary Angioplasty (PCVI-CUBA) study randomized 413 patients with a normal direct or reverse Allen test to undergo coronary angiography followed or not by PCI through a transradial versus a transulnar approach. The two methods were associated with similar access success (96% vs. 93%), PCI success (96% vs. 95%), and asymptomatic access-site artery occlusion (5% vs. 6%) rates.[33] A more recent noninferiority-designed randomized trial comparing the two approaches showed somewhat more conflicting results.[34] In this study, the transulnar approach was associated with more attempts before successful access (three vs. one, $P < .001$), longer procedural time, higher contrast volume, and much higher rates of crossover (32.3% vs. 5.9%, $P = .004$). Although the composite primary end point of crossover and major adverse cardiovascular and vascular events at 60 days was inconclusive, the transulnar approach appears to be only an alternative to transradial access for PCI and not a first-line strategy. Indeed, it remains technically more challenging; and with the ulnar nerve being closer to the ulnar artery, nerve injury remains an issue during puncture attempts and the hemostasis phase.

COST-EFFECTIVENESS

Systematic and concordant evidence suggests that because of a shorter length of hospital stay, reduced nursing workload, reduced rates of complications, and absence of need for closure devices, the transradial approach is associated with significant cost reductions in both diagnostic angiography and PCI settings.[35,36]

PRACTICAL CONSIDERATIONS FOR A TRANSRADIAL APPROACH

Contraindications to the Transradial Approach

The contraindications to a transradial approach are the presence of forearm arteriovenous fistula or a proven absence of collateral ulnar circulation (e.g., known occlusion of the ulnar artery). The transradial approach should be considered with precaution and after assessing the balance between other access-site complications and the risk of radial access in end-stage renal disease patients with the potential need for forearm arteriovenous fistula and in patients with small or heavily calcified radial arteries.

Assessment of Ulnopalmar Arterial Arches

The assessment of collateral ulnar circulation has traditionally been recommended prior to the transradial approach to PCI. The early postprocedure occlusion of the radial artery could occur in 0% to 19% of patients depending on the clinical or ultrasound assessment of the radial artery patency, the type of procedure (diagnostic or interventional), whether anticoagulation was used, the duration of arterial compression after the procedure, and the size of the introducers and catheters.[11,37-39] In 40% to 60% of cases, the pulse could be redetected within hours to weeks after the occlusion, which remained asymptomatic in virtually all patients.[40,41] Nevertheless, description of incomplete palmar arches and very rare cases of transient or definitive hand or finger ischemia have been reported, theoretically justifying the evaluation of the ulnopalmar arch prior to the radial puncture. However, most reported cases of distal ischemia have been associated with distal emboli and normal Allen testing prior to catheterization. Although the assessment of the collateral ulnar circulation is of theoretic interest, the low specificity of the Allen test and the absence of symptomatic ischemic complications in the abundant literature have made this recommendation obsolete in many experienced radial centers.

The Allen Test

A simple clinical way of testing the adequacy of the collateral ulnar circulation is the modified Allen test (Fig. 31-1, *A* and *B*). The test consists of the simultaneous compression of radial and ulnar arteries, followed by several flexion-extension movements of the fingers, leading to an uncoloring of the palm. The ulnar compression is then ceased. The recoloration time of the palm after the end of the ulnar artery compression defines the Allen test: normal is less than 5 seconds, intermediate is 5 to 10 seconds, and abnormal is 10 seconds or more. The reverse Allen test, comprising all steps with the exception of a transient radial—instead of ulnar—compression, could be used in case of a transulnar approach.

A potentially more accurate method for the evaluation of the ulnopalmar arch may be the plethysmooxymetric test (see Fig. 31-1, *C* and *D*, and Video 31-1). The radial artery is compressed after the detector is positioned on the thumb. The persistent damping of the plethysmographic curve and a decrease of the blood oxygen saturation indicate inadequate ulnar collateral circulation. Barbeau and colleagues[42] compared such a method with the Allen test in 1010 consecutive patients. The study showed that 6.3% of patients would be excluded based on the Allen test, but only 1.5% had an abnormal plethysmooxymetric test.

In clinical practice, the use of the Allen test is highly variable from one center or operator to another. In centers where the test is systematically performed, the transradial approach is usually attempted in normal or intermediate patient groups. The issue is highly controversial because on one hand, many operators do not test the collateral circulation, and on another, in most clinical trials, the abnormality of the test is an exclusion criterion.

One recent study demonstrated reduced blood flow and increased capillary lactate levels in the thumb following 30 minutes of occlusive compression of the radial artery in patients with an abnormal Allen test compared with those with a normal test,[43] which suggests potential ischemic complications in patients with an abnormal test. A more recent trial in 203 patients undergoing a transradial approach with a normal, intermediate, or abnormal Allen test did not confirm the previous findings on increased lactate levels.[44] Moreover, the latter study—based on plethysmographic frame counts—demonstrated an enhancement of the ulnar flow only in patients with an abnormal Allen test after radial artery occlusion. Hence the prognostic relevance of the Allen test remains controversial, and its relation to the safety of the procedure has never been shown. A few cases of severe hand

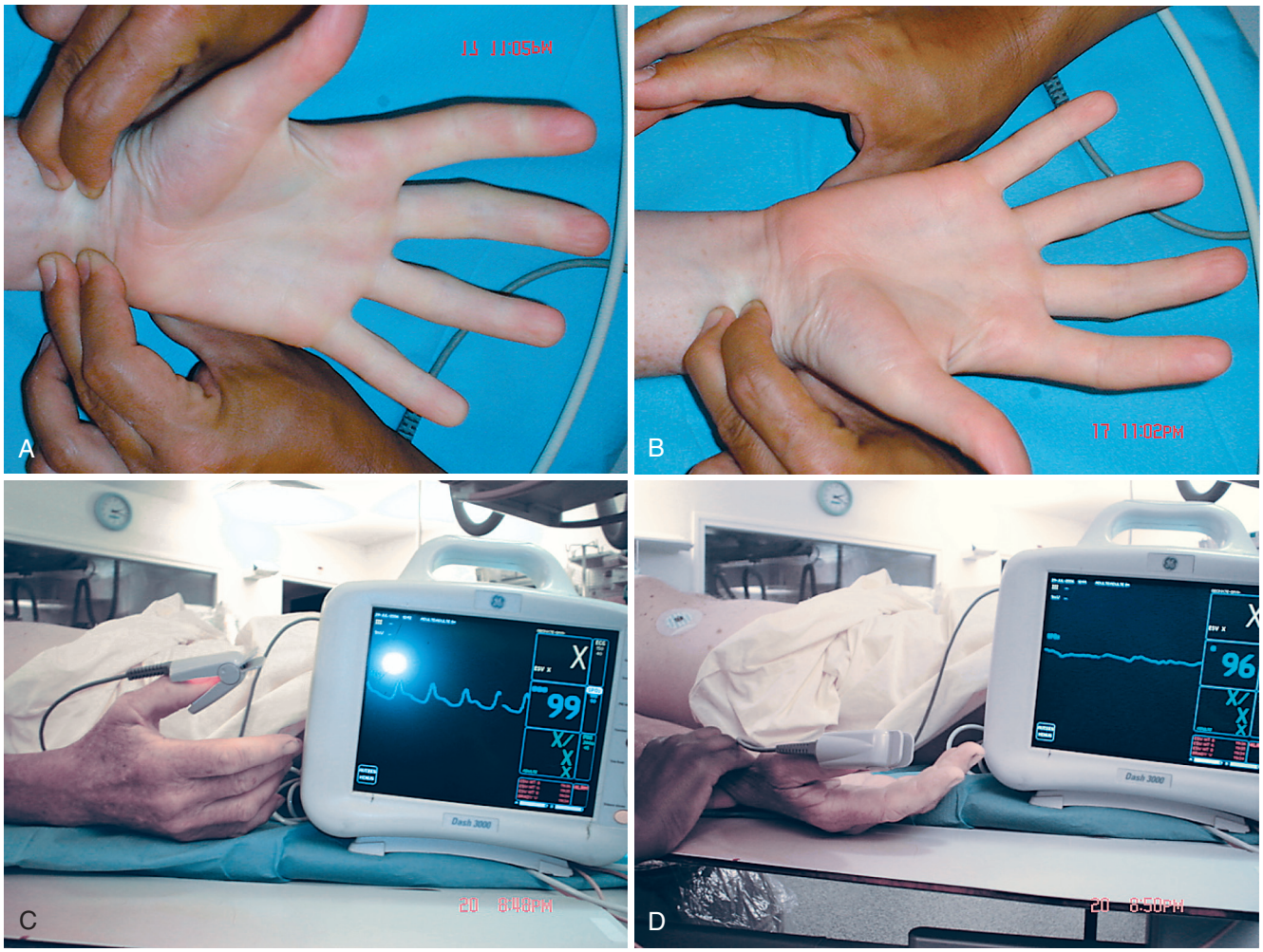

FIGURE 31-1 Ulnopalmar arch assessment. **A,** Allen test: compression of both radial and ulnar arteries. **B,** Allen test: homogenous recoloration of the palm after ulnar artery compression is released in a patient with normal palmar arch. **C,** Plethysmooxymetric test: before radial artery compression. **D,** Plethysmooxymetric test: dumping of the plethysmographic curve and decrease of oxygen saturation of the thumb after radial compression in a patient with incomplete palmar arch.

ischemia have been reported but never in relation with an abnormal Allen test.

Because of the rare occurrence of radial artery occlusion and the exceptionally symptomatic character of such a complication, the prognostic value of neither of the previous tests has been demonstrated, and many operators use the transradial approach without prior evaluation of the ulnopalmar arch. Nevertheless, an abnormal Allen test should be confirmed by the plethysmooxymetric test and then considered as a contraindication to the transradial approach, leading the clinician to another access point.

A Right Versus Left Transradial Approach

The left radial access may have some advantages over the right transradial approach. Such reported advantages include more comfort and less hypothetic risk in case of hand ischemia for the right-handed majority of patients, easier coronary cannulation using standard Judkins catheters, less guidewire usage, lower rates of unusual artery branching or vessel tortuosity needing less catheter manipulation, shorter procedure and fluoroscopy times, and selective opacification of the left internal thoracic artery bypass grafts.

In a randomized trial that compared 232 left and 205 right transradial diagnostic procedures, the left approach was associated with shorter duration of catheter manipulation and shorter procedure and fluoroscopy times, as well as lower rates of guidewire usage, suggesting increased procedural efficacy.[45] A recently published meta-analysis that involved 22 randomized trials and included more than 10,000 patients confirms the lower fluoroscopy time and contrast volume with the left, compared with the right, transradial approach.[46]

Nevertheless, the right transradial approach is clearly more ergonomic for the majority of operators, and the differences between the two approaches may not be of clinical relevance. The choice of the side remains mainly a matter of operator preference, the right radial approach being the default side in 90% of cases.

As mentioned before, previous biinternal thoracic artery CABG is a specific situation in which a double left and right radial approach could be used, allowing direct access to internal thoracic arteries' ostia for further intervention through the grafts.

Patient Preparation, Arterial Puncture, and Sheath Insertion (Video 31-2)

Explanations and premedication should be given to patients based on local practice. Because excessive anxiety may favor radial artery spasm, premedication may be used prior to radial artery puncture (see below). When possible, local anesthesia of the puncture site with an anesthetic

FIGURE 31-2 **A,** Right transradial approach. **B,** Left ulnar sheath approach. **C,** Bilateral radial approach for selective catheterization of both internal thoracic arteries.

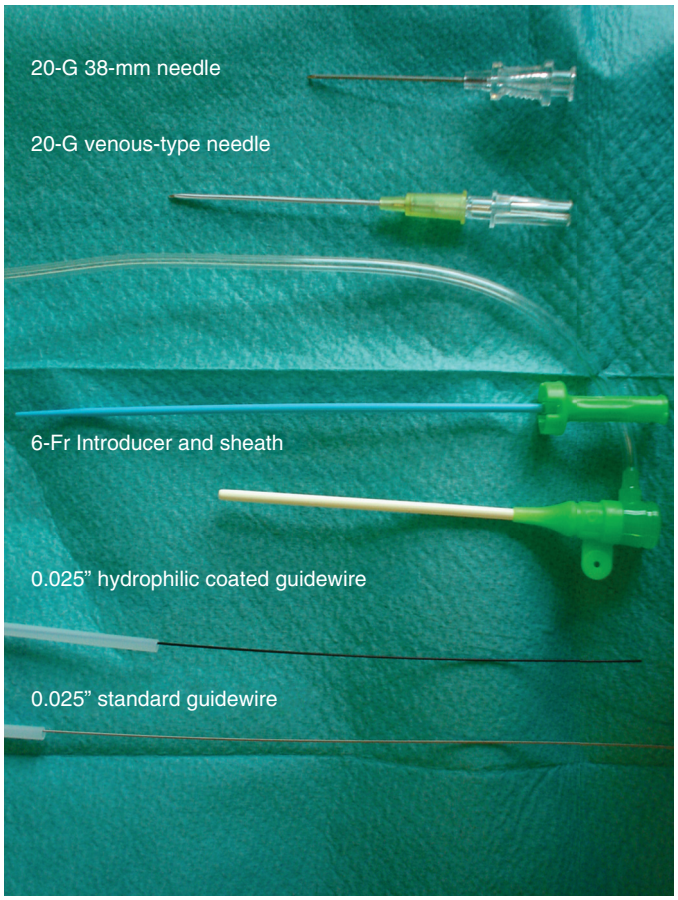

FIGURE 31-3 Transradial approach kit (Terumo Medical, Somerset, NJ).

cream 30 to 60 minutes prior to the puncture may improve patient comfort and can reduce risk of radial artery spasm and cannulation failure.

Some operators also recommend local vasodilation by apposition of a nitrate patch or paste on the puncture site. To be effective, it seems that the treatment must be administered at least 1 hour prior to radial puncture. The forearm should be shaved if necessary and aseptically prepared. Usually the groins are also prepared in case of radial access failure or if greater than 7-Fr material is needed. The arm and wrist rest on an armrest, and a roll of gauze can be inserted under the wrist to make the puncture easier.

Prior to puncture, a small dose of subcutaneous lidocaine 1% or 2% solution (0.5 to 2 mL) is injected at the puncture site. The radial artery might be accessed either by direct (anterior) puncture or using a through-and-through technique. Although access is somewhat faster with the through-and-through technique, the choice remains a matter of operator preference because there are no differences in the rate of complications. The artery is punctured either with a short 18- to 19-gauge entry needle (anterior) or a 20-gauge venous-type catheter entry needle, usually with a 30-degree angle to the horizontal plane. The needle is advanced until blood appears and stops. The inner needle is then retrieved in case of venous-type needle use. The needle or the catheter is then retrieved until a pulsatile blood flow appears. A 0.025-inch straight, preferably hydrophilic coated guidewire is introduced through the needle or the catheter, which is then removed. A 70-mm long arterial hydrophilic sheath is then introduced on the wire eventually after a very small superficial skin incision. Figure 31-2 shows single right radial, left ulnar, and bilateral radial sheaths in place. The use of hydrophilic coated sheaths (Fig. 31-3) and the smallest sheath size—4 Fr for diagnostic and 5 Fr for PCI, with further upsizing if needed to 6, 7, or even 8 Fr—are recommended because they are associated with less radial artery occlusion and spasm and less extraction force at removal.[47] The use of long sheaths (23 cm), initially recommended, has now been largely abandoned.

Prevention of Radial Artery Spasm

An intraarterial spasmolytic drug or drug cocktail is injected through the sheath after its introduction. Different cocktails have been evaluated based on various treatments—nitroglycerin, nitroprusside, molsidomine, phentolamine, diltiazem, or verapamil—alone or in combination.

In a randomized trial that included 406 patients, the rates of clinical and/or angiographic radial artery spasm were significantly reduced by the intraarterial injection of nitroglycerin 100 μg with or without combination therapy with verapamil 1.25 mg (3.8% and 4.4%, respectively) compared with placebo (20.4%).[48] However, the effect of nitrates depends on the dose used, and a high dose is recommended when used alone. In another randomized trial that included 1219 patients, the combination of verapamil 2.5 mg and molsidomine 1 mg was associated with less radial spasm (4.9%) compared with verapamil 2.5 mg or 5 mg (8.3% and 7.9%) or molsidomine 1 mg (13.3%) alone and placebo (22.2%).[49] In another randomized trial, verapamil 2.5 mg alone was more effective in the prevention of radial artery spasm compared with the alpha-blocker phentolamine 2.5 mg (spasm rates were 13.8% vs. 23.2%, respectively).[50]

The intraarterial injection of verapamil, nitroglycerin, or a combination of the two seems to be associated with the lowest spasm rates and could be recommended in all patients after the introduction of the sheath in the radial artery. Patients should be warned that they might experience cold and/or heat lasting a few seconds in the forearm and arm after the intraarterial injection.

A recent randomized trial of 2013 patients compared an association of intravenous (IV) opioid/benzodiazepine with no treatment during the preparation of the access site in patients undergoing elective transradial PCI. In this study, patients received intraarterial glyceryl trinitrate (GTN) and verapamil and guiding catheters smaller than 7 Fr were used, and researchers found a significant reduction of angiography-confirmed radial artery spasm (2.6% vs. 8.3%, OR 0.29, $P < .001$) with significant reductions of access-site crossover rates and patient discomfort.[51] The general use of such a strategy may nevertheless increase the complexity of a routine procedure performed on an outpatient basis.

Anticoagulation

Because of the potential risk of radial artery occlusion, and for the full control of local bleeding complications, all patients not already on anticoagulation therapy undergo full-dose anticoagulation after the arterial sheath is placed in the radial artery prior to both diagnostic and interventional procedures. In a series of 415 consecutive patients, Spaulding and colleagues[52] showed a high correlation between heparin therapy and the postprocedure radial artery occlusion that occurred in 71% of untreated patients, 24% of patients who received 2000 to 3000 IU, and only 4.3% of those who received 5000 IU of unfractionated heparin. No specific data concerning other regimens of anticoagulation in the specific setting of transradial PCI are available. A small pilot study has reported the feasibility and security of an ad-hoc PCI strategy with bivalirudin after an initial angiography with low-dose unfractionated heparin (1000 or 2500 IU).[53] Such a strategy remains to be validated by further studies. Overall full anticoagulation is recommended in all patients undergoing transradial procedures, and different regimens should be considered based on validated guidelines and local practice: fixed-dose, weight-adjusted, or activated clotting time (ACT)–adjusted unfractionated heparin; weight-adjusted low-molecular-weight heparin; bivalirudin, and so on. Anticoagulants may be injected through the arterial sheath or through venous access because the route has not been associated with the risk of radial artery occlusion.

Glycoprotein IIb/IIIa Inhibitors and Fibrinolytics

Because of the extremely low vascular site complication rates, the transradial approach to PCI is clearly the method of choice in the setting of PCI with highly active antithrombotic regimens and early or rescue PCI after thrombolysis. In a series of mostly ACS patients undergoing PCI with abciximab through transradial ($n = 83$) or transfemoral access ($n = 67$), the 30-day rate of major acute coronary events was similar between the two approaches, but bleeding complications occurred in 0% of the former versus 7.4% of the latter ($P = .04$).[54]

In another consecutive series of 119 patients undergoing primary PCI with systematic GP IIb/IIIa inhibition by abciximab, compared with the transfemoral approach ($n = 55$), the transradial approach ($n = 67$) was associated with fewer major access-site complications (5.5% vs. 0%, $P = .03$), shorter hospital stay, and comparable procedural time but higher x-ray exposure time and dose product.[55]

A retrospective analysis of postthrombolysis rescue PCI with adjuvant GP IIb/IIIa inhibitor therapy was undertaken in 111 patients, among whom 47 had a transradial approach, and it showed lower rates of access-site bleeding (0% vs. 9%, $P = .04$) and transfusion (4% vs. 19%, $P = .02$) with the transradial access. The fluoroscopy time, contrast media volume, and time to first balloon inflation were comparable between the two approaches.[56]

A small, randomized pilot trial compared transradial and transfemoral approaches for urgent PCI in 50 patients after thrombolysis (in 66% of patients) and/or GP IIb/IIIa inhibitor therapy (94%) and reported comparable results in procedural success rates (only 1 failure occurred in the transradial group) and vascular complication rates (1 pseudoaneurysm in each group) but slightly longer average local anesthesia–to–first balloon time in the transradial group (32 vs. 26 min, $P = .04$).[23] In the noninferiority, randomized Early Discharge After Transradial Stenting of Coronary Arteries (EASY) study, which compared transradial PCI either with same-day discharge and abciximab bolus or hospitalization and abciximab infusion in 1005 patients (66% with unstable angina), the 30-day composite end point of death, MI, urgent revascularization, major bleeding, repeat hospitalization, access-site complications, and severe thrombocytopenia were comparable. The overall rates of access-site complication (4.8% vs. 4.2%), major bleeding (0.8% vs. 0.2%), and transfusion were impressively low.[57]

Finally, a post-hoc analysis of the ATOLL randomized trial limited to the population receiving GP IIb/IIIa inhibition in the setting of primary PCI for STEMI found that such drugs were used more safely and with lower rates of major bleeding with a transradial approach compared with other access sites (4% vs. 9%, $P = .03$).[58] Despite absence of adequately sized randomized trials in the specific setting of transradial PCI with GP IIb/IIIa inhibitors or after thrombolysis, the extremely low access-site–related bleeding complications associated with such an approach firmly suggests its use in patients receiving highly active antithrombotic therapy.

Guiding Catheters

The guidewire used for the transradial approach is usually a standard 0.032- to 0.035-inch guidewire. In case of anatomic difficulties, such as radial or subclavian loops, a hydrophilic coated guidewire could be used. The progression of the guidewire should be done under fluoroscopic control, especially with hydrophilic coated guidewires. The catheter exchange can be done using a long, 260- to 300-cm exchange guidewire or with a wire placed in the aortic root using a flush syringe to inject over the wire. The syringe and the catheter are retrieved during the flush injection, under fluoroscopic control (Video 31-3). Such exchange methods are extremely useful in case of difficult access.

The cannulation of the coronary arteries via a left or right transradial approach can be done using standard Judkins right and left catheters in a majority of patients. The cannulation of both right and left coronary ostia is very similar between the left radial and transfemoral approaches, and all standard catheters can be used through such access. In a series of 412 consecutive left transradial diagnostic procedures, only 5.5% of left main and 3% of right coronary ostia needed to be cannulated by catheters other than standard left or right Judkins catheters.[52]

For the right transradial approach, both left and right Judkins catheters usually end up in the right coronary or noncoronary sinuses. The

TABLE 31-4 Guiding Catheters Used for Transradial Percutaneous Coronary Intervention

Guiding Catheter (Curves)	Left Coronary	Right Coronary	Bypass Grafts
Standard Catheters			
Judkins left (3.5 or 4)	+	– (+3.5 curve)	–
Judkins right (4)	–	++++	Left/ right IMA
Amplatz left (2)	++	+	Left SVG
Amplatz right	–	+	–
Extra back-up (3.0 or 3.5)	++++	–	–
Multipurpose	+	+	Right SVG
Internal mammary	–	–	Left/right IMA
LCB/RCB	–	–/+	Left/right SVG
Ikari left	+	+	
Brand Name Catheters			
Kimny (Boston Scientific)	+	+	–
MUTA L/R (Boston Scientific)	+	+	–
Radial curve (Boston Scientific)	+	+	–
Fajadet's L/R (Cordis)	+	+	–
Mann IM (Boston Scientific)	–	–	Left or right IMA
Barbeau L/R (Cordis)	+	+	–
Brachial type K (Terumo Medical)	+	+	–
Tiger II (Terumo Medical)	+	+	–

IMA, Internal mammary artery; *LCB,* left coronary bypass; *RCB,* right coronary bypass; *SVG,* saphenous vein graft.

Judkins right catheters are to be manipulated similarly as through transfemoral access, intubating the right coronary ostia after a slight clockwise rotation. For the cannulation of the left main coronary ostium, an initial clockwise rotation is needed, eventually followed first by a gentle pull or push and then a slight anticlockwise rotation.

In most high-volume centers, the guiding catheters used are the long-tip extra back-up 3.5 to 4 for left coronary and Judkins right 4 for right coronary PCI. Several other guiding catheters have been used for transradial PCI such as the Amplatz left 2, Champ, or a multipurpose catheter, used for both left and right transradial approaches. Finally, specific transradial guiding catheters have been developed, although a majority of operators use standard guiding catheters. A list of guiding catheters used for the transradial approach is given in Table 31-4.

The diameter of the guiding catheters is also to be considered because 6-Fr guide catheters are more often associated with spasm and radial artery occlusion than 5-Fr catheters. The limitations of the 5-Fr compared with the 6-Fr catheter are less strong backup due to higher flexibility of the catheters and incompatibility with some devices (rotational atherectomy, thrombectomy, and distal protection devices; >4 mm coronary stents) or procedures (kissing stent or balloon for bifurcation lesions). Special attention should also be paid to the possibility of bubble formation as a result of the Venturi effect when balloons or devices are rapidly removed from a 5-Fr catheter. On the other hand, deep but cautious arterial intubation can be performed with 5-Fr catheters when needed; for example, for crossing calcified coronary curves. The use of a GuideLiner catheter (Vascular Solutions, Maple Grove, MN) with a 6-Fr catheter can be helpful to deeply intubate a coronary artery or graft when extra support is needed.

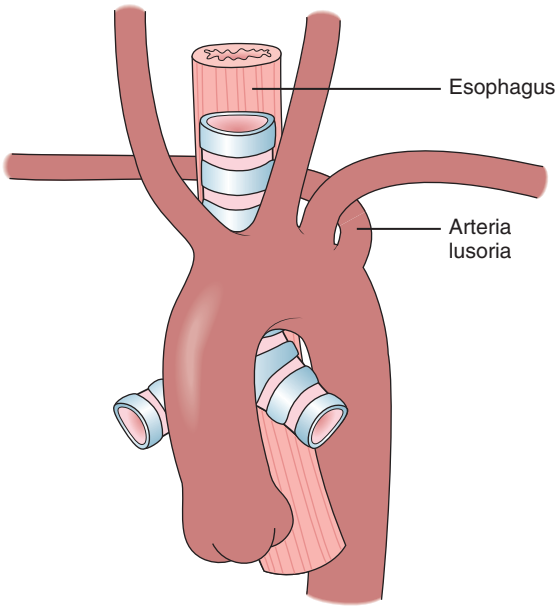

FIGURE 31-4 Schematic representation of retroesophageal subclavian artery (arteria lusoria).

Difficult Anatomy

The arterial circulation of the upper limbs is subject to frequent variation among patients. During the initial phase of the learning curve, the failure of the transradial approach is usually the result of puncture failure, whereas for experienced operators, the failure is related to difficult radial artery anatomy. A series of 1191 consecutive cases reported anomalous upper branching of the radial artery in 3.2%, a high origin of the radial artery in 2.4%, and radial or brachial artery tortuosity in 4.2% (arteries were S and omega shaped in 31% each).[8]

In another series of 2211 consecutive patients, the authors reported a 98.9% success rate, and 22.8% of patients had anatomic variations that included tortuosity (3.8%), stenosis (1.7%), hypoplasia (7.7%), abnormal origin of the radial artery (8.3%), and retroesophageal (lusoria) subclavian artery (0.45%).[59] Notably, rates of success in this experienced radial center were high in all anatomic variations (83% to 96.7%) except the lusoria subclavian artery (60% success rate), which should be considered a contraindication to the transradial approach (Fig. 31-4). The most common anatomic variations and difficulties are listed in Table 31-5, and some examples are shown in Figures 31-5 through 31-8 and in Videos 31-4 through 31-6.

Repetition of Transradial Procedures

Because of the risk of postprocedure radial artery occlusion, although such complication is rare and usually asymptomatic, repeated procedures may be questioned. In a series of 812 Japanese patients with a first transradial success, the rates of access failure through the same radial artery in men and women were, respectively, 3.5% and 7.9% for the second, 10% and 20% for the third, and 30% and 50% for a fifth attempt.[60] Such data should be considered with caution because the number of patients with multiple procedures was very low in the previous study. Furthermore, in another series of 117 repeated ipsilateral transradial procedures, the success rate for the second procedure was similar to the first, although the rates of postprocedure radial artery occlusion assessed by ultrasound were higher after the second procedure (2.6%, vs. 0%, $P = .01$).[61] In a series of consecutive 480 patients with more than two repeat radial access procedures, the same radial artery could be used up to ten times, but each repeat attempt was associated with a 5% failure rate due to chronic radial artery occlusion.[62]

TABLE 31-5 Anatomic Abnormalities

Anatomic Difficulties	Solution
Forearm	
Lateral position of the radial artery on the wrist	Change puncture site or access site
Hypoplasic radial artery	Change access site
Radial artery remnants	Guidewire progression under angiographic control
Radial artery loops	Hydrophilic coated guidewires under angiographic control, 0.014″ angioplasty guidewires; change access site in case of calcified, "unloopable" loops
Arm	
Brachial artery remnants	Guidewire progression under angiographic control
High origin of the radial artery	Hydrophilic coated guidewires under angiographic control, 0.014″ angioplasty guidewires; change access site in case of calcified, "unloopable" loops
Brachial artery loops	
Shoulder-Thorax	
Axillary or subclavian artery loops	Hydrophilic coated guidewires under angiographic control, deep inspiration
Arteria lusoria (retroesophageal right subclavian artery)	Change access site in case of calcified, "unloopable" loops
Brachiocephalic arterial trunk abnormalities	Guidewire progression under angiographic control, deep inspiration
Posterior origin	Guidewire progression under angiographic control, deep inspiration, catheters adapted to aortic angulation
Bicarotidian trunks	
Thoracic aortic rotations	

FIGURE 31-5 Radial artery omega-shaped complete loop *(arrow)*.

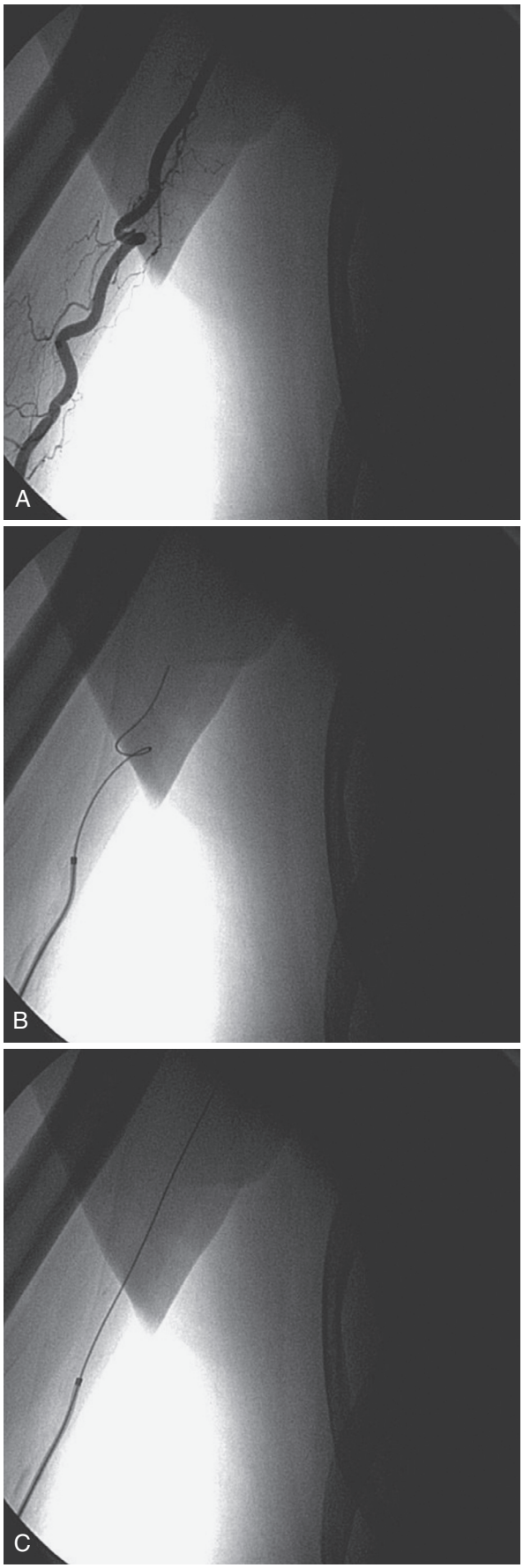

FIGURE 31-6 Brachial artery loop. **A,** Before wiring. **B,** During wiring. **C,** Artery unlooped by a hydrophilic coated guidewire.

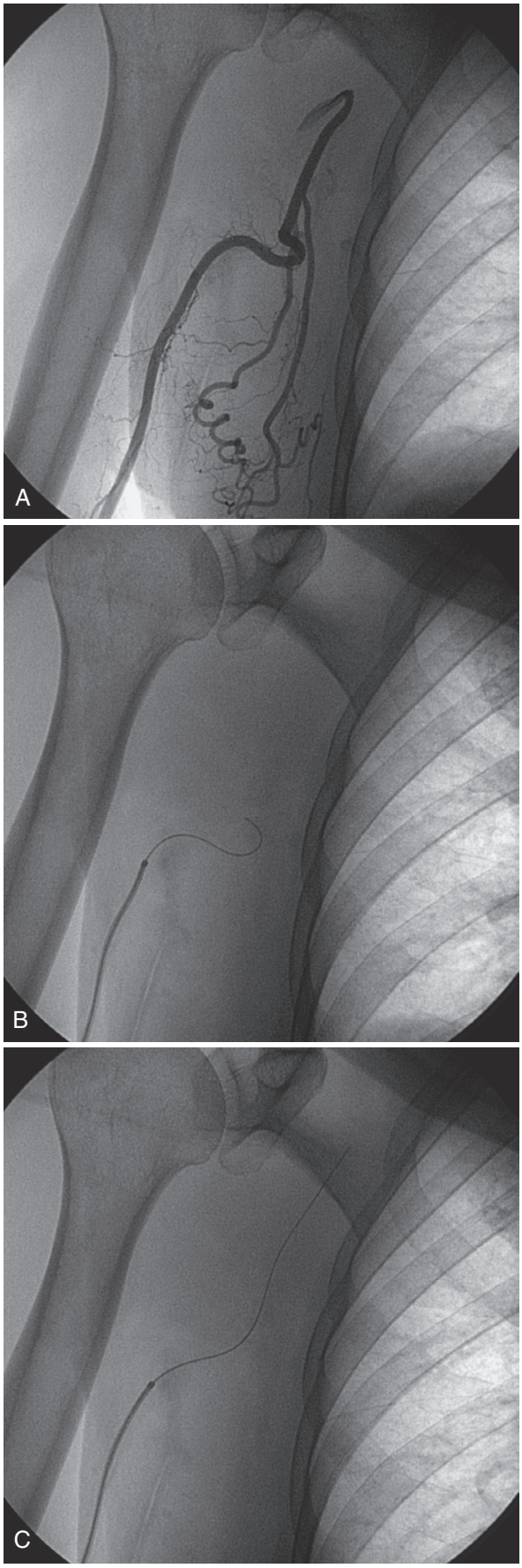

FIGURE 31-7 High brachial artery loop. **A,** Before wiring. **B,** During wiring. **C,** Artery unlooped by a hydrophilic coated guidewire.

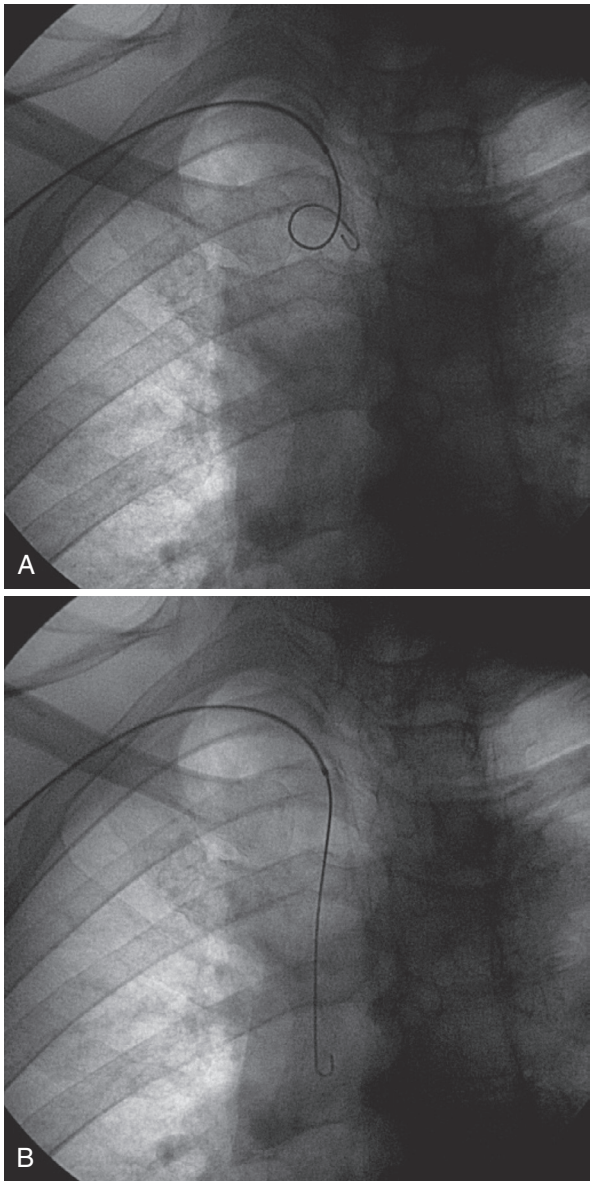

FIGURE 31-8 Subclavian loop. **A,** Before wiring. **B,** Artery unlooped by a standard preshaped guidewire.

Finally, pathology examinations of radial arteries used for coronary artery bypass graft, as well as optical coherence tomography (OMT), have provided evidence of acute and chronic injuries such as intimal and medial tears and dissection, intimal thickening, and stenosis (Fig. 31-9), especially in those with repeat transradial interventions.[63] Such findings have led some to recommend that a transfemoral approach be considered in patients at low risk of femoral access-site complication and high risk of repeated procedures, such as those with complex, multivessel lesions with a high restenosis risk or heart transplant recipients undergoing systematic annual angiography. However, this does not appear to be a concern at high-volume radial centers.

Complications

The transradial access is associated with very low major access-site–related complications. The two most common complications are radial

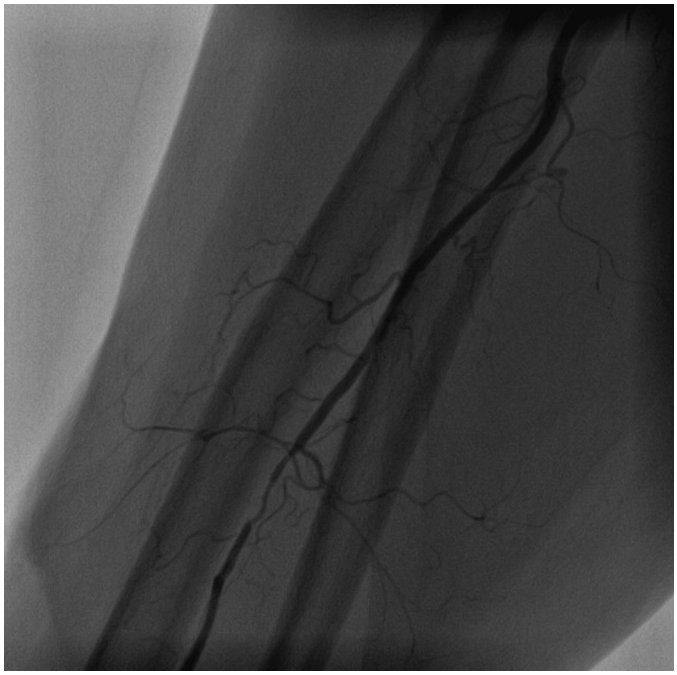

FIGURE 31-9 Radial artery stenosis (visualized after transulnar opacification).

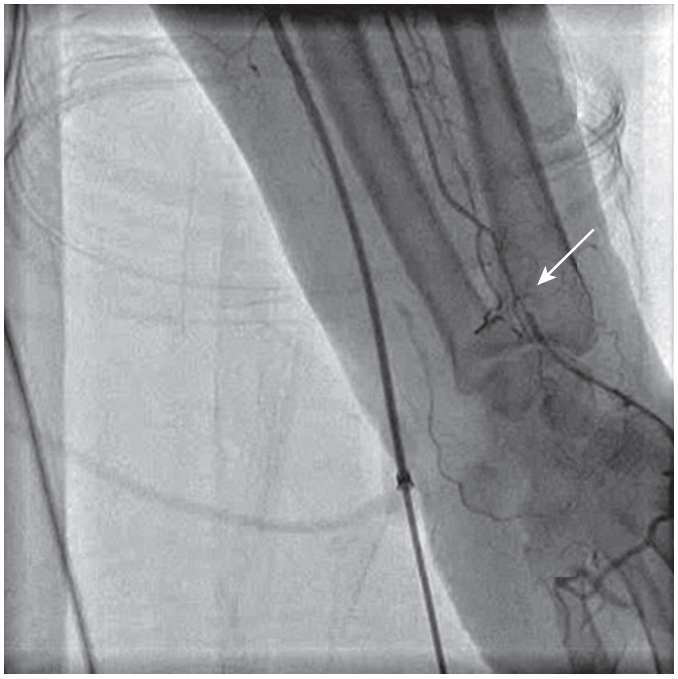

FIGURE 31-10 Radial artery spasm.

TABLE 31-6 Transradial Approach–Related Reported Complications

Complications	Frequency	Prevention	Solution
Asymptomatic loss of radial pulse (reversible in ~50% of cases)	0% to 9%	Spasmolytic cocktail, 5-Fr catheters	—
Radial artery spasm	4% to 23%	Lidocaine cream prior to puncture; anxiolytic preparation; avoid excessive catheter manipulation and change; preventive spasmolytic cocktail; hydrophilic coated sheath guidewires and catheters	Spasmolytic cocktail General sedation
Radial artery extraction (refractory spasm)	Exceptional	Avoid excessive force to remove catheter or sheath	Spasmolytic cocktail General sedation
Radial artery false aneurysm	Exceptional	—	Local compression Surgery
Arteriovenous fistula	Exceptional	Avoid perforation	Local compression Surgery
Symptomatic finger and/or hand ischemia	Exceptional	Avoid radial puncture if Allen test is inadequate; 5-Fr catheters; adequate antithrombotic cocktails; spasmolytic cocktails	Anticoagulation Surgery
Bleeding at the puncture site	0% to 2%	—	Local compression
Forearm hematoma and compartment syndrome	Exceptional	Control progression of guidewire; long arterial sheath to stop the bleeding in case of perforation; covered stent in case of uncontrollable perforation	Surgery Leeches
Vascular injury/dissection (radial, brachial, subclavian, carotid arteries)	Exceptional	Control progression of guidewire, especially hydrophilic coated wires	Anticoagulation Stent Surgery

artery spasm (Fig. 31-10; Videos 31-7 and 31-8), often related to painful procedures or excessive catheter manipulations, and asymptomatic, often reversible radial artery occlusion (Video 31-9) that may occur in 3.8% to 22% and 0% to 19% of patients, respectively.[9,39,40,64] Female sex, diabetes, small body surface area, low body mass index, short stature, smoking history, small diameter of the radial artery, number of catheters used, and catheter size (6 Fr vs. 5 Fr) have been related to radial artery spasm.[51,64,65] Reported predictors of radial artery occlusion are small radial artery diameter, low difference between radial artery and sheath diameters, diabetes, low-dose or no anticoagulation, and repeated procedures using the same access site.[61,65] Predicting the risk of radial artery spasm may be possible before puncture by the ultrasound assessment of the arterial diameter and the flow-mediated artery dilation. Nevertheless, the clinical usefulness of such a strategy remains hypothetic. A list of reported transradial access–related complications is provided in Table 31-6. More recently, the concept of patent hemostasis has emerged as a nonpharmacologic method of ensuring lower risks of radial artery occlusion. Indeed, it seems that occlusive hemostasis is a strong predictor of radial artery occlusion.[66]

CONCLUSIONS

Bleeding complications after PCI have been associated with higher rates of hard clinical events, including mortality. The transradial approach is associated with a dramatic risk reduction for entry-site complication, compared with the transfemoral approach, and appears to be the easiest, safest, and most cost-effective way to control bleeding complications and improve clinical outcome, including survival, after PCI. Growing evidence in large observational studies and randomized trials tends to show significant reduction in major cardiovascular events and even mortality with the transradial approach to PCI in the setting of STEMI, as recently demonstrated in the randomized RIVAL and RIFLE-STEACS trials. Transradial access is associated with easy entry-point hemostasis, more comfort for patients, quick postprocedure ambulation, and the possibility of outpatient procedures.

The only theoretic contraindication to the transradial approach is the inadequate ulnar collateral circulation detected by the more and more controversial Allen test, although most operators proceed without such test because of its unknown value in predicting post-procedure complications. Initially appearing to be a more difficult access site, compared with the femoral artery, after a short learning curve and with knowledge of potential anatomic difficulties and ways to overcome such difficulties, the procedural success rates of the transradial approach become virtually identical to those of the transfemoral approach, without the access-site complications. There still is a need for more adequately sized randomized trials, as well as academic educational programs to promote a transradial approach among interventionalists, in order to develop this obviously superior technique.

The transradial approach considered initially as an alternative to transfemoral access is already the preferred method for PCI in many centers, and its generalization as the first-line method is likely to be just a matter of time.

REFERENCES

1. Campeau L: Percutaneous radial artery approach for coronary angiography. *Catheter Cardiovasc Diagn* 16:3–7, 1989.
2. Rao SV, Ou FS, Wang TY, et al: Trends in the prevalence and outcomes of radial and femoral approaches to percutaneous coronary intervention: a report from the national cardiovascular data registry. *J Am Coll Cardiol* 1:379–386, 2008.
3. Feldman DN, Swaminathan RV, Kaltenbach LA, et al: Adoption of radial access and comparison of outcomes to femoral access in percutaneous coronary intervention: an updated report from the national cardiovascular data registry (2007-2012). *Circulation* 127:2295–2306, 2013.
4. Montalescot G, Cayla G, Collet JP, et al: Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. *JAMA* 302:947–954, 2009.
5. Montalescot G, Zeymer U, Cohen M, et al: ATOLL: an international randomized study comparing IV enoxaparin to IV UFH in primary PCI. *Eur Heart J* 31:2042, 2010.
6. Hildick-Smith DJ, Lowe MD, Walsh JT, et al: Coronary angiography from the radial artery–experience, complications and limitations. *Int J Cardiol* 64:231–239, 1998.
7. Hess CN, Peterson ED, Neely ML, et al: The learning curve for transradial percutaneous coronary intervention among operators in the United States: a study from the National Cardiovascular Data Registry. *Circulation* 129:2277–2286, 2014.
8. Yoo BS, Yoon J, Ko JY, et al: Anatomical consideration of the radial artery for transradial coronary procedures: arterial diameter, branching anomaly and vessel tortuosity. *Int J Cardiol* 101:421–427, 2005.
9. Saito S, Miyake S, Hosokawa G, et al: Transradial coronary intervention in Japanese patients. *Catheter Cardiovasc Interv* 46:37–41, discussion 42, 1999.
10. Cheaito R, Benamer H, Hovasse T, et al: Feasibility and safety of transradial coronary interventions using a 6.5-F sheathless guiding catheter in patients with small radial arteries: a multicenter registry. *Catheter Cardiovasc Interv* 2014. doi: 10.1002/ccd25508. [Epub ahead of print].
11. Michael TT, Alomar M, Papayannis A, et al: A randomized comparison of the transradial and transfemoral approaches for coronary artery bypass graft angiography and intervention: the radial-CABG trial (radial versus femoral access for coronary artery bypass graft angiography and intervention). *J Am Coll Cardiol* 6:1138–1144, 2013.
12. Abdelaal E, Brousseau-Provencher C, Montminy S, et al: Risk score, causes, and clinical impact of failure of transradial approach for percutaneous coronary interventions. *J Am Coll Cardiol* 6:1129–1137, 2013.
13. Jolly SS, Yusuf S, Cairns J, et al: Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet* 377:1409–1420, 2011.
14. Agostoni P, Biondi-Zoccai GG, de Benedictis ML, et al: Radial versus femoral approach for percutaneous coronary diagnostic and interventional procedures; systematic overview and meta-analysis of randomized trials. *J Am Coll Cardiol* 44:349–356, 2004.
15. Jolly SS, Amlani S, Hamon M, et al: Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. *Am Heart J* 157:132–140, 2009.
16. Bertrand OF, Belisle P, Joyal D, et al: Comparison of transradial and femoral approaches for percutaneous coronary interventions: a systematic review and hierarchical bayesian meta-analysis. *Am Heart J* 163:632–648, 2012.
17. Brayton KM, Patel VG, Stave C, et al: Same-day discharge after percutaneous coronary intervention: a meta-analysis. *J Am Coll Cardiol* 62:275–285, 2013.
18. Cox N, Resnic FS, Popma JJ, et al: Comparison of the risk of vascular complications associated with femoral and radial access coronary catheterization procedures in obese versus nonobese patients. *Am J Cardiol* 94:1174–1177, 2004.
19. Louvard Y, Benamer H, Garot P, et al: Comparison of transradial and transfemoral approaches for coronary angiography and angioplasty in octogenarians (the octoplus study). *Am J Cardiol* 94:1177–1180, 2004.
20. Vuurmans T, Byrne J, Fretz E, et al: Chronic kidney injury in patients after cardiac catheterisation or percutaneous coronary intervention: a comparison of radial and femoral approaches (from the British Columbia Cardiac and Renal Registries). *Heart* 96:1538–1542, 2010.
21. Kooiman J, Seth M, Dixon S, et al: Risk of acute kidney injury after percutaneous coronary interventions using radial versus femoral vascular access: insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. *Circulation Cardiovasc Interv* 7:190–198, 2014.
22. Montalescot G, Ongen Z, Guindy R, et al: Predictors of outcome in patients undergoing PCI. Results of the RIVIERA study. *Int J Cardiol* 129:379–387, 2008.
23. Cantor WJ, Puley G, Natarajan MK, et al: Radial versus femoral access for emergent percutaneous coronary intervention with adjunct glycoprotein IIb/IIIa inhibition in acute myocardial infarction–the RADIAL-AMI pilot randomized trial. *Am Heart J* 150:543–549, 2005.
24. Cruden NL, Teh CH, Starkey IR, Newby DE: Reduced vascular complications and length of stay with transradial rescue angioplasty for acute myocardial infarction. *Catheter Cardiovasc Interv* 70:670–675, 2007.
25. Hetherington SL, Adam Z, Morley R, et al: Primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction: changing patterns of vascular access, radial versus femoral artery. *Heart* 95:1612–1618, 2009.
26. Pancholy S, Patel T, Sanghvi K, et al: Comparison of door-to-balloon times for primary PCI using transradial versus transfemoral approach. *Catheter Cardiovasc Interv* 75:991–995, 2010.
27. Vorobcsuk A, Konyi A, Aradi D, et al: Transradial versus transfemoral percutaneous coronary intervention in acute myocardial infarction systematic overview and meta-analysis. *Am Heart J* 158:814–821, 2009.
28. Bernat I, Horak D, Stasek J, et al: ST-segment elevation myocardial infarction treated by radial or femoral approach in a multicenter randomized clinical trial: the STEMI-RADIAL trial. *J Am Coll Cardiol* 63:964–972, 2014.
29. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al: Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (radial versus femoral randomized investigation in ST-elevation acute coronary syndrome) study. *J Am Coll Cardiol* 60:2481–2489, 2012.
30. Steg PG, James SK, Atar D, et al: ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 33:2569–2619, 2012.
31. Kiemeneij F, Laarman GJ, Odekerken D, et al: A randomized comparison of percutaneous transluminal coronary angioplasty by the radial, brachial and femoral approaches: the ACCESS study. *J Am Coll Cardiol* 29:1269–1275, 1997.
32. Benit E, Missault L, Eeman T, et al: Brachial, radial, or femoral approach for elective Palmaz-Schatz stent implantation: a randomized comparison. *Catheter Cardiovasc Diagn* 41:124–130, 1997.
33. Aptecar E, Pernes JM, Chabane-Chaouch M, et al: Transulnar versus transradial artery approach for coronary angioplasty: the PCVI-CUBA study. *Catheter Cardiovasc Interv* 67:711–720, 2006.
34. Hahalis G, Tsigkas G, Xanthopoulou I, et al: Transulnar compared with transradial artery approach as a default strategy for coronary procedures: a randomized trial. The Transulnar pr Transradial Instead of Coronary Transfemoral Angiographies Study (the AURA of ARTEMIS study). *Circulation Cardiovasc Interv* 6:252–261, 2013.
35. Roussanov O, Wilson SJ, Henley K, et al: Cost-effectiveness of the radial versus femoral artery approach to diagnostic cardiac catheterization. *J Invasive Cardiol* 19:349–353, 2007.
36. Amin AP, House JA, Safley DM, et al: Costs of transradial percutaneous coronary intervention. *J Am Coll Cardiol* 6:827–834, 2013.
37. Kim MH, Cha KS, Kim HJ, et al: Primary stenting for acute myocardial infarction via the transradial approach: a safe and useful alternative to the transfemoral approach. *J Invasive Cardiol* 12: 292–296, 2000.
38. Valsecchi O, Musumeci G, Vassileva A, et al: Safety, feasibility and efficacy of transradial primary angioplasty in patients with acute myocardial infarction. *Ital Heart J* 4:329–334, 2003.
39. Valsecchi O, Musumeci G, Vassileva A, et al: Safety and feasibility of transradial coronary angioplasty in elderly patients. *Ital Heart J* 5:926–931, 2004.
40. Kiemeneij F, Laarman GJ, de Melker E: Transradial artery coronary angioplasty. *Am Heart J* 129:1–7, 1995.
41. Nagai S, Abe S, Sato T, et al: Ultrasonic assessment of vascular complications in coronary angiography and angioplasty after transradial approach. *Am J Cardiol* 83:180–186, 1999.
42. Barbeau GR, Arsenault F, Dugas L, et al: Evaluation of the ulnopalmar arterial arches with pulse oximetry and plethysmography: comparison with the Allen's test in 1010 patients. *Am Heart J* 147:489–493, 2004.
43. Greenwood MJ, Della-Siega AJ, Fretz EB, et al: Vascular communications of the hand in patients being considered for transradial coronary angiography: Is the Allen's test accurate? *J Am Coll Cardiol* 46:2013–2017, 2005.
44. Valgimigli M, Campo G, Penzo C, et al: Transradial coronary catheterization and intervention across the whole spectrum of Allen test results. *J Am Coll Cardiol* 63:1833–1841, 2014.
45. Kawashima O, Endoh N, Terashima M, et al: Effectiveness of right or left radial approach for coronary angiography. *Catheter Cardiovasc Interv* 61:333–337, 2004.
46. Guo X, Ding J, Qi Y, et al: Left radial access is preferable to right radial access for the diagnostic or interventional coronary procedures: a meta-analysis involving 22 randomized clinical trials and 10287 patients. *PLoS ONE* 8:e78499, 2013.
47. Rathore S, Stables RH, Pauriah M, et al: Impact of length and hydrophilic coating of the introducer sheath on radial artery spasm during transradial coronary intervention: a randomized study. *J Am Coll Cardiol* 3:475–483, 2010.
48. Chen CW, Lin CL, Lin TK, Lin CD: A simple and effective regimen for prevention of radial artery spasm during coronary catheterization. *Cardiology* 105:43–47, 2006.
49. Varenne O, Jegou A, Cohen R, et al: Prevention of arterial spasm during percutaneous coronary interventions through radial artery: the SPASM study. *Catheter Cardiovasc Interv* 68:231–235, 2006.
50. Ruiz-Salmeron RJ, Mora R, Masotti M, Betriu A: Assessment of the efficacy of phentolamine to prevent radial artery spasm during cardiac catheterization procedures: a randomized study comparing phentolamine vs. Verapamil. *Catheter Cardiovasc Interv* 66: 192–198, 2005.
51. Deftereos S, Giannopoulos G, Raisakis K, et al: Moderate procedural sedation and opioid analgesia during transradial coronary interventions to prevent spasm: a prospective randomized study. *J Am Coll Cardiol* 6:267–273, 2013.
52. Spaulding C, Lefevre T, Funck F, et al: Left radial approach for coronary angiography: results of a prospective study. *Catheter Cardiovasc Diagn* 39:365–370, 1996.
53. Venkatesh K, Mann T: Transitioning from heparin to bivalirudin in patients undergoing ad hoc transradial interventional procedures: a pilot study. *J Invasive Cardiol* 18:120–124, 2006.

54. Choussat R, Black A, Bossi I, et al: Vascular complications and clinical outcome after coronary angioplasty with platelet IIb/IIIa receptor blockade. Comparison of transradial vs transfemoral arterial access. *Eur Heart J* 21:662–667, 2000.
55. Philippe F, Larrazet F, Meziane T: Dibie A: Comparison of transradial vs. transfemoral approach in the treatment of acute myocardial infarction with primary angioplasty and abciximab. *Catheter Cardiovasc Interv* 61:67–73, 2004.
56. Kassam S, Cantor WJ, Patel D, et al: Radial versus femoral access for rescue percutaneous coronary intervention with adjuvant glycoprotein IIb/IIIa inhibitor use. *Can J Cardiol* 20:1439–1442, 2004.
57. Bertrand OF, De Larochelliere R, Rodes-Cabau J, et al: A randomized study comparing same-day home discharge and abciximab bolus only to overnight hospitalization and abciximab bolus and infusion after transradial coronary stent implantation. *Circulation* 114:2636–2643, 2006.
58. Iqbal Z, Cohen M, Pollack C, et al: Safety and efficacy of adjuvant glycoprotein IIb/IIIa inhibitors during primary percutaneous coronary intervention performed from the radial approach for acute ST segment elevation myocardial infarction. *Am J Cardiol* 111:1727–1733, 2013.
59. Valsecchi O, Vassileva A, Musumeci G, et al: Failure of transradial approach during coronary interventions: anatomic considerations. *Catheter Cardiovasc Interv* 67:870–878, 2006.
60. Sakai H, Ikeda S, Harada T, et al: Limitations of successive transradial approach in the same arm: the Japanese experience. *Catheter Cardiovasc Interv* 54:204–208, 2001.
61. Yoo BS, Lee SH, Ko JY, et al: Procedural outcomes of repeated transradial coronary procedure. *Catheter Cardiovasc Interv* 58: 301–304, 2003.
62. Abdelaal E, Molin P, Plourde G, et al: Successive transradial access for coronary procedures: experience of Quebec Heart-Lung Institute. *Am Heart J* 165:325–331, 2013.
63. Yonetsu T, Kakuta T, Lee T, et al: Assessment of acute injuries and chronic intimal thickening of the radial artery after transradial coronary intervention by optical coherence tomography. *Eur Heart J* 31:1608–1615, 2010.
64. Coppola J, Patel T, Kwan T, et al: Nitroglycerin, nitroprusside, or both in preventing radial artery spasm during transradial artery catheterization. *J Invasive Cardiol* 18:155–158, 2006.
65. Hildick-Smith DJ, Walsh JT, Lowe MD, et al: Transradial coronary angiography in patients with contraindications to the femoral approach: an analysis of 500 cases. *Catheter Cardiovasc Interv* 61:60–66, 2004.
66. Pancholy SB, Bertrand OF, Patel T: Comparison of a priori versus provisional heparin therapy on radial artery occlusion after transradial coronary angiography and patent hemostasis (from the PHARAOH study). *Am J Cardiol* 110:173–176, 2012.
67. Kiemeneij F, Laarman GJ: Percutaneous transradial artery approach for coronary Palmaz-Schatz stent implantation. *Am Heart J* 128:167–174, 1994.
68. Kiemeneij F, Laarman GJ: Transradial artery Palmaz-Schatz coronary stent implantation: results of a single-center feasibility study. *Am Heart J* 130:14–21, 1995.
69. Louvard Y, Ludwig J, Lefevre T, et al: Transradial approach for coronary angioplasty in the setting of acute myocardial infarction: a dual-center registry. *Catheter Cardiovasc Interv* 55:206–211, 2002.
70. Mulukutla SR, Cohen HA: Feasibility and efficacy of transradial access for coronary interventions in patients with acute myocardial infarction. *Catheter Cardiovasc Interv* 57:167–171, 2002.
71. Mann JT, 3rd, Cubeddu MG, Schneider JE, Arrowood M: Right radial access for PTCA: a prospective study demonstrates reduced complications and hospital charges. *J Invasive Cardiol* 8(Suppl D):40D–44D, 1996.
72. Mann T, Cubeddu G, Bowen J, et al: Stenting in acute coronary syndromes: a comparison of radial versus femoral access sites. *J Am Coll Cardiol* 32:572–576, 1998.
73. Mann T, Cowper PA, Peterson ED, et al: Transradial coronary stenting: comparison with femoral access closed with an arterial suture device. *Catheter Cardiovasc Interv* 49:150–156, 2000.
74. Louvard Y, Lefevre T, Allain A, Morice M: Coronary angiography through the radial or the femoral approach: the CARAFE study. *Catheter Cardiovasc Interv* 52:181–187, 2001.
75. Saito S, Tanaka S, Hiroe Y, et al: Comparative study on transradial approach vs. transfemoral approach in primary stent implantation for patients with acute myocardial infarction: results of the test for myocardial infarction by prospective unicenter randomization for access sites (TEMPURA) trial. *Catheter Cardiovasc Interv* 59:26–33, 2003.
76. Slagboom T, Kiemeneij F, Laarman GJ, van der Wieken R: Outpatient coronary angioplasty: feasible and safe. *Catheter Cardiovasc Interv* 64:421–427, 2005.
77. Brasselet C, Tassan S, Nazeyrollas P, et al: Randomised comparison of femoral versus radial approach for percutaneous coronary intervention using abciximab in acute myocardial infarction: results of the FARMI trial. *Heart* 93:1556–1561, 2007.
78. Li WM, Li Y, Zhao JY, et al: Safety and feasibility of emergent percutaneous coronary intervention with the transradial access in patients with acute myocardial infarction. *Chinese Med J* 120:598–600, 2007.
79. Achenbach S, Ropers D, Kallert L, et al: Transradial versus transfemoral approach for coronary angiography and intervention in patients above 75 years of age. *Catheter Cardiovasc Interv* 72:629–635, 2008.
80. Chódor P, Krupa H, Kurek T, et al: RADIal versus femoral approach for percutaneous coronary interventions in patients with Acute Myocardial Infarction (RADIAMI): a prospective, randomized, single-center clinical trial. *Cardiol J* 16:332–340, 2009.
81. Chódor P, Kurek T, Kowalczuk A, et al: Radial vs femoral approach with StarClose clip placement for primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction. RADIAMI II: a prospective, randomised, single centre trial. *Kardiol Pol* 69:763–771, 2011.

32 The Role of the Cardiac Surgeon

G. RUSSELL REISS | MATHEW R. WILLIAMS

KEY POINTS

- The role of the cardiac surgeon in the catheterization laboratory (cath lab) has been traditionally one of providing surgical backup or standby for the interventional cardiologist. The need for such service waxes and wanes parallel to the development and mastery of new interventional procedures and correlates with the advancement of medical device technology.
- Despite low incidence, emergency revascularization surgery for failed percutaneous coronary intervention (PCI) still persists and portends mortality rates that approach 15% in some centers. With national PCI volumes contracting, performance of elective or high-risk PCI is not recommended without on-site surgical backup or a defined plan for expeditious surgical intervention at a nearby cardiac surgery center.
- New minimally invasive interventional procedures are founded upon the open surgical approach and take a defined pathway from conception to clinical acceptance. This pathway requires collaboration among surgeons, interventionalists, medical device makers, and the U.S. Food and Drug Administration (FDA).
- The "heart team" model with true face-to-face communication between surgeon and cardiologist should be considered the standard of care in all cardiac centers for approaching complex coronary lesions and structural heart defects such as aortic stenosis and mitral regurgitation.
- The future of interventional cardiology and cardiac surgery will require close collaboration between the surgeon and the cardiologist, thus an overlapping clinical training pathway that incorporates certain fundamental principles and skills from both surgical and cardiology training programs will be necessary to ensure the appropriate training of future cardiovascular interventionalists.
- A hybrid cardiovascular interventional program in which patients can receive expert treatment from both surgeons and interventionalists in the same setting requires multidisciplinary input from the entire heart team, including anesthesia and radiology in addition to technical and ancillary staff from both the operating room (OR) and the cath lab.

The role of the cardiac surgeon in the cath lab can be broadly described in three categories: the first is that of a standby operator backing up the interventional cardiologist in case of any untoward complication or emergency requiring surgical intervention. This role waxes and wanes with the advent and subsequent mastery of new procedures. "Formal" surgical standby for routine PCI, in which a surgeon is preemptively notified and is waiting in the hospital, is no longer required or routine because complications that require surgical intervention have become quite uncommon in established PCI centers. However, current published guidelines for elective PCI still recommend the availability of an experienced surgical team that can be activated quickly in the event of an emergency in the cath lab.[1,2] Some evidence suggests that primary PCI performed at certain highly experienced centers without an existing cardiac surgery program may be reasonable and provides some benefit over the alternative use of fibrinolytic therapy for acute myocardial infarction (MI).[3] This concept is currently not promoted by consensus of the cardiovascular community.[1,2]

The second role the cardiac surgeon plays in the cath lab is that of an interventionalist or hybrid cardiac surgeon. The hybrid cardiac surgeon takes an active role in interventional procedures and, in some cases, has formal cross-training in interventional cardiology. This has established a new identity for the cardiac surgeon who traditionally remained outside the cath lab awaiting surgical referrals or the occurrence of a cardiovascular emergency. Hybrid cardiac surgeons serve an important function in today's more complex interventional procedures such as transcatheter aortic valve replacement (TAVR), percutaneous mitral valvuloplasty, perivalvular leak intervention, and combined coronary artery bypass grafting (CABG)/PCI or valve/PCI procedures. With the heart team model becoming widely adopted, hybrid surgeons will help shape the cath lab of the future. This convergence of cardiology and cardiac surgery has necessitated the need to have the simultaneous skill sets of a surgeon and interventionalist both present at the interventional table.

The third role of the cardiac surgeon is that of an innovation consultant. The cardiovascular surgeon's intraoperative experience and technical development is deeply rooted in the surgical correction of structural heart disease. With strict adherence to traditional surgical principles, cardiac surgeons develop a unique perspective that can only be gained by years of performing open-heart procedures and mastering a true three-dimensional understanding of the anatomy of the heart and the great vessels. The cardiac surgeon continues to contribute valuable insight to the development and refinement of new techniques and procedures, which will ultimately become the standard of care for the cardiovascular interventionalist of tomorrow.

HISTORICAL PERSPECTIVE

Throughout history, alongside their colleagues in cardiology, radiology, and other disciplines, surgeons have led pioneering efforts for the most significant invasive procedures and technical innovations in cardiovascular medicine. The input of the surgeon has always been regarded as the gold standard for advice on the anatomic aspects and physiologic practicality of a proposed invasive procedure. Once deemed surgically feasible, new clinical techniques become adopted by the medical community often with a less invasive approach. Over the years, numerous subspecialties have been spawned based on the initial curiosity and investigation of the surgeon and his colleagues. This evolution and transference of skill sets has occurred in several fields such as gastroenterology with endoscopy, pulmonary critical care with bronchoscopy, and more recently, with interventional radiologists performing vascular intervention, tumor biopsy, thoracostomy, abscess drainage, and more. The field of interventional cardiology has likewise evolved with surgical advancement as its backdrop and foundation. Before the advent of modern angiography and cath labs, surgeons routinely performed their own angiograms to define the vascular anatomy prior to embarking on surgical intervention. The concept of having proper imaging and a "road map" before undertaking an intervention has been a well-accepted practice in cardiovascular surgery for decades.

Looking back to 1929, Werner Forssmann, a surgical trainee at the time, passed a urinary catheter through the vein in his own arm to his heart and subsequently irradiated himself. After successfully demonstrating the catheter to be in the right atrium, Forssmann was credited

TABLE 32-1 Indications for Emergency Coronary Bypass Surgery After Failed Percutaneous Coronary Intervention

Periods	1979-1994	1995-1999	2000-2003
Indication	(*n* = 258 of 8905)	(*n* = 56 of 7605)	(*n* = 21 of 6577)
Abrupt vessel closure	55 (21%)	2 (4%)	3 (14%)
Dissection	88 (34%)	12 (21%)	3 (14%)
Incomplete revascularization	26 (10%)	7 (13%)	4 (19%)
Perforation	1 (0.4%)	1 (2%)	2 (10%)
Unsuccessful dilation	67 (26%)	28 (50%)	7 (33%)
Other	21 (8%)	6 (10%)	2 (10%)

Modified from Yang EH, Gumina RJ, Lennon RJ, et al: Emergency coronary artery bypass surgery for percutaneous interventions: changes in the incidence, clinical characteristics, and indications from 1979 to 2003. *J Am Coll Cardiol* 46:2004-2009, 2005.

with performing the first cardiac catheterization. He received the Nobel Prize in 1956, along with Andre Cournand and Dickinson Richards, for "the role of heart catheterization and angiocardiography in the advancement of medicine."[4,5] In 1953, Sven-Ivar Seldinger, who trained briefly as a surgeon before becoming a radiologist, developed a percutaneous approach for the introduction of vascular catheters for both right and left heart catheterization.[6] This technique is now the most common percutaneous approach used for gaining access to the vascular tree. In 1977, Andreas Grüntzig, along with his surgical colleague Richard Myler, inflated the first catheter-guided balloon in a coronary artery during a coronary bypass operation.[7] Grüntzig's novel procedure eventually became known as *percutaneous transluminal coronary angioplasty* (PTCA) and set the stage for modern interventional cardiology and PCI. The list of events and milestones that illustrates surgeons remaining steadfast beside their nonsurgical colleagues as fundamental partners in developing and advancing nearly every invasive discipline in medicine is impressive.

Today, the cardiac surgeon remains a key team member in any successful and innovative interventional cardiovascular program. The magnitude and activity of the surgeon's role in the day-to-day activities of the interventional suite is not always a steady one; rather, it depends on the risk level of each intervention and the learning curve associated with the introduction of each new procedure, along with the hands-on interest of the individual surgeon. As new procedures such as TAVR alter the current standard of care and are adopted into practice, it is critical for the cardiac surgeon's role to increase until the entire heart team reaches a new comfort zone regarding safety and efficacy.

SURGICAL STANDBY

During the early years of PTCA and PCI, surgeons were by necessity compelled to remain in house on "surgical standby" for urgent consultations and surgical emergencies that resulted from early interventional procedures. Fraught with technical pitfalls and clinical unknowns, more often than not, early complications in the cath lab required an emergent trip to the OR, often with a patient in extreme cardiogenic shock.[8-11] As a result, indications for emergency CABG after failed PCI have become well established over time. The most common indications include abrupt vessel closure, dissection, incomplete revascularization, perforation, and unsuccessful dilation or PCI in addition to other miscellaneous clinical scenarios (Table 32-1).[12]

As angiography, PTCA, and surgical techniques improved and medical equipment became more advanced, surgeons were no longer required to remain in such close proximity to the cath lab.[13,14] This was particularly true after introduction of the Gianturco-Roubin stent and its rapid adoption as a "bailout catheter" by the interventional cardiology community.[15,16] Almost uniformly, and for decades, active PCI centers have enjoyed a steady reduction in the percentage of cases that require emergency CABG after failed PCI (Fig. 32-1).[17] However, it must be noted that despite near universal trends that demonstrate decreased morbidity and mortality from PCI, the consequences of complications in the cath lab remain potentially catastrophic. Thus it

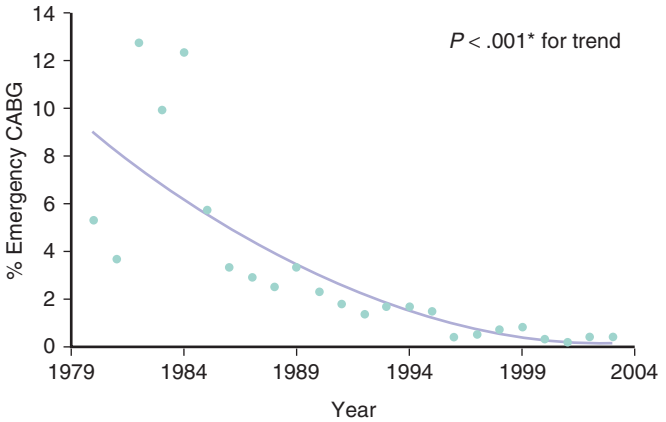

FIGURE 32-1 Percentage of patients who required emergency coronary artery bypass grafting (CABG) after percutaneous coronary intervention from 1979 to 2003 (*N* = 23,087). The Armitage test for trend is indicated by an asterisk. (From Yang EH, Gumina RJ, Lennon RJ, et al: Emergency coronary artery bypass for percutaneous interventions: changes in the incidence, clinical characteristics, and indications from 1979 to 2003. *J Am Coll Cardiol* 46:2004-2009, 2005.)

is still common practice today, and it is recommended by the American College of Cardiology (ACC)/American Heart Association (AHA)/Society of Cardiovascular and Angiography and Interventions (SCAI) practice guidelines, that the majority of elective PCI be performed at centers with an active open-heart surgery program and that certain interventional decisions be discussed with a cardiac surgeon before proceeding with PCI.[1,2] In the event of emergent need for aortocoronary bypass, outcomes have been shown to be better in centers with an open-heart surgery program (Table 32-2; Fig. 32-2).[12,17] According to current guidelines, on-site surgical backup should provide emergency hemodynamic support and expeditious revascularization to manage complications that cannot be addressed in the cath lab (Table 32-3).[18] Often, these PCI complications are life threatening, with hemodynamic instability and associated prolonged periods of ischemia. Such emergencies require the availability of a cardiac surgery team experienced in emergency aortocoronary operations and on-site cardiac surgical backup to provide all aspects of readily available cardiac surgical support.

Percutaneous Coronary Intervention Without On-Site Surgical Backup

On-site cardiac surgical backup is a surrogate for an institution's overall capability to provide a highly experienced and promptly available team to respond to a cath lab emergency.[1,2] "The ACC/AHA/SCAI 2014

TABLE 32-2 Coronary Artery Bypass Grafting and Mortality Rates Following Percutaneous Coronary Intervention at Hospitals Without and With On-Site Coronary Artery Bypass Grafting Surgery

Outcomes	PATIENTS (%)		Unadjusted *P* Value	Adjusted OR (95% CI)*	Adjusted *P* Value
	Without On-Site CABG	With On-Site CABG			
All PCIs					
No. of patients	8,168	617,686		621,530†	
Mortality	492 (6)	20,393 (3.3)	<.001	1.29 (1.14-1.47)	<.001
CABG	160 (2)	8,321 (1.4)	<.001	1.05 (0.87-1.27)	.59
Primary/Rescue PCI					
No. of patients	1,795	34,537		36,235†	
Mortality	202 (11.3)	4,209 (12.2)	0.24	0.93 (0.80-1.08)	.34
CABG	82 (4.6)	1,772 (5.1)	0.29	0.95 (0.73-1.22)	.67
Nonprimary/Rescue PCI					
No. of patients	6,373	583,149		585,295†	
Mortality	290 (4.6)	16,184 (2.8)	<.001	1.38 (1.14-1.67)	.001
CABG	78 (1.2)	6,549 (1.1)	.45	0.92 (0.73-1.17)	.52

Data from Wennberg DE, Lucas FL, Siewers AE, et al: Outcomes of percutaneous coronary interventions performed at centers without and with on-site coronary artery bypass graft surgery. *JAMA* 292:1965, 2004.
*Adjusted for age, gender, race, year, Charison comorbidity score, primary diagnosis of acute myocardial infarction, acuity, multivessel PCI, and stent use.
†Adjusted models excluded 4324 patients (0.7%) missing on patient covariates; 45 (4 among primary/rescue PCI) among patients without on-site CABG and 4279 (93 among primary/rescue PCI) among patients with on-site CABG.
CABG, Coronary artery bypass grafting; *CI,* confidence interval; *OR,* odds ratio; *PCI,* percutaneous coronary intervention.

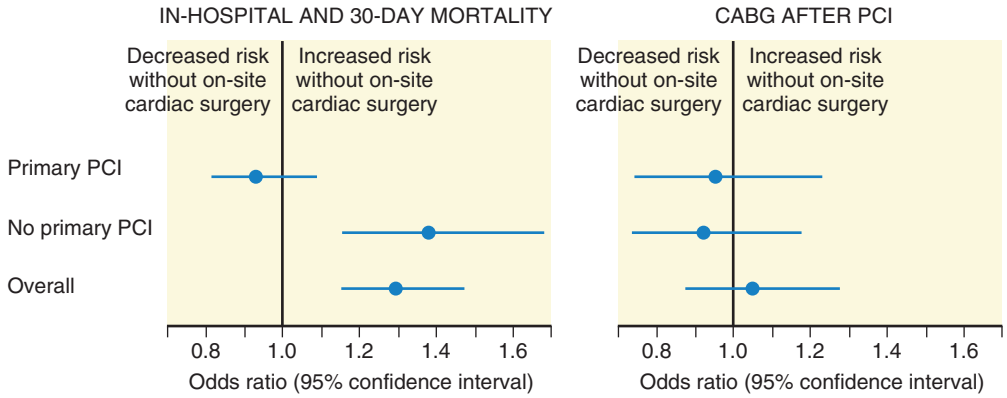

FIGURE 32-2 The increased risk of post–percutaneous coronary intervention (PCI) mortality in institutions without a cardiac surgery program persisted after adjustment for differences in case mix. Overall, the odds of death for patients who had an in-hospital PCI without on-site cardiac surgery was 29% higher than for patients who had PCIs in hospitals with cardiac surgery (odds ratio 1.29; 95% confidence interval). *CABG,* Coronary artery bypass grafting. (From Wennberg DE, Lucas FL, Siewers AE, et al: Outcomes of percutaneous coronary interventions performed at centers without and with on-site coronary artery bypass graft surgery. *JAMA* 292:1965, 2004.)

Expert Consensus Document" provides recommendations for PCI without on-site surgery that are a composite of recommendations from the 2007 SCAI expert consensus statement, the 2011 PCI guidelines, the 2012 expert consensus document on cardiac catheterization laboratory standards, the 2013 PCI competency statement, recommendations from the policy statement of the AHA, and requirements for the Mission Lifeline program and the D2B Alliance. These recommendations include requirements for both facilities and personnel.[2] The issues of cardiac surgical backup and the level of committed resources needed are frequently revisited, and most centers use the first-available OR model to remain efficient and maximize resources. Some centers rely on off-site surgical backup, but this is the exception rather than the rule; such practice exposes the patient to a finite but potentially fatal risk, and it can be deemed unnecessary in most areas. Recommendations for primary PCI for ST-elevation myocardial infarction (STEMI) without on-site cardiac surgery are given in Table 32-4.[18] The apparent success of centers that perform PCI without on-site cardiac surgery programs, among other things such as operator experience and volume, can be attributed to fairly strict patient selection (Table 32-5) and criteria (Table 32-6).[19] It should be noted that in low-volume centers (<200 PCIs per year), adverse event estimates lose stability and may therefore be unreliable (Fig. 32-3).[1]

The 2013 PCI competency document identified a signal that suggested an institutional volume threshold of fewer than 200 PCIs per year was associated with worse outcomes. Thus laboratories that perform fewer than 200 procedures annually and that are not serving isolated or underserved populations should be questioned, and any laboratory that cannot maintain satisfactory outcomes should be closed. Multiple low-volume and partial-service PCI centers within a geographic area diffuse the PCI expertise, increase costs for the overall health care system, and have not been shown to improve access. If the transfer time is 30 minutes or less, it is reasonable to assume that transfer to the nearest PCI center will provide reperfusion as rapidly as if it were available at the first hospital. For transport times longer than 30 minutes, performing PCI on site is likely to be quicker than a transfer. The development of PCI facilities within a 30-minute

TABLE 32-3 Role of On-Site Cardiac Surgical Backup for Percutaneous Coronary Intervention

Class I
Elective PCI should be performed by operators with acceptable annual volume (at least 75 procedures per year) at high-volume centers (more than 400 procedures annually) that provide immediately available on-site emergency cardiac surgical services. (Level of Evidence: B)
Primary PCI for patients with STEMI should be performed in facilities with on-site cardiac surgery. (Level of Evidence: B)
Class III
Elective PCI should not be performed at institutions that do not provide on-site cardiac surgery. (Level of Evidence: C)*

Data from Wennberg DE, Lucas FL, Siewers AE, et al: Outcomes of percutaneous coronary interventions performed at centers without and with on-site coronary artery bypass graft surgery. *JAMA* 292:1965, 2004.
*Several centers have reported satisfactory results on the basis of careful case selection with well-defined arrangements for immediate transfer to a surgical program. Wennberg and colleagues found higher mortality in the Medicare database for patients undergoing elective PCI in institutions without on-site cardiac surgery (6.0% vs. 3.3%, respectively; adjusted $P < .001$). This recommendation may be subject to revision as clinical data and experience increase.
PCI, Percutaneous coronary intervention; *STEMI,* ST-elevation myocardial infarction.

TABLE 32-4 Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction Without On-Site Cardiac Surgery

Class IIb
PCI for patients with STEMI might be considered in hospitals without on-site cardiac surgery provided that appropriate planning for program development has been accomplished. This should include appropriately experienced physician operators (more than 75 total PCIs and, ideally, at least 11 primary PCIs per year for STEMI); an experienced catheterization team on an all-day, all-week call schedule; and a well-equipped catheterization laboratory with digital imaging equipment, a full array of interventional equipment, and intraaortic balloon pump capability. A proven plan for rapid transport to a cardiac surgery operating room in a nearby hospital with appropriate hemodynamic support capability for transfer should be in place. The procedure should be limited to patients with STEMI or MI with new or presumably new LBBB on ECG and should be performed in a timely fashion (balloon inflation within 90 min of presentation) by persons skilled in the procedure (at least 75 PCIs per year) and at hospitals that perform a minimum of 36 primary PCI procedures per year. (Level of Evidence: B)
Class III
Primary PCI should not be performed in hospitals without on-site cardiac surgery and without a proven plan for rapid transport to a cardiac surgery operating room in a nearby hospital or without appropriate hemodynamic support capability for transfer. (Level of Evidence: C)

ECG, Electrocardiogram; *LBBB,* left bundle branch block; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention; *STEMI,* ST-elevation myocardial infarction.

emergency transfer time to an established facility is therefore strongly discouraged.[2]

THE SURGICAL INTERVENTIONALIST

Today, many procedures that used to be performed as open surgeries exclusively by surgeons are now routinely performed percutaneously, or with a cutdown, in the cath lab or interventional suite by interventionalists of various disciplines, including cardiovascular surgeons, cardiologists, and interventional radiologists. These procedures are growing in number and variety and include pacemaker insertion, mechanical ablation of atrial fibrillation (Maze procedure), closure of patent foramen ovale, and repair of atrial septal defect, in addition to endovascular alternatives to open carotid endarterectomy, repair and resection of abdominal and thoracic aortic aneurysms, and peripheral artery bypass (Table 32-7). The most recent surgical procedures performed with a small cutdown or percutaneous interventional approach include TAVR and mitral valvuloplasty or clipping. Although not as prevalent as vascular surgeons performing many of their traditionally open surgeries percutaneously in the interventional suite (i.e.,

TABLE 32-5 Patient Selection for Primary Percutaneous Coronary Intervention and Emergency Aortocoronary Bypass at Hospitals Without On-Site Cardiac Surgery

Avoid intervention in hemodynamically stable patients with:
- Significant (≥60%) stenosis of an unprotected left main coronary artery upstream from an acute occlusion in the left coronary system that might be disrupted by the angioplasty catheter
- Extremely long or angulated infarct-related lesions with TIMI grade 3 flow
- Infarct-related lesions with TIMI grade 3 flow in stable patients with three-vessel disease
- Infarct-related lesions of small or secondary vessels
- Hemodynamically significant lesions in other than the infarct artery

Transfer for emergency aortocoronary bypass surgery patients with:
- High-grade residual left main or multivessel coronary disease and clinical or hemodynamic instability present after primary PCI of occluded vessels, preferably with IABP support

Data from Wharton TP Jr, McNamara NS, Fedele FA, et al: Primary angioplasty for the treatment of acute myocardial infarction: experience at two community hospitals without cardiac surgery. *J Am Coll Cardiol* 33:1257-1265, 1999.
IABP, Intraaortic balloon pump; *PCI,* percutaneous coronary intervention; *TIMI,* Thrombolysis in Myocardial Infarction.

TABLE 32-6 Criteria for the Performance of Primary Percutaneous Coronary Intervention at Hospitals Without On-Site Cardiac Surgery

- The operators must be experienced interventionalists who regularly perform elective PCI at a surgical center (≥75 cases per year). The catheterization laboratory must perform a minimum of 36 primary PCI procedures per year.
- The nursing and technical catheterization laboratory staff must be experienced in handling acutely ill patients and must be comfortable using interventional equipment. They must have acquired experience in dedicated interventional laboratories at a surgical center. They participate in an all-day, all-year call schedule.
- The catheterization laboratory itself must be well equipped with optimal imaging systems, resuscitative equipment, and IABP support, and it must be well stocked with a broad array of interventional equipment.
- The cardiac care unit nurses must be adept in hemodynamic monitoring and IABP management.
- The hospital administration must fully support the program and enable the fulfillment of the above institutional requirements.
- For immediate and efficient transfer of patients to the nearest cardiac surgical facility, formalized written protocols that are reviewed or tested on a regular (quarterly) basis must be in place.
- Primary PCI must be performed routinely as the treatment of choice around the clock for a large proportion of patients with AMI to ensure streamlined care paths and increased case volumes.
- Case selection for the performance of primary PCI must be rigorous. Criteria for the types of lesions appropriate for primary PCI and for the selection for transfer for emergency aortocoronary bypass surgery are shown in Table 32-5.
- There must be an ongoing program of outcomes analysis and formalized periodic case review.
- Institutions should participate in a 3- to 6-month period of implementation, during which time a formalized primary PCI program that includes establishment of standards, training of staff, detailed logistic development, and creation of a quality-assessment and error-management system is developed and instituted.

Data from Wharton TP Jr, McNamara NS, Fedele FA, et al: Primary angioplasty for the treatment of acute myocardial infarction: experience at two community hospitals without cardiac surgery. *J Am Coll Cardiol* 33:1257-1265, 1999.
AMI, Acute myocardial infarction; *IABP,* intraaortic balloon pump; *PCI,* percutaneous coronary intervention.

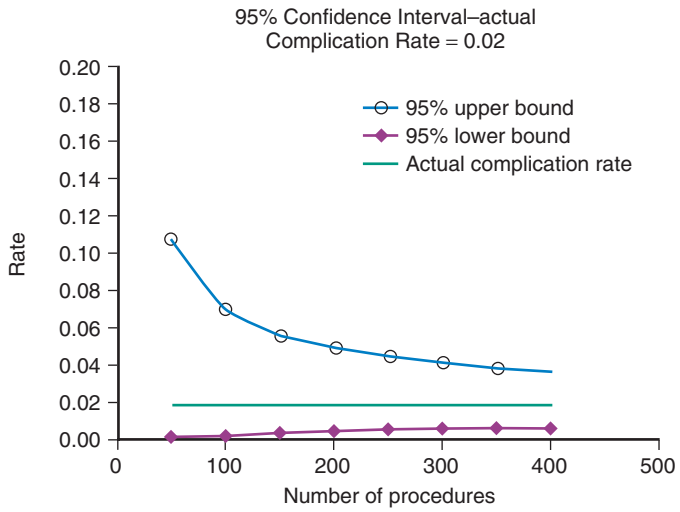

FIGURE 32-3 Plot of an actual adverse event rate of 2% over a procedure number range from 25 to 400. The horizontal line at 0.02 represents the actual adverse event rate. The curved lines above and below the horizontal line represent the upper and lower bounds of the 95% confidence interval of the estimate of the adverse event rate. Note that as the number of procedures decreases, the range between the upper and lower bounds increases, which indicates lack of stability of any adverse event rate estimate at procedure numbers below 200. (From Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al: ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention]. *Circulation* 113:e166-e286, 2006.)

TABLE 32-7 Surgical Procedures Currently Performed in the Interventional Suite

- Angiography
- Right and left heart volume pressure evaluation
- Temporary and long-term venous access
- Pacemaker implantation
- Atrial fibrillation surgery (Maze procedure)
- Vena cava filter implantation
- Valvuloplasty
- Congenital heart defect repairs
- Atrial septal defect and patent foramen ovale closure
- Arterial and venous stenosis
- Carotid endarterectomy
- Abdominal aortic aneurysm repair
- Thoracic aortic aneurysm repair
- Peripheral arterial disease interventions
- Temporary left ventricular assist device implantation
- Aortic valve replacement
- Mitral valve repair
- Gene and stem cell therapy

endovascular abdominal aneurysm repair [EVAR]), analogous procedures such as thoracic endovascular aortic repair (TEVAR) are performed more and more in the cath lab by cardiac surgeons. In addition, a few hybrid cardiac surgeons have actually acquired coronary angiography and PCI skills sufficient for hospital privileging.

TRANSCATHETER AORTIC VALVE REPLACEMENT

With TAVR now commercially available in the United States, cardiac surgeons are required to be part of the transcatheter heart team that performs these high-risk procedures.[20] Because of the rapid development and miniaturization of valve-deployment technology, growing worldwide experience, and the rapid adoption of new technology by interventional cardiologists, the transfemoral approach used for TAVR, also known as *transfemoral transcatheter aortic valve replacement* (TF-TAVR), will likely become the domain of the interventional cardiologist. In contrast to TF-TAVR and inherent to the design of the procedures, transapical TAVR (TA-TAVR) and transaortic TAVR (TAo-TAVR) can only be performed in a hybrid OR with a trained cardiac surgeon who can gain exposure to and manage surgical control of the ascending aorta and left ventricle (LV). These approaches require the ready availability of the cardiopulmonary bypass machine and an experienced perfusionist.

In the TA-TAVR procedure, a small left anterolateral thoracotomy is made over the point of maximal impulse (PMI) on the anterolateral chest wall to gain control of the apex of the LV (Fig. 32-4, *A*). This allows the surgeon to place a circular series of pledgeted sutures in the myocardium before the apical puncture and to place a transmyocardial guidewire using the Seldinger technique (see Fig. 32-4, *B*). Once control of the LV apex is attained and guidewire placement across the aortic valve is confirmed, a long sheath is placed, and a balloon aortic valvuloplasty (BAV) is performed. Following the BAV, the balloon-expandable transcatheter heart valve (THV) bioprosthesis is deployed in the aortic position under rapid ventricular pacing (see Fig. 32-4, *C* and *D*). The integrity and position of the newly placed THV is confirmed intraoperatively by both aortography and transesophageal echocardiography (TEE) before the chest is closed by the surgeon.

In the TAo-TAVR procedure, a partial J sternotomy or a right anterior mini thoracotomy (Fig. 32-5)[21] is used for gaining access to the ascending aorta. Appropriate preoperative planning entails careful evaluation of the position of the ascending aorta in the chest with respect to the sternum using a computed tomography (CT) scan (Fig. 32-6).[21] A partial J sternotomy suffices in most TAo cases; however, with unusual anatomy where 50% of the aorta lies to the right of the outer table of the sternum, a second intercostal approach may provide better access. Once the aorta has been surgically exposed, a site is selected that is at least the minimum distance requirement from the annulus for proper THV deployment (Fig. 32-7).[21] This site should be free of excessive calcium and in a location that will allow sufficient sheath depth for proper THV deployment. The sheath must be placed in a straight line to the annulus after properly identifying the "TAo zone" along the upper outer quadrant of the aorta (Fig. 32-8). Two purse-string sutures large enough to accommodate the THV sheath are placed, and heparin is administered. Using the Seldinger technique, the aortic lumen is entered and the native valve is crossed, exchanging a stiff, preshaped wire into the LV using a multipurpose catheter and standard exchange techniques. The large THV sheath is then positioned above the native valve over the stiff wire for deployment of the THV, which is performed under fluoroscopy with rapid pacing similar to other THV approaches. Once the THV has been deployed and postdeployment echocardiography assessment is complete, the sheath is removed and the purse-string sutures are secured. The chest is then closed in standard surgical fashion.

It is with procedures such as the TAVR, which will ultimately be combined with PCI in the same setting, that the new cardiac interventionalist will come of age. For the increasingly frail, aging population in the United States, an attractive alternative to current open-heart surgery will be to have well-trained cardiovascular interventionalists who can perform minimally invasive surgical and interventional procedures expeditiously in one setting, thus eliminating the need for multiple costly hospital visits and repeated exposures to anesthesia.

The Cardiac Surgeon in Innovation

New interventional procedures are largely based on open surgical approaches, converted first to minimally invasive procedures by surgeons and later translated to percutaneous techniques by interventionalists. These procedures take a defined pathway from conception to

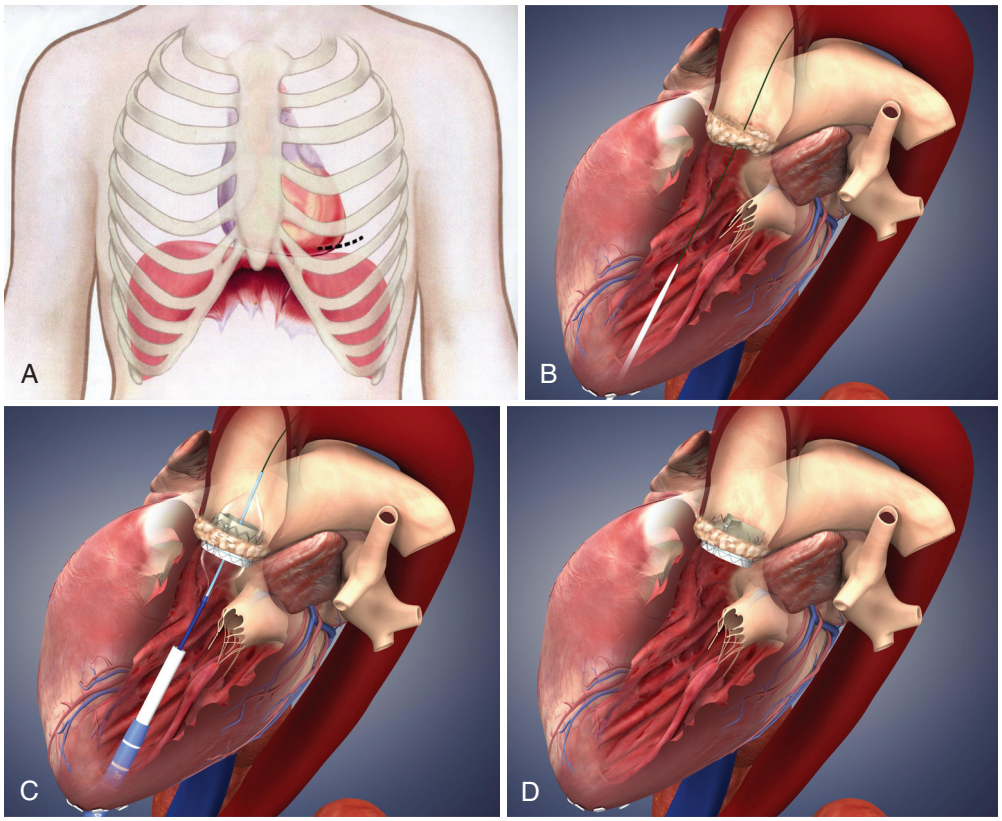

FIGURE 32-4 Transapical transcatheter aortic valve insertion (TA-TAVR). **A,** Keyhole left anterolateral thoracotomy for apical access. **B,** Seldinger technique used for wire insertion and dilation of transmural myocardial tract before balloon aortic valvuloplasty. **C,** Balloon expansion of percutaneous aortic valve. **D,** Well-seated percutaneous bioprosthesis in the aortic position.

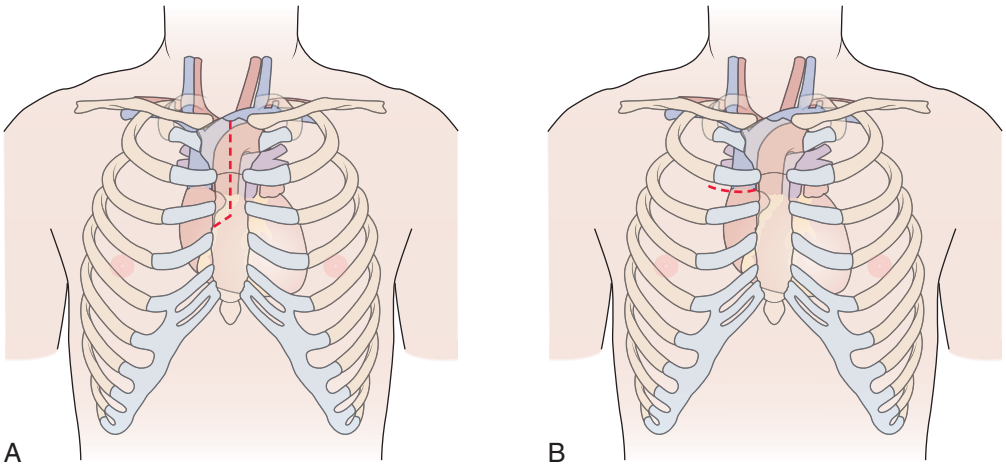

FIGURE 32-5 Transaortic (TAo) approach. **A,** Access ascending aorta, J sternotomy to second or third right intercostal space. **B,** Anterior right mini thoracotomy, second intercostal space. Used if partial J-sternotomy is not possible because of previous surgery or unusual anatomy.

clinical acceptance as the standard of care, a pathway that requires collaboration among surgeons, interventionalists, medical device makers, and the FDA.

Creation and Development of Interventional Procedures and Devices

As new therapeutic alternatives come to light in the OR, a surgical hypothesis is formulated. A prototype is then developed, often makeshift and primitive at first but functional to the point of proving a basic concept with a degree of feasibility. As the validation process progresses, more prototyping equipment and instruments needed for the procedure are developed either in a laboratory or, in some cases, in the clinical theater. Because of regulatory restrictions, the latter can only take place in a setting where the new procedure can be implemented with little modification of existing applications or through a combination of existing medical technologies used in a similar homologous approach. At this point, a new procedure or medical device can then take a variety of directions. A simple modification based on existing

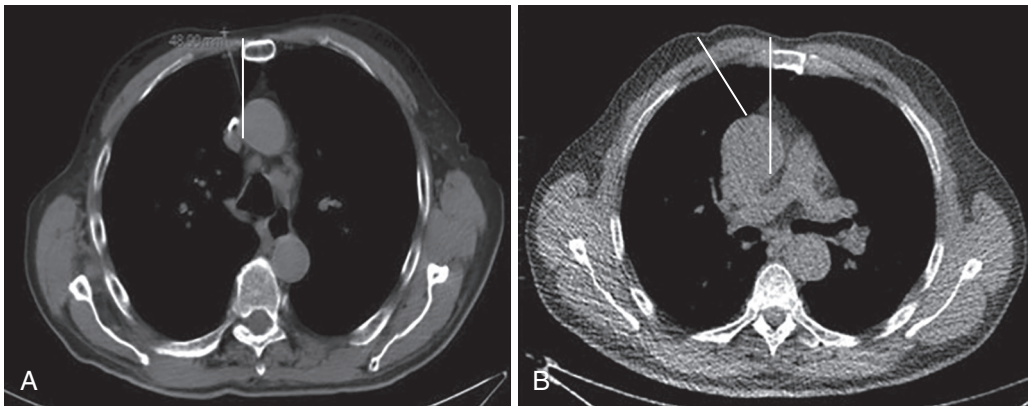

FIGURE 32-6 Transaortic (TAo) access-site selection. Computed tomography (CT) scan is used to screen for TAo approach. **A,** CT slice at the upper end of the aorta at the level of the second intercostal (IC) space demonstrates a left-sided aortic arch (*white line* from outer table of sternum perpendicularly down the aorta). **B,** CT slice of right-sided aorta present when 50% of the aorta lies to the right of a line drawn from the outer table of the sternum. The second IC approach can be used in this case.

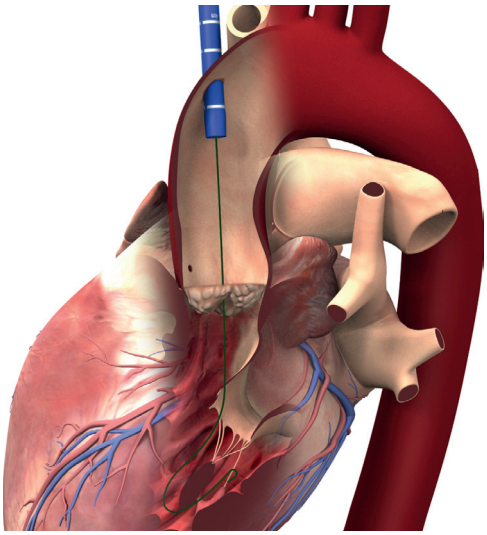

FIGURE 32-7 Transaortic (TAo) access-site selection. Access site is selected that is at least the minimum distance required from the annulus for proper transcatheter heart valve deployment. The access site should be free of calcium and should allow the sheath to be placed in a straight line perpendicular to the annulus.

art already in practice, or a predicate device currently in clinical use, can often be placed into practice with an expedited regulatory pathway known in the United States as *510K*. However, for most novel interventions, the regulatory pathway is much more involved and can require an expensive and lengthy premarket approval (PMA) process or investigational device exemption (IDE) that can take years and tens of millions of dollars before the device is adopted in the commercial marketplace. This regulatory process is less challenging outside of the United States and has led to a clear global disparity in current available technologies, with our European colleagues being quite advanced by comparison.

Prior to receiving regulatory approval, new technologies are generally tested in the laboratory on large animals. This allows refinement of the device and its materials in terms of size, cost, and efficiency. It also allows exploration of the tolerance extremes that may be experienced in the clinical setting. After a device application has been thoroughly investigated in a preclinical animal model, it needs to be tested systematically first in humans. These first-in-human (FIH) studies are followed by safety and feasibility phase I trials and larger phase II trials, with the latter usually randomized and all with constant communication and approval from the FDA.

In the United States, the regulatory process alone can take years and quickly exhausts vast resources and capital. Once a device does gain FDA regulatory approval and is appropriately financed through the commercialization stage, it still needs to be championed by the end users—in this case, surgeons and interventionalists. Adoption of a procedure as standard of care is ultimately based on clinical efficacy, safety, and cost. If not minimally invasive or percutaneous at first, these approaches can be further developed in the clinical setting. New technology and innovation developed to assist with the conversion of a procedure to a more minimally invasive technique continues as a device progresses through its total clinical product life cycle. This cycle of continual refinement of interventional tools and equipment requires close collaboration among surgeons, interventionalists, and industry partners to continually provide state-of-the-art care to cardiovascular patients.

The Hybrid Suite

For most hospitals, the decision to create a hybrid suite is largely based on return on investment in addition to usefulness for clinicians. With variable economics among medical centers, several models have emerged. The first approach is to perform a retrofit to allow the hybrid team to carry out endovascular interventions and structural heart procedures in existing facilities. This can be done through two separate pathways, starting with either an existing cath lab or an existing OR. An existing cath lab suite can be outfitted with formal anesthesia equipment; appropriate heating, ventilating, and air conditioning (HVAC); scrub sinks; and substerile areas, and it should be fully stocked with instruments and disposables most often used by hybrid surgeons. Note that multiple disciplines are interested in using hybrid rooms today, so stocking for all these specialties can escalate costs quickly in addition to making space utilization challenging. In the case of preparing a hybrid cath lab for major cardiac surgical interventions, including aortocoronary bypass and open valve procedures, additional space and storage are also required for a perfusion team and for equipment; this is essential for ensuring the best outcome during a planned cardiac hybrid case or a "conversion to open" emergency scenario. This is not the preferred scenario for cardiac surgeons because both the cardiac OR and the OR staff provide a familiar environment for maximal efficiency in an emergency. As an alternative, an OR can be retrofitted with the appropriate cath lab equipment and imaging technology to become a functional hybrid suite. The minimum equipment required comprises an image intensifier (I-I) for high-quality fluoroscopy with digital cineography, corresponding flat screens, monitors, an interventional

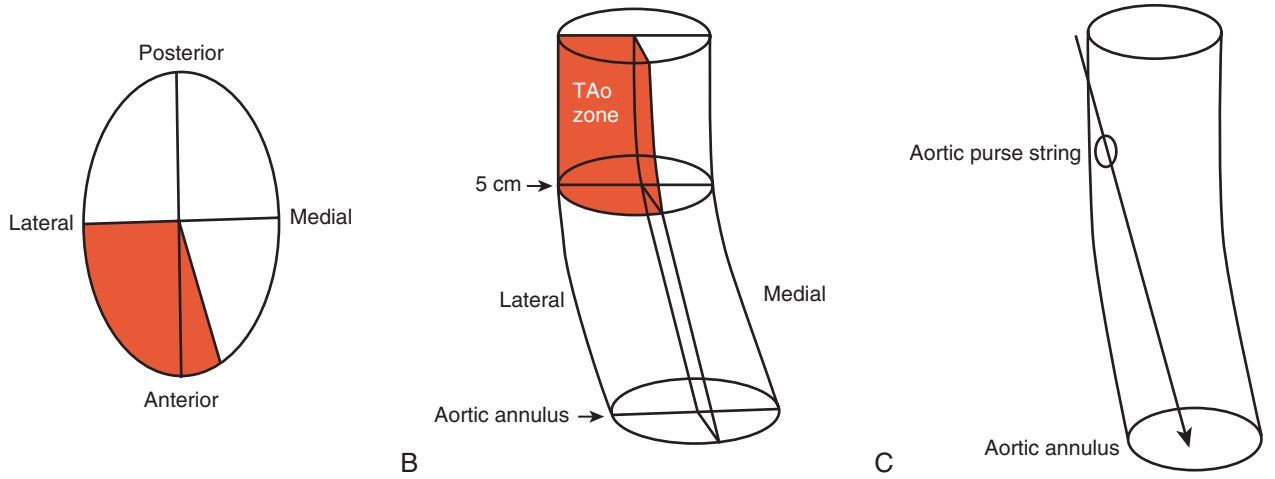

FIGURE 32-8 **A** and **B,** The transaortic (TAo) zone for cannulation of the aorta along the upper outer quadrant. **C,** This will allow for a direct line of approach perpendicular to the aortic valve. (From Bapat V, Attia R: Transaortic transcatheter aortic valve implantation: step-by-step guide. *Semin Thorac Cardiovasc Surg* 24:206-211, 2012.)

table, lead shielding, and a full stock of wires, balloons, stents, and other disposables (Fig. 32-9). The additional space needed to accommodate such a retrofit cannot be underestimated; often the hybrid team finds itself suddenly constricted in an ill-planned, undersized operating theater. This can, at times, be potentially unsafe in challenging cardiovascular procedures because the operator has to be constantly prepared to convert to an open-chest approach. The gold standard is to design a hybrid suite from scratch during a major renovation or initial construction of an OR. Hybrid suites are now recognized as a necessity in larger hospitals and centers of excellence.

A body of literature discusses the proper methodology and construction of hybrid suites based on the extensive trial-and-error experiences of some of the earliest and most experienced hybrid centers.[22-24] The authors' own experiences have led to several lessons, most of which could only have been realized after the construction and extensive use of multiple different hybrid suites (Table 32-8). We have concluded that one of the most important parts of creating and running a successful hybrid suite occurs long before actual construction and lies in extensive multidisciplinary coordinated planning. This includes extensive input from ancillary staff responsible for the day-to-day operations of the suite. No one relishes large committee meetings surrounding the purchase and construction of new clinical equipment and resources; however, because new hybrid suites will be used by multiple disciplines and for procedures not yet developed, these planning meetings are a necessity. Trivial details often taken for granted in the cath lab and OR can easily be overlooked by ill planning, bringing major high-risk procedures to an untimely standstill while staff scramble to make adjustments so the procedure can continue. Invariably, these delays occur at the most inconvenient time and while treating a patient who is very ill. Therefore it is wise to perform only routine, low-risk procedures during the beginning usage, while the shortcomings of the hybrid suite can be realized and corrected. Routine parts of any hybrid procedure—for example, prepping and draping the patient—should be well thought out before commencing the procedure so that the interventional cardiologist and the surgeon can work without hindering each other. Even the simplest detail, such as having the OR staff remember to position defibrillator pads out of the path of the image intensifier or using a radiolucent variety, can avoid costly time and risks in the hybrid room. For these reasons, the authors recommend that a standard operating procedure and case cards for each hybrid procedure be created, assembled, and integrated into a formal operations manual that contains all procedures for a particular hybrid room and is available to all staff. This type of rigid organization has been shown to improve quality of care, quality assurance, and quality control

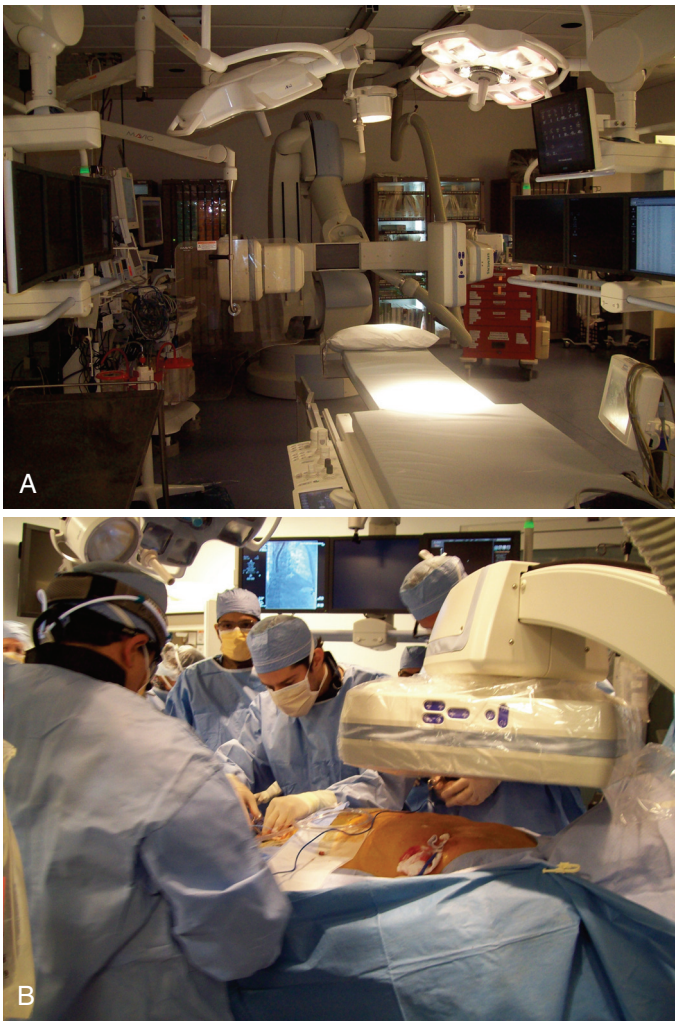

FIGURE 32-9 Hybrid suite. **A,** Hybrid interventional suite. **B,** Transapical transcatheter aortic valve implantation (intraoperative photo). Note the cardiac surgeon in the foreground in proximity to the left mini thoracotomy used to access and control the left ventricular apex. Interventional cardiologists prepare the groin for instrumentation on the far side of the operating table.

and also helps those planning complex clinical interventions that require high-level coordination among a large team in an unfamiliar setting such as the hybrid suite.

Convergence of Surgery and Interventional Cardiology

Unfortunately, the discipline of cardiac surgery will remain too complex for practicing interventional cardiologists to cross-train without completing a lengthy formal residency in surgery. However, focused and well-thought-out surgical rotations integrated throughout medical residency training and cardiology fellowship could prepare a surgeon to perform more complex and minimally invasive techniques in conjunction with surgical colleagues. It is important to note, however, that as the integument is violated in an increasingly invasive manner, the risk and magnitude of major complications escalates rapidly, and there is no substitute for the complete mastery of grounded surgical principles and technique. Likewise, presuming that much of the discipline of interventional cardiology can be mastered in short courses that claim to impart interventional "wire skills" is of equal misconception and fraught with great hazard. The true mastery of such a specialized discipline requires intense study through a formal interventional cardiovascular fellowship, which is currently almost exclusively available through the traditional cardiology pathway. Formal hybrid interventional cardiology fellowships are available at select institutions administered jointly by the departments of surgery and medicine and require fellows to function clinically in both cardiac surgery and cardiology. The most advanced fellowships are 1 year in length and impart excellent experience in all aspects of general interventional cardiology, including diagnostic angiography, PCI, TAVR, endovascular graft techniques, and hybrid cardiac surgery procedures.

TABLE 32-8 List of Lessons and Pitfalls in Hybrid Construction

- Consider input from all those who will potentially be working in the room. This includes staff from anesthesiology, nurses from both the operating room (OR) and the catheterization laboratory (cath lab) in addition to technical staff from both.
- It is imperative to make the hybrid room large enough and to consider patterns of entry and egress of personnel in light of the additional and cumbersome clinical equipment, such as the image intensifier (I-I) and the perfusion machine. Accommodations should be made for space and pathways used for additional clinical equipment and personnel that may not always be present during every case, such as intraaortic balloon pump apparatus and staff.
- Proper ceiling height that is adequate to allow flat screens and monitors to retract reasonably above head level should be ensured. This can be quite costly and can require significant engineering input because routing of modern heating, ventilating, and air conditioning (HVAC) and air-handling units must be considered.
- Plan carefully for anesthesia personnel and equipment (including echo), in particular with regard to the placement of the I-I.
- Develop a plan for preparing and draping the patient in advance to accommodate both the surgeon and the interventional cardiologist. This often requires stocking a combination of standard prep packs from both the cath lab and the OR in the hybrid suite.
- Use of radiolucent defibrillator pads and careful placement of all lines, tubes, and wires such that they are not within the path of the I-I are important. This requires repeated education of all staff, including frequently rotating residents and fellows who often position and prep the patient.
- Ensure connectivity of all imaging and monitoring equipment, including echocardiography equipment. All imaging should be readily visible in real time to the operating staff and to those in the control room.
- Development and continued updating of standard operating procedures (SOPs) and the operations manual are critical.

Hybrid Coronary Revascularization

Hybrid procedures that have gained the most acceptance today include hybrid coronary revascularization (HCR), hybrid valve surgery with PTCA or PCI, and hybrid procedures for atrial fibrillation. In addition, some centers have also undertaken hybrid therapies for coronary artery disease associated with carotid artery disease and aortic arch pathology. In centers with busy hybrid programs, HCR most often refers to minimally invasive direct coronary artery bypass (MIDCAB), in which the anastomosis of the left internal mammary artery (LIMA) to the left anterior descending artery (LADA) is the focus of the surgical portion of the operation and is combined with PCI with drug-eluting stents (DESs) to the non-LADA targets.[25-29] This approach accepts the notion that the surgical LIMA-to-LADA anastomosis is the most durable form of revascularization available today but also recognizes that the patency rates of traditional saphenous vein grafts (SVGs) are less than robust, and their ability to remain open in the long term is greatly inferior to the LIMA approach.[27-31]

In the era of the modern DES, the SVG as a conduit for CABG must become suspect. Whereas excellent data exist that demonstrate 10- to 20-year patency for the LIMA-to-LADA anastomosis, similar data on SVG patency are quite discouraging; thus the DES is now an attractive alternative.[27] The LIMA-to-LADA portion of the HCR procedure can be performed in a variety of ways, including totally endoscopic atraumatic CABG, robotically assisted CABG, or CABG performed through a keyhole incision. In these approaches, the LIMA is taken down either endoscopically or robotically, and a LIMA-LADA anastomosis is either performed by hand or with robotic assistance on an arrested or beating heart. The design and techniques for these procedures are still evolving, but several dedicated operators have made great progress toward bringing them to the forefront of mainstream cardiovascular medicine.

Table 32-9 summarizes the results of a recently published series on HCR that used only DESs.[22-25,32] The reported stent restenosis at an average follow-up of 6 to 33 months is quite low at 0% to 6.6%, and

TABLE 32-9 Results of Hybrid Coronary Revascularization for Series That Used Only Drug-Eluting Stents for Percutaneous Coronary Intervention

Author, Publication Year	*N*	30-Day Mortality	In-Hospital Morbidity (%)	Immediate LIMA Patency Rate (%)	Mean FU (Months)	Stent RS (%)	Event-Free Survival (%)
MIDCAB and PCI							
Gilard et al,[25] 2007	70	1.4	4.2	N/A	33	2.3	97
Kon et al,[26] 2008	15	0	0	100	12	3	93
TECAB and PCI							
Vassiliades et al,[27] 2006	47	0	0	99	7	6.6	90
Bonatti et al,[24] 2007	5	0	0	100	6	0	100

Data from Leacche M, Umakanthan R, Zhao DX, Byrne JG: Surgical update: hybrid procedures. Do they have a role? *Circ Cardiovasc Interv* 3:512, 2010.
FU, Follow-up; *LIMA,* left internal mammary artery; *MIDCAB,* minimally invasive direct coronary artery bypass; *N,* number of patients; *N/A,* not available; *PCI,* percutaneous coronary intervention; *RS,* restenosis; *TECAB,* totally endoscopic coronary artery bypass.

TABLE 32-10 Results of Hybrid Valve Surgery or Percutaneous Coronary Intervention

Author, Publication Year	N	Age (Y*)	ACS (%)	CHF (%)	Reop. (%)	MIS (%)	Operative Mortality (%)
PTCA ± PCI and MVR, AVR, or both							
Byrne et al,[34] 2005	26	72 (53-91)	92	N/A	42	30.8	3.8
PCI and AVR							
Brinster et al,[33] 2006	18	75 (56-89)	N/A	N/A	27.8	100	5.6
PCI and MVR							
Umakanthan et al,[34] 2009	32	69 (44-85)	15	43	38	100	3

Data from Leacche M, Umakanthan R, Zhao DX, Byrne JG: Surgical update: hybrid procedures. Do they have a role? *Circ Cardiovasc Interv* 3:514, 2010.
*Data presented as median (range).
ACS, Acute coronary syndrome; *AVR,* aortic valve replacement; *CHF,* congestive heart failure; *MIS,* minimally invasive surgery; *MVR,* mitral valve replacement; *N,* number of patients: *N/A,* not available; *PCI,* percutaneous coronary intervention; *PTCA,* percutaneous transluminal coronary angioplasty; *Reop.,* reoperative procedure.

the incidence of major adverse cardiac events (MACEs) is between 0% and 4.2%.[29]

Clearly, larger randomized trials need to be undertaken, but these data are strong evidence to support the continued exploration of this type of hybrid approach. With the aging population, the hybrid alternative to the traditional CABG or valve operation has also become a reality.[33-35] Following the same premise that the LIMA-LADA is the most durable method of surgical coronary revascularization with SVG being a distant contender, valve surgery with PCI using drug-eluting stenting (DES) to non-LADA targets, such as the RCA and the circumflex, is now a viable option. This is especially true in the case of frail older adults who have already undergone cardiac surgery. This approach allows the surgeon to perform minimally invasive valve surgery using only a mini thoracotomy or partial sternotomy to replace or repair the valve, thus minimizing overall morbidity. The non-LADA coronary revascularization portion of the procedure can be done with PCI with a DES either in the same setting or during a second-stage procedure. The results of published series of hybrid valve surgery or PCI are summarized in Table 32-10.[31-34] Again, more investigation needs to take place, but the benefits derived from the current hybrid approach for treating valvular disease seem quite apparent at this initial stage.

THE CARDIOVASCULAR INTERVENTIONALIST

With time, many elective open-heart surgical procedures will become less prevalent. However, complications and challenging scenarios such as hostile chest entry and difficult intravascular access to vital structures will remain. Because of this, a need for surgeons who are facile with open-heart surgical techniques and who can proceed expeditiously with prowess will persist, especially for the patient presenting in extremis. With this stated, the future cardiovascular surgeon will likely need to become more of a cardiovascular interventionalist than currently envisioned. Related fields such as vascular surgery have shown that additional formal endovascular training can and must be integrated into fellowship programs to achieve excellence. Despite ongoing clinical domain disputes with interventionalists from other disciplines such as interventional radiology, today's vascular surgical community is comfortable in the interventional suite performing complex vascular interventions that combine percutaneous, endovascular, and cutdown approaches to achieve the desired clinical result. Cardiovascular surgery must follow suit to maintain excellence and safety in treating the growing aging, more complex patient population.

Surgeons across the board have continued to perform open-heart surgeries while keeping their eyes on more minimally invasive approaches. Femoral cannulation allows major operations to be performed through "mini sternotomies" or via keyhole thoracotomy incisions with very fine surgical instruments; miniature jaws and extended hand pieces that facilitate even the most delicate maneuvers required for complex minimally invasive surgical procedures, such as mitral valve reconstruction, are now available. Despite these strides toward less invasive techniques, some patients remain better served without the trauma of any surgery, in particular surgery that involves cardiopulmonary bypass.

Advancing in parallel to their surgical colleagues, interventional cardiologists for decades have been performing all their cath lab procedures through the percutaneous approach. They have been extremely successful in traversing the peripheral vasculature to perform a spectrum of cardiovascular procedures ranging from very delicate coronary interventions for coronary artery disease to stenting of larger proximal and distal vessels for peripheral vascular disease and to now replacing the aortic valve via the femoral artery. With both disciplines working from opposite directions—the surgeon from open to minimally invasive and the interventional cardiologist from straightforward PTCA to transcatheter valve therapies—it has now become clear that the two disciplines are poised to intersect and converge, overlapping in an unprecedented manner. It is only through close collaboration and open recognition of each other's unique, yet complementary, skill set that the field of cardiovascular medicine can advance and new therapies can manifest.

REFERENCES

1. American College of Cardiology/American Heart Association Task Force on Practice Guidelines, ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention, et al: ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation* 113:e166–e286, 2006.
2. Dehmer GJ, Blankenship JC, Cilingiroglu M, et al: SCAI/ACC/AHA Expert Consensus Document: 2014 update on percutaneous coronary intervention without on-site surgical backup. *J Am Coll Cardiol* 63(23):2624–2641, 2014.
3. Aversano T, Aversano LT, Passamani E, et al: Thrombolytic therapy vs primary percutaneous coronary intervention for myocardial infarction in patients presenting to hospitals without on-site cardiac surgery: a randomized controlled trial. *JAMA* 287:1943–1951, 2002.
4. Bourassa MG: The history of cardiac catheterization. *Can J Cardiol* 21:1011–1014, 2005.
5. Forssmann-Falck R: Werner Forssmann: a pioneer of cardiology. *Am J Cardiol* 79:651–660, 1997.
6. Seldinger SI: Catheter replacement of the needle in percutaneous arteriography: a new technique. *Acta Radiol* 39:368–376, 1953.
7. Roubin GS, Grüntzig AR, Casarella WJ: Percutaneous coronary angioplasty: technique, indications, and results. *Cardiovasc Intervent Radiol* 9:261–272, 1986.
8. Anderson HV, Roubin GS, Leimgruber PP, et al: Primary angiographic success rates of percutaneous transluminal coronary angioplasty. *Am J Cardiol* 56:712–717, 1985.
9. Parsonnet V, Fisch D, Gielchinsky I, et al: Emergency operation after failed angioplasty. *J Thorac Cardiovasc Surg* 96:198–203, 1988.
10. Greene MA, Gray LA, Jr, Slater AD, et al: Emergency aortocoronary bypass after failed angioplasty. *Ann Thorac Surg* 51:194–199, 1991.
11. Lazar HL, Jacobs AK, Aldea GS, et al: Factors influencing mortality after emergency coronary artery bypass grafting for failed percutaneous transluminal coronary angioplasty. *Ann Thorac Surg* 64:1747–1752, 1997.
12. Yang EH, Gumina RJ, Lennon RJ, et al: Emergency coronary artery bypass surgery for percutaneous coronary interventions: changes in the incidence, clinical characteristics, and indications from 1979 to 2003. *J Am Coll Cardiol* 46:2004–2009, 2005.
13. Barakate MS, Bannon PG, Hughes CF, et al: Emergency surgery after unsuccessful coronary angioplasty: a review of 15 years' experience. *Ann Thorac Surg* 75:1400–1405, 2003.
14. Seshadri N, Whitlow PL, Acharya N, et al: Emergency coronary artery bypass surgery in the contemporary percutaneous coronary intervention era. *Circulation* 106:2346–2350, 2002.
15. Sutton JM, Ellis SG, Roubin GS, et al: Major clinical events after coronary stenting. The multicenter registry of acute and elective Gianturco-Roubin stent placement. The Gianturco-Roubin

Intracoronary Stent Investigator Group. *Circulation* 89:1126–1137, 1994.
16. Dean LS, George CJ, Roubin GS, et al: Bailout and corrective use of Gianturco-Roubin flex stents after percutaneous transluminal coronary angioplasty: operator reports and angiographic core laboratory verification from the National Heart, Lung, and Blood Institute/New Approaches to Coronary Intervention Registry. *J Am Coll Cardiol* 29:934–940, 1997.
17. Wennberg DE, Lucas FL, Siewers AE, et al: Outcomes of percutaneous coronary interventions performed at centers without and with onsite coronary artery bypass graft surgery. *JAMA* 292:1961–1968, 2004.
18. American College of Cardiology/American Heart Association Task Force on Practice Guidelines, American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention, et al: ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention–summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation* 113:156–175, 2006.
19. Wharton TP, Jr: Nonemergent percutaneous coronary intervention with off-site surgery backup: an emerging new path to access. *Crit Pathw Cardiol* 4:98–106, 2005.
20. Leon MB, Smith CR, Mack M, et al: Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 363:1597–1607, 2010.
21. Bapat V, Attia R: Transaortic transcatheter aortic valve implantation: step-by-step guide. *Semin Thorac Cardiovasc Surg* 24(3):206–211, 2012.
22. Nollert G, Wich S: Planning a cardiovascular hybrid operating room: the technical point of view. *Heart Surg Forum* 12:E125–E130, 2009.
23. Sikkink CJ, Reijnen MM, Zeebregts CJ: The creation of the optimal dedicated endovascular suite. *Eur J Vasc Endovasc Surg* 35:198–204, 2008.
24. Bonatti J, Vassiliades T, Nifong W, et al: How to build a cath-lab operating room. *Heart Surg Forum* 10:E344–E348, 2007.
25. Gilard M, Bezon E, Cornily JC, et al: Same-day combined percutaneous coronary intervention and coronary artery surgery. *Cardiology* 108:363–367, 2007.
26. Kon ZN, Brown EN, Tran R, et al: Simultaneous hybrid coronary revascularization reduces postoperative morbidity compared with results from conventional off-pump coronary artery bypass. *J Thorac Cardiovasc Surg* 135:367–375, 2008.
27. Vassiliades TA, Jr, Douglas JS, Morris DC, et al: Integrated coronary revascularization with drug-eluting stents: immediate and seven-month outcome. *J Thorac Cardiovasc Surg* 131:956–962, 2006.
28. Alexander JH, Hafley G, Harrington RA, et al: Efficacy and safety of edifoligide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery: PREVENT IV: a randomized controlled trial. *JAMA* 294:2446–2454, 2005.
29. Balacumaraswami L, Taggart DP: Intraoperative imaging techniques to assess coronary artery bypass graft patency. *Ann Thorac Surg* 83:2251–2257, 2007.
30. Puskas JD, Williams WH, Mahoney EM, et al: Off-pump vs conventional coronary artery bypass grafting: early and 1-year graft patency, cost, and quality-of-life outcomes: a randomized trial. *JAMA* 291:1841–1849, 2004.
31. Tatoulis J, Buxton BF, Fuller JA: Patencies of 2127 arterial to coronary conduits over 15 years. *Ann Thorac Surg* 77:93–101, 2004.
32. Leacche M, Umakanthan R, Zhao DX, et al: Surgical update: hybrid procedures. Do they have a role? *Circ Cardiovasc Interv* 3:511–518, 2010.
33. Brinster DR, Byrne M, Rogers CD, et al: Effectiveness of same day percutaneous coronary intervention followed by minimally invasive aortic valve replacement for aortic stenosis and moderate coronary disease ("hybrid approach"). *Am J Cardiol* 98:1501–1503, 2006.
34. Byrne JG, Leacche M, Unic D, et al: Staged initial percutaneous coronary intervention followed by valve surgery ("hybrid approach") for patients with complex coronary and valve disease. *J Am Coll Cardiol* 45:14–18, 2005.
35. Umakanthan R, Leacche M, Petracek MR, et al: Combined PCI and minimally invasive heart valve surgery for high-risk patients. *Curr Treat Options Cardiovasc Med* 11:492–498, 2009.

Restenosis

33

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KEY POINTS

- Restenosis is a pathologic response to injury that leads to narrowing of the vessel segment as a result of negative vascular remodeling and neointimal proliferation of vascular smooth muscle cells.
- Clinical and angiographic predictors of stent restenosis include diabetes, nonsmoking status, female sex, acute coronary syndrome, previous percutaneous coronary intervention (PCI), saphenous vein graft disease, small vessel diameter, long lesions, high angiographic complexity, ostial location, and chronic total occlusions.
- The lumen size achieved at the end of the procedure is an important modifiable predictor of restenosis.
- The central roles of cellular proliferation and growth factor signaling within the restenotic lesion provide the basis for contemporary drug-eluting stent (DES) technology.
- DES use has drastically reduced angiographic and clinical restenosis across broad lesion and patient subsets, but those with restenotic lesions, diabetes mellitus, bypass graft disease, and bifurcations continue to be problematic.
- In contemporary trials using newer-generation DESs, adverse events are driven as much by progression of coronary artery disease (CAD) in untreated sites (de novo disease) as by target-lesion failure, with similar predictors.

Nature does nothing without purpose or uselessly.
Aristotle, 384-322 BC

Restenosis, the arterial wall healing response to mechanical injury, has plagued cardiologists since the introduction of balloon angioplasty by Grüntzig and collaborators.[1] This chapter will describe our current understanding of the mechanisms, clinical features, and impact of restenosis in contemporary percutaneous coronary intervention.

MECHANISMS OF RESTENOSIS

Normal Versus Pathologic Response to Arterial Injury

The initial consequences of balloon angioplasty or coronary stenting are deendothelialization; mechanical disruption of atherosclerotic plaque, often with dissection into the tunica media and occasionally the adventitia; and stretch of the entire artery.[2] Endothelial injury, platelet aggregation, inflammatory cell infiltration, release of growth factors, medial smooth muscle cell (SMC) modulation and proliferation, proteoglycan deposition, and extracellular matrix (ECM) remodeling are the major milestones in the temporal sequence of the response to trauma. In the majority of patients, the healing response includes reendothelialization of the artery without significant reduction in vessel diameter. In contrast, restenosis is a pathophysiologic response to injury that leads to narrowing of the vessel segment as a result of negative vascular remodeling or neointimal proliferation (Fig. 33-1).[3] Whereas bare-metal stents were developed to mitigate elastic recoil and negative remodeling, they remain prone to neointimal hyperplasia, which ultimately is a result of inappropriate migration and proliferation of vascular SMCs but appears to be driven by multiple factors (Fig. 33-2). Whereas a great deal is known about the general response to injury, what remains less clear are the particular mechanisms that differentiate pathologic restenosis from an optimal healing pattern, leading to reendothelialization without neointimal hyperplasia.

Endothelial Injury and Platelet Activation

In animal models, endothelial injury is sufficient for the development of neointimal hyperplasia. Several mechanisms appear to directly link endothelial activation or denudation to restenosis. First, nitric oxide–mediated responses to flow and shear stress provide a protective function. Therefore the loss of a functional endothelium likely contributes to pathologic healing.[4] Second, endothelial injury leads to the production of cytokines such as platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-β), which can induce migration and proliferation of vascular smooth muscle cells (VSMCs).[5] Endothelial response to injury also promotes platelet adhesion. Platelet activation and deposition has been shown to occur almost immediately after endothelial injury in vivo[6,7] and results in platelet production of cytokines and growth factors, including PDGF. Elevated platelet reactivity measured at the time of PCI has been associated with increased restenosis rates after balloon angioplasty.[8]

Inflammation

The central role that inflammatory pathways play in the pathophysiology of restenosis is also generally well accepted.[9] After a layer of platelets and fibrin are deposited at the injured site, adhesion molecules such as P-selectin on platelets attach to circulating leukocytes via receptors such as P-selectin glycoprotein ligand 1 (PSGL-1) to promote leukocyte rolling along the injured surface. Leukocytes then bind tightly to platelets through the interaction of leukocyte Mac-1 with platelet glycoprotein (GP) Ibα and through leukocyte integrin cross-linking with fibrinogen that is bound to the platelet GP IIb/IIIa receptor. Chemotaxis of leukocytes occurs across the platelet-fibrin layer as these cells migrate through tissue, driven by chemical gradients of chemokines released from SMCs and resident macrophages.

The precise cellular and molecular mechanisms of inflammation following arterial injury are dependent on the specific type of injury (i.e., atherogenic vs. balloon mechanical vs. stent). For example, experimental stent deployment in animal arteries causes sustained elevation of monocyte chemoattractant protein-1 (MCP-1) after injury (~14 days) compared with balloon-injured arteries (<24 hours).[10] Antibody-mediated blockade of the C-C chemokine receptor-2 (CCR2), a primary leukocyte receptor for MCP-1, markedly diminished neointimal thickening after stent-induced, but not balloon-induced, injury in nonhuman primates.[11]

Inflammatory responses to the stent have also been proposed. Innate immune responses that have a predominance of monocyte/macrophage infiltrates have been described. Antigen-specific adaptive immune hypersensitivity responses typified by infiltration of T cells and B cells in conjunction with eosinophils may also play a role in restenosis (reviewed[12]). The corrosion of stent material that leads to the activation of thrombospondin-1–dependent inflammatory pathways may also play a role in the restenotic processes following stenting.[13]

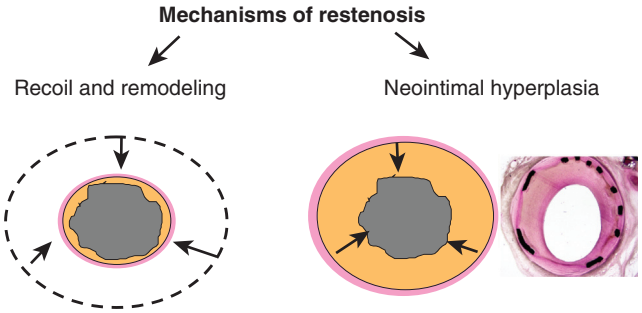

FIGURE 33-1 Illustration of the two main mechanisms of restenosis. Negative vessel remodeling and elastic recoil are mainly observed after balloon angioplasty, whereas in-stent restenosis is mainly associated with intimal hyperplasia (in-stent restenosis histology, *right panel*).

Investigators have pursued antirestenosis strategies using systemic antiinflammatory therapies, including liposome-encapsulated bisphosphonates,[14] prednisone,[15] anti-cluster of differentiation 18 (CD18) or anti-CCR2 blockade,[11] and peroxisome proliferator-activated receptor-γ (PPAR-gamma) activator rosiglitazone. Experimental observations support a causal relationship between inflammation and experimental restenosis. Antibody-mediated blockade[16,17] or the selective absence of Mac-1[18] diminished leukocyte accumulation and limited neointimal thickening after experimental angioplasty or stent implantation. Corticosteroids have long been shown to reduce the influx of mononuclear cells, inhibit monocyte and macrophage function, and influence VSMC proliferation.[19] However, clinical trials with systemic steroid therapy to prevent restenosis have shown disappointing results.[20]

Smooth Muscle Cell Proliferation

The smooth muscle cell is vital to the healing process after arterial injury[21] because of its ability to migrate, proliferate, and synthesize

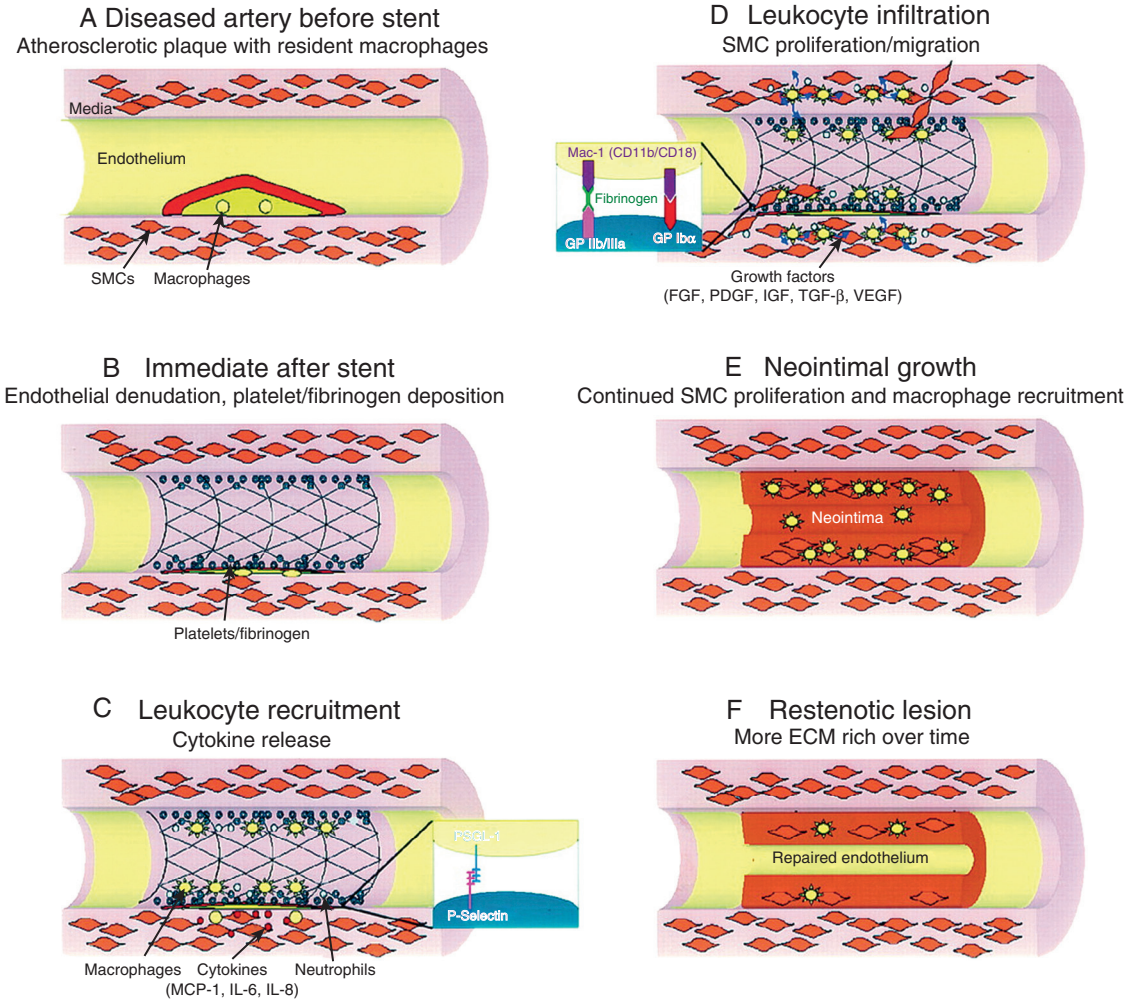

FIGURE 33-2 Schematic of the integrated cascade of restenosis. **A,** Atherosclerotic vessel before intervention. **B,** Immediate result of stent placement with endothelial denudation and platelet/fibrinogen deposition. **C** and **D,** Leukocyte recruitment, infiltration, and smooth muscle cell (SMC) proliferation and migration in the days after injury. **E,** Neointimal thickening in the weeks after injury, with continued SMC proliferation and monocyte recruitment. **F,** Long-term (weeks to months) change from a predominantly cellular to a less cellular and more extracellular matrix-rich plaque. *ECM,* Extracellular matrix; *FGF,* fibroblast growth factor; *GP,* glycoprotein; *IGF,* insulin-like growth factor; *IL,* interleukin; *MCP,* monocyte chemoattractant protein-1; *TGF-β,* tumor growth factor beta; *VEGF,* vascular endothelial growth factor. (Reprinted with permission from Frederick GP, Welt FGP, Rogers C: Inflammation and restenosis in the stent era, *Arterioscler Thromb Vasc Biol* 22:1769-1776, 2002).

ECM upon stimulation.[22] Growth factors released from platelets, leukocytes, and VSMC stimulate a granulation or cellular proliferation phase. SMCs from the media and adventitia migrate into the intimal layer. Aided by fracture of the internal elastic membrane, these cells migrate into the intima, where they shift from a contractile to the synthetic phenotype. VSMCs may proliferate from 24 hours to 2 to 3 months after vascular injury, returning to a contractile phenotype after this period. The platelet-derived growth factor (PDGF) is a potent promoter of this SMC migration.[23] Adventitial myofibroblasts (α-actin staining cells) also proliferate and migrate into the neointima[24] and appear to play an important role in supplying the intima with proliferative cellular elements for new lesion formation. Assessment of cellular proliferation status in atherectomy suggests that cells of the monocyte/macrophage lineage also proliferate within human in-stent restenotic tissue.

Whereas cellular division is essential for the subsequent development of restenosis, so too is the synthesis of various collagen subtypes and proteoglycans.[25] Over a longer period of time, the artery enters a phase of remodeling that involves ECM protein degradation and resynthesis. Accompanying this phase is a shift to less cellular elements and greater production of ECM. This ECM actually constitutes the major component of the restenotic lesion.[26]

Cell-Cycle Regulation and the Rationale for Drug-Eluting Stent Development

The central role of cellular proliferation and growth factor signaling within the restenotic lesion provided the basis for antirestenosis pharmacologic strategies to target cell-cycle division early after stent implantation. The clinical success targeting cellular division pathways illustrates the central role these pathways play in the formation of neointimal hyperplasia.

In the absence of injury, SMCs are quiescent and exhibit very low levels of proliferative activity. However, during restenosis, SMCs that migrate to the intima progress through the G_1/S transition of the cell cycle.[27] The different phases of the cell cycle of eukaryotic cells are regulated by a series of protein complexes composed of cyclins (D, E, A, and B), cyclin-dependent kinases (CDKs; CDK4, CDK2, and $p34^{cdc2}$), and their cyclin-dependent inhibitors (CDIs; $p27^{Kip1}$, p70, $p16^{INK4}$). The function of CDIs is regulated by changes in their concentration, as well as in their localization in the cell.[28] SMC $p27^{Kip1}$ is downregulated after arterial injury when cell proliferation increases; $p21^{Cip1}$ is not observed in normal arteries but is upregulated along with $p27^{Kip1}$ in later phases of arterial healing response and is associated with a significant decline in cell proliferation and an increase in procollagen and TGF-β synthesis.[28] These findings suggest that $p27^{Kip1}$ and $p21^{Cip1}$ are endogenous regulators of G1 transit in vascular SMC and inhibit cell proliferation after arterial injury. In addition, $p27^{Kip1}$ and $p21^{Cip1}$ bind and alter the activities of cyclin D-, cyclin E-, and cyclin A-dependent kinases (CDK2) in quiescent cells, leading to failure of G_1/S transition and cell-cycle arrest.[29,30] Overexpression of $p27^{Kip1}$ results in cell-cycle arrest in the G1 phase. Conversely, inhibition of $p27^{Kip1}$ increases the number of cells in S phase.[31]

The level of $p27^{Kip1}$ is also regulated by constituents of the ECM. Mature collagen (polymerized type 1 collagen) suppresses $p70^{S6k}$ and has been shown to increase the levels of $p27^{Kip1}$, whereas monomeric collagen present during degradation of ECM in the synthesis phase of restenosis causes $p27^{Kip1}$ downregulation.[32] Consistent with its regulatory role in SMC proliferation and the pathobiology of restenosis, polymorphisms in $p27^{Kip1}$ that enhance the production of this cell-cycle inhibitor are associated with reduced SMC proliferation and decreased risk of restenosis following PCI.[33]

Sirolimus and Its Analogues

Sirolimus (Rapamycin) was initially discovered in 1975 as an antifungal produced by *Streptomyces hygroscopicus* isolated from an Easter Island soil sample.[34] Sirolimus binds the ubiquitously expressed FK506-binding protein 12 (FKBP12) and blocks activation of the serine/threonine kinase known as *mammalian target of rapamycin* (mTOR).[35] Blockade of mTOR in this manner leads to inhibitory effects on cell-cycle kinases that include p27, cyclins, and pRb phosphorylation, resulting in cell-cycle arrest at the G_1/S phase (Fig. 33-3).[36] In cellular models and animal experiments, sirolimus inhibits VSMC migration and proliferation[37] and also has important antiinflammatory effects.[38,39]

Newer-generation drug-eluting stents have used sirolimus analogues with only minor pharmacokinetic differences. For example, the chemical structure of zotarolimus differs from sirolimus at the carbon 40 position, in which a tetrazole substitution is made in place of the hydroxyl group of sirolimus. This modification does not affect FKBP12 binding nor does it impact in vitro T-cell and VSMC effects. It does, however, lead to more lipophilicity and a shorter half-life compared with sirolimus.[40] Everolimus is another sirolimus analogue with a 2-hydroxyethyl substitution at position 40. It results in decreased in vitro potency but similar in vivo efficacy in immunosuppression and transplant models.[41,42]

Paclitaxel

Paclitaxel (Taxol) was discovered from the bark of the Pacific yew tree and is noted to have potent antiproliferative properties. Its mechanism of action is achieved through induction of tubulin polymerization, which leads to cell-cycle arrest and cyostasis at G_0 (see Fig. 33-3). Systemically administered paclitaxel had favorable effects in preclinical models of restenosis.[43] In addition to blocking VSMC migration and proliferation, paclitaxel has also been shown to inhibit neutrophil function,[44] endothelial cell migration, angiogenesis, and allogenic T-cell responses.[45] Paradoxically, the effect of paclitaxel on macrophages is stimulatory in a manner similar to lipopolysaccaride.[46,47]

CLINICAL FEATURES OF RESTENOSIS

Definitions: Angiographic Restenosis

Angiographically detected obstruction of 50% diameter stenosis (DS) or more at the site of a previously treated coronary segment has been historically defined as restenosis.[48] This apparently arbitrary cutoff point was, in fact, founded on good scientific evidence: physiologic experimental studies demonstrated that coronary flow reserve becomes impeded when the arterial lumen diameter is reduced to 50% or less.[49] For purposes of scientific studies, many definitions of angiographic restenosis have been used, although the classical binary definition based on percentage DS is the most widely accepted. Unfortunately, percent DS does not depict the degree of deterioration in lumen diameter and does not convey a measure of the vessel's response to injury.[50,51]

In view of these considerations, clinical restenosis studies have been adopting a more comprehensive approach in reporting findings from both perspectives (categoric and continuous) to determine whether the agent under investigation had restraining or inhibitory effect and whether the ultimate clinical/angiographic outcome has been improved by the use of any new therapy. However, the more subtle facets of potent antiproliferative devices such as DESs challenge the validity of conventional angiographic parameters,[52-54] and advanced imaging techniques such as intravascular ultrasound (IVUS)[55] and optical coherence tomography (OCT)[56,57] have greatly improved the ability to visualize restenosis and make quantitative assessments of neointimal thickness, neointimal volume, and minimal lumen diameter (MLD).

Late loss (LL) is a continuous angiographic measure of lumen deterioration. LL is conventionally calculated by subtracting the MLD value at follow-up (FU) from postprocedural MLD. These computations are made irrespective of the locations of MLD measurements. LL has traditionally served as a major outcome measure in bare-metal stent (BMS) trials and continues to play a similar role in the era of DES.[58,59] It represents a surrogate marker of neointimal hyperplasia, when measurements are performed within stented segments, because

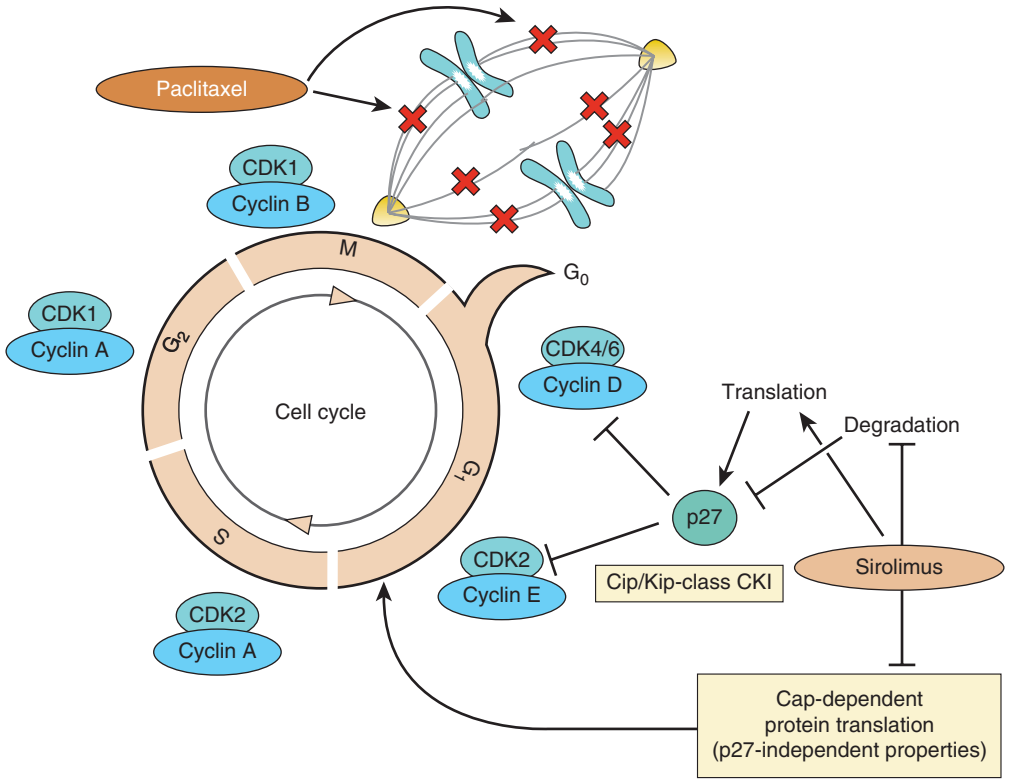

FIGURE 33-3 Schematic representation of vascular smooth muscle cell cycle regulation and the mechanisms of sirolimus and paclitaxel. *CDK,* Cyclin-dependent kinase; *CKI,* cyclin-dependent inhibitors.

stents abolish the remodeling component of the restenotic process.[50,60] However, conventional LL measurements may be methodologically flawed because of changes in the location of minimal lumen diameter between postprocedure and follow-up measurements.[54,61] As a result, LL frequently derives from measurements performed in different (unmatched) locations in the target segment. Sites with higher degrees of lumen deterioration and neointimal proliferation may be overlooked, potentially leading to inaccurate conclusions regarding the antiproliferative efficacy of a given device.

Angiographic restenosis parameters have been reported in two ways, by in-lesion and in-stent analyses (Fig. 33-4). It is nevertheless important to note that in-lesion LL will not necessarily be higher than in-stent LL. Given that in-lesion analysis encompassed the stented segment and 5 mm distally and proximally in an attempt to depict edge restenosis, these somewhat conflicting data occur because of the *MLD relocation phenomenon*. Furthermore, in-lesion LL is affected by vascular remodeling or vessel spasm and cannot be used as a surrogate for intimal hyperplasia or to determine antiproliferative device efficacy.

Clinical and research assessment of restenosis has also been markedly improved by both IVUS and OCT, which enable high-fidelity measurement of restenotic area, neointimal volume, and MLD in addition to enabling three-dimensional rendering of restenotic segments. OCT is a particularly useful technology for evaluation of stent healing and restenosis because current-generation commercially available OCT systems no longer require coronary artery balloon occlusion; and by using light, rather than ultrasound, OCT produces high-resolution in vivo images of coronary arteries and deployed stents with 10- to 15-μm resolution compared with the 150 to 200 μm resolution of IVUS. Although limited in its ability to image deep into the blood vessel wall, OCT increases the diagnostic accuracy of luminal atherosclerosis imaging, enabling visualization of small structures such as the thin fibrous caps associated with plaque rupture, and it increases the diagnostic accuracy of stent and restenosis imaging, enabling high-resolution assessment of lumen features and neointima (reviewed[57]; Fig. 33-5). In initial clinical trials, OCT outperformed IVUS for the detection of small degrees of neointimal hyperplasia[62] and was more sensitive in detecting stent malapposition.[63] In addition, OCT-based single-stent strut-level analysis provides clear assessment of stent-strut coverage and apposition,[64] which are important clinical parameters that have been linked to DES-induced delayed arterial healing and risk of stent thrombosis.[65,66]

Clinical Restenosis

Although angiography has been widely used as the guiding tool for coronary disease management, the clinician should also consider functional assessment of the restenotic lesion—either invasive or noninvasive—before referring the patient to additional coronary revascularization. Restenosis may cause no symptoms in up to 50% of patients, although silent ischemia may be present.[67] Exercise electrocardiograph (ECG) testing has limited value to detect "silent" restenotic lesions,[68] and computed tomography angiography (CTA) detection of restenosis can be unreliable because of stent metal radiographic artifacts.[69,70] Other noninvasive tests, such as thallium scintigraphy and cardiac and stress echocardiography, have been used to improve the sensitivity and specificity of noninvasive assessment of restenosis.[71] On the other end of the clinical spectrum, restenosis may present itself in the form of an acute coronary syndrome (ACS) in up to a third of patients, which challenges the notion that restenosis is benign.[72,73] Restenosis is of particular concern following left main coronary artery PCI because of the potential risk of sudden cardiac death associated with early "silent" restenosis.

Target-lesion revascularization (TLR), defined as any repeat percutaneous intervention of the treated coronary segment or bypass surgery of the target vessel, has been proposed as the most specific clinical

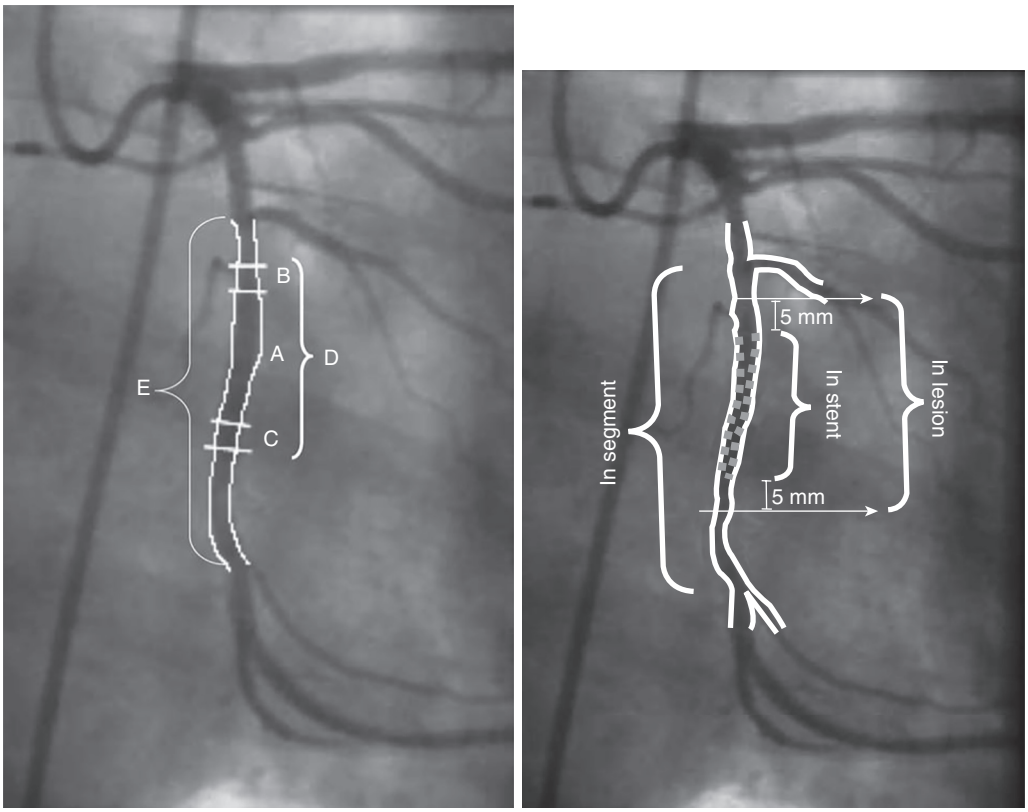

FIGURE 33-4 Coronary angiography and model illustrating a segmental approach to analyze and report the effects of drug-eluting stents on coronary arteries. *Right panel:* In-stent (*A*), which better describes the antiproliferative effect of the biologic agent; proximal-edge (*B*); distal-edge (*C*); and in-lesion (*D*) dimensions determine potential paradoxic effects of low drug concentrations at traumatized stent edges ("edge effect"). The in-segment dimension (*E*) is the ultimate determinant of angiographic success from a patient's perspective. (Reprinted with permission from Sousa JE, Serruys PW, Costa MA: New frontiers in cardiology: drug-eluting stents: Part II, *Circulation* 107[18]:2383-2389, 2003).

restenosis end point among other clinical markers (i.e., death, myocardial infarction [MI], symptom recurrence, or combined major adverse cardiac events [MACEs]).[50] *Target-vessel revascularization* (TVR) expands the definition of TLR to include repeat percutaneous intervention of the target vessel irrespective of the location of the stenosis within the treated segment.

In routine clinical practice, noninvasive assessment of recurrence of restenosis (symptomatic status and ischemia tests) seems an appropriate approach. This latter recommendation is based on a series of previous observations: (1) routine angiographic follow-up may have increased morbidity and mortality, albeit such an increase would be slight; (2) asymptomatic patients with nonfunctional angiographic restenosis experience a benign course[74]; and (3) the so-called oculostenotic reflex leads to a higher rate of repeat revascularization with no clear clinical benefit at 12 months after the initial intervention.[75] If repeat angiography is carried out without clear clinical evidence of ischemia, sensor-tipped guidewires for measurement of distal flow velocity or pressure may be useful to assess functional status of restenotic lesions in the catheterization laboratory and to assist physiologic-based decision making regarding the need for reintervention.[76]

Incidence of Restenosis

The incidence of late loss and binary restenosis in key stent clinical trials are described in Table 33-1.[59,77-88] When interpreting clinical trial restenosis data, it is important to consider differences in timing of follow-up assessments, the percentage of patients with angiographic follow-up data, and patient populations.

Patterns of Restenosis

In-stent restenosis has been characterized angiographically as *focal* (≤10 mm in length), *diffuse* (>10 mm), or *proliferative* (>10 mm extending outside the stent) or a *total occlusion* in patients treated with a Palmaz-Schatz BMS. This classification correlated with outcomes after reintervention and was largely adopted in the era of bare-metal stenting.[89] After Palmaz-Schatz stent implantation, restenosis was focal in 42% of patients, diffuse in 21%, and proliferative in 30%; total occlusion occurred in 7%.[89,90] The midstent articulation, which provided less scaffolding support, was likely associated with the somewhat high frequency of focal restenosis in Palmaz-Schatz stents. The same classification has been used to evaluate restenosis after DES, although modern stents do not have articulation, and longer stents are used more often. Nevertheless, the pattern of in-stent restenosis has changed with DES use and appears to be specific for each type of device. For example, restenosis after sirolimus-eluting stents is mostly focal (>90%) and is usually located at the stent edges,[91,92] whereas diffuse intimal proliferation or total occlusion accounts for approximately half of the restenosis cases after polymer-coated paclitaxel-eluting stents.[93]

Assuming that intimal hyperplasia is almost completely blocked in nondiabetic patients with de novo, short (<20 mm) stenoses in nonbifurcated native coronary arteries, it stands to reason that restenosis is likely caused by technique-related failures. As a result, restenosis would be mostly focal and would be observed at the stent edges or in gaps between stents in these noncomplex cases (Fig. 33-6). On the other hand, biologic and mechanical failures likely contribute to more

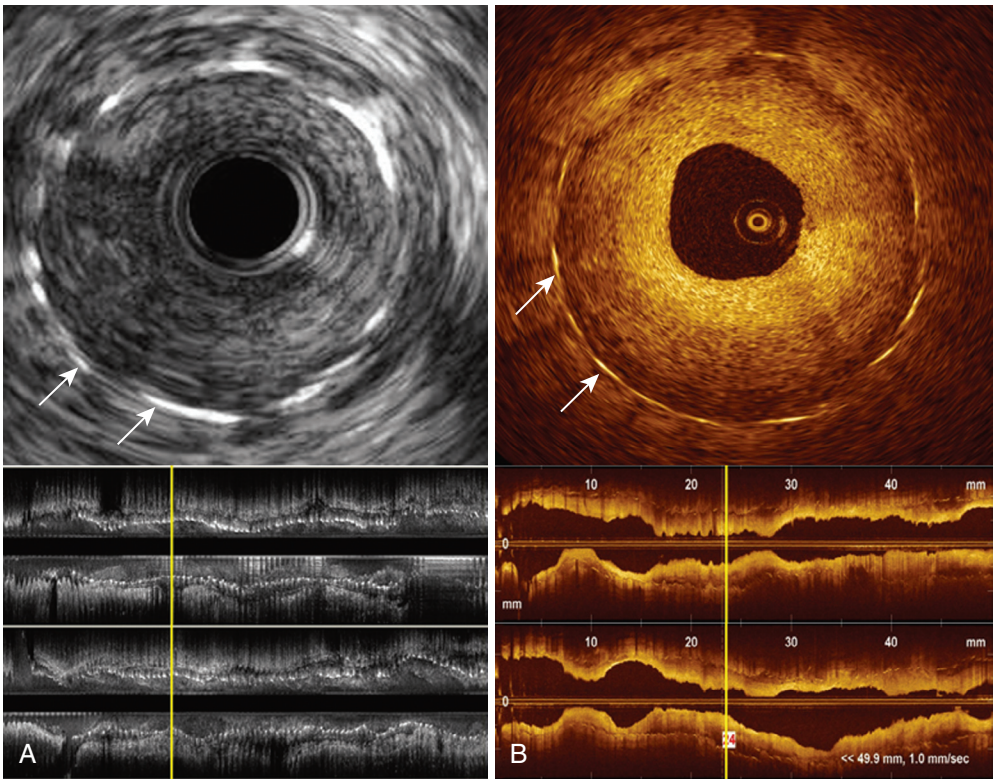

FIGURE 33-5 Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) imaging of bare-metal stent restenosis. Six months after implantation in a human coronary artery, a 3.0 x 32 mm Taxus Liberte stent was evaluated by IVUS with the Boston Scientific Atlantis IVUS Catheter (**A**) or by OCT with the Light Lab-M3 TD-OCT catheter (**B**). Stent struts (*white arrows*) are clearly visible in the cross-sectional images (*top panels*). The higher resolution OCT system enables markedly better visualization and quantification of neointimal tissue compared with IVUS in both cross-sectional (*top panels*) and longitudinal representations (*bottom panels*). In addition, compared with IVUS (0.097″), the smaller profile of the TD-OCT imaging catheter (0.016″) enables visualization and quantification of neointimal stenosis in areas of critical narrowing, where the neointimal tissue completely contacts the IVUS catheter.

diffuse patterns of in-stent restenosis, seen mostly in more challenging clinical scenarios, such as in patients with in-stent BMS, bypass graft disease, or diabetes mellitus. An exception to this rule is restenosis after bifurcation PCI, which should be classified separately because it is frequently associated with focal stenosis at the ostium of the side branch.[94]

Predictors of Restenosis

Identification of factors associated with higher risk of restenosis may be useful in counseling patients whether to select PCI or coronary artery bypass (CABG) surgery (Table 33-2). For instance, diabetes mellitus has consistently been demonstrated to be an important clinical risk factor for restenosis, whether it be after balloon angioplasty, BMS, or DES implantation.[95]

Anatomic features have also been implicated with increased likelihood of restenosis: saphenous vein graft disease, small vessel diameter, long lesions, and chronic total occlusion have been associated with a higher incidence of angiographic restenosis after stenting with a BMS.[96-100] Angiographic and IVUS studies have extensively demonstrated that the principal determinant of restenosis is the lumen size achieved at the end of the procedure.[101,102]

Although DES use has drastically reduced angiographic and clinical restenosis across broad lesion and patient subsets, certain anatomic and clinical scenarios—such as with diabetes mellitus, restenotic lesions after brachytherapy or DES use,[103] bypass graft disease,[104] and bifurcations—continue to be problematic.[84,105]

Technical Factors

The "bigger is better" philosophy,[106] in which the lumen size obtained after PCI ultimately determines the occurrence of restenosis, was largely accepted in the BMS era. The use of IVUS to optimize stent expansion, however, has not been shown to impact restenosis after bare-metal stenting. Nevertheless, the Multicenter Ultrasound Stenting in Coronaries (MUSIC) IVUS study reported an 8.3% incidence of restenosis, which is likely the lowest rate ever reported in patients treated with bare-metal stenting.[79]

Somewhat paradoxically, the potent antiproliferative effects of drug-eluting stenting exposed the importance of procedural factors as major causes of restenosis. Neointimal hyperplasia is mostly abolished within the DES, and as a result, neointimal proliferation or negative remodeling secondary to vessel trauma or untreated disease at the segments adjacent to the DES become amplified. For example, the prospective evaluation of the Impact of Stent Deployment Techniques on Clinical Outcomes of Patients Treated With the Cypher Stent (STLLR) trial[107] was a large-scale study ($n = 1567$ with 43 participating institutions) to prospectively investigate sirolimus-eluting stent (SES) deployment technique and its relationship to clinical outcomes in the modern PCI era. This study reported a high incidence of geographic miss, which was independently associated with an increased risk of TVR and MI, and provided the first scientific evidence of the negative impact of procedure-related factors on clinical restenosis. Other mechanical failures that can trigger restenosis include stent underexpansion[108] and strut fracture,[109] which are both associated with higher rates of TLR.

TABLE 33-1 Summary of Drug-Eluting Stent Clinical Data

Study	*N*	Drug/Agent	Device Type	In-Stent Late Loss* (Months of Follow-Up)	In-Lesion Restenosis (Months of Follow-Up)
Pivotal Stent Trials					
STRESS	410	None	Palmaz-Schatz Balloon angioplasty	0.74 mm (6 mo)** 0.38 mm (6 mo)**	31.6% (6 mo) 42.1% (6 mo)
BENESTENT	520	None	Palmaz-Schatz Balloon angioplasty	0.65 mm (6 mo)** 0.32 mm (6 mo)**	22% (6 mo) 42% (6 mo)
MUSIC†	161	None	IVUS-guided, Palmaz-Schatz	0.77 mm (6 mo)	8.3% (6 mo)
Pivotal Drug-Eluting Stent Trials					
RAVEL	238	Sirolimus	BX Velocity BX Velocity	–0.01 mm (6 mo) 0.8 mm (6 mo)	0% (6 mo) 26.6% (6 mo)
SIRIUS	1058	Sirolimus None	BX Velocity BX Velocity	0.17 mm (8 mo)	8.9% (9 mo)
TAXUS IV	1314	Paclitaxel (SR) None	Express 2 Express 2	0.39 mm (9 mo) 0.92 mm (9 mo)	7.9% (9 mo) 26.6% (9 mo)
ENDEAVOR II	1197	Zotarolimus None	Driver Driver	0.61 mm (9 mo) 1.03 mm (9 mo)	13.2% (9 mo) 35% (9 mo)
Head-to-Head Trials					
REALITY	1386	Sirolimus Paclitaxel	BX Velocity Express 2	0.09 mm (8 mo) 0.31 mm (8 mo)	9.6% (8 mo) 11.1% (8 mo)
SIRTAX	1012	Sirolimus Paclitaxel	BX Velocity Express 2	0.13 mm (9 mo) 0.25 mm (9 mo)	6.7% (9 mo) 11.9% (9 mo)
SPIRIT IV‡	1002	Everolimus Paclitaxel	Vision Express 2	0.14 mm (8 mo) 0.28 mm (8 mo)	8.9% (8 mo) 4.7% (8 mo)
Diabetes Trials					
DIABETES-I	160	Sirolimus None	BX Velocity BX Velocity	0.08 mm (9 mo) 0.66 mm (9 mo)	7.7% (9 mo) 33% (9 mo)
DIABETES-II†	80	Paclitaxel	Express 2	0.42 mm (9 mo)	7.6% (9 mo)
ISAR-DIABETES	250	Sirolimus Paclitaxel	BX Velocity Express 2	0.19 mm (6 mo) 0.49 mm (6 mo)	6.9% (6 mo) 16.5% (6 mo)

*Data are provided for pivotal trials for the active treatment groups only. All trials were randomized except where noted.
**In-lesion late loss is provided for bare metal stent studies because in-stent angiography measurements were not applied. Drug-eluting stent figures reflect in-stent late loss.
†Nonrandomized
‡Randomized 2:1
IVUS, Intravascular ultrasound; *SR,* slow release.

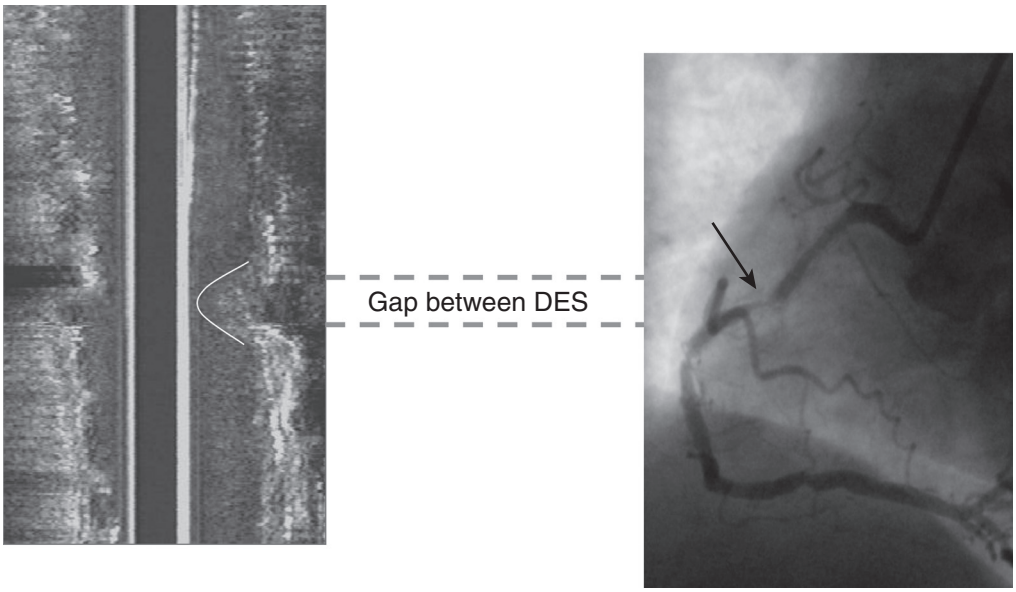

FIGURE 33-6 Longitudinal intravascular ultrasound image shows a focal intimal hyperplasia formation (delineated) in a gap between two sirolimus-eluting stents. Note the lack of intimal hyperplasia within the stents. Right panel shows the corresponding focal angiographic restenosis (*black arrow*). Mechanical and procedural related factors are key determinants of restenosis after use of a drug-eluting stent (DES).

TABLE 33-2 Clinical and Angiographic Predictors of Bare-Metal Stent Restenosis

Diabetes mellitus
Nonsmoking status
Female sex
Acute coronary syndrome
Previous PCI
Small vessel diameter
Lesion length greater than 20 mm
Multiple stents
ACC/AHA type C lesion
Ostial location

ACC, American College of Cardiology; *AHA,* American Hospital Association; *PCI,* percutaneous coronary intervention.

Drug-Eluting Stent Restenosis

As with BMS restenosis, stent underexpansion appears to predispose to restenosis after DES implantation.[110] For example, in a cohort 76 patients who underwent IVUS for DES restenosis, 42% had stent underexpansion, a problem particularly important for longer stents, in which underexpansion may be more difficult to recognize without intravascular imaging.[111]

Stent- or polymer-induced inflammation has also been identified as a possible contributor to DES restenosis and stent thrombosis. Polymer-induced inflammation might be especially operant when late DES failure (restenosis >6 months after implantation) or late stent thrombosis (>12 months after implantation) occurs long after DES antiproliferative dugs have eluted from the polymer.[13,112,113]

Further evidence for altered arterial healing with DES use comes from studies that demonstrate impaired endothelial function in arterial segments distal to the stented sites in DES- compared with BMS-treated arteries.[114,115] Even 6 months after implantation of a DES, intracoronary acetylcholine injection[116] and hand-grip exercise provocation[117] both induce abnormal vasoconstrictive responses in artery segments distal to the DES.[118] DES-associated abnormalities in endothelial function could be related to delayed vascular repair and not to the DES drug, because the kinetics of a DES are such that the drugs are completely eluted within months after implantation.[119-122] It is possible, however, that in certain circumstances, drug accumulation in the arterial wall[123] and in the lipophilic core of a stented atheroma results in prolonged drug retention/release and ongoing vascular dysfunction. The mechanism of DES-associated endothelial dysfunction has not been established, and other than the direct effect of lingering drug, potential etiologies could be related to decreased nitric oxide bioavailability and/or abnormal release of vasoactive autacoids. Recent studies have demonstrated variability in the severity of DES-associated endothelial dysfunction among specific DES agents.[124-126] It is unclear whether DES-associated vascular dysfunction influences clinical outcomes following DES implantation. One small study demonstrated impaired endothelial function in patients who present with in-stent restenosis compared with matched controls;[127] however, this association will require validation in larger prospective investigations.

TREATMENT OF RESTENOSIS

Restenosis after balloon angioplasty has a relatively benign outcome after PCI. The 18% rate of repeat restenosis for patients treated with a BMS compares favorably with data after treatment of de novo lesions.[128] Conversely, treatment of in-stent restenosis has been associated with high (>35%) rates of repeat TLR.[129] At the 4-year follow-up, event-free survival was 69% after repeat BMS use and 64% after balloon angioplasty.[130]

Intracoronary radiation therapy was the sole therapeutic approach that proved its efficacy clinically for the treatment of BMS restenosis.[131] However, the treatment paradigm for in-stent restenosis has changed, and DES use is currently the treatment of choice for restenosis after BMS. Both SESs and paclitaxel-eluting stents (PESs) have been shown to be superior to brachytherapy for the treatment of BMS restenosis.[132-134] No data are available on the use of drug-eluting stenting for the treatment of postangioplasty restenosis.

Despite its lower frequency compared with that using a BMS, DES restenosis is a particularly vexing problem, and the most appropriate treatment strategy for restenosis after DES use remains to be defined. A recent randomized investigation study that utilized 6- to 8-month angiographic follow-up demonstrated that SESs and PESs were equally effective at treating DES restenosis; however, late loss (~0.40 mm), binary restenosis (~20%), and TLR rates (~15.5%) were relatively high in both groups. In terms of safety outcomes, the rates of death/MI (6.1% SES vs. 5.8% PES; $P = .86$) and stent thrombosis (0.4% SES vs. 0.4% PES; $P > .99$) were similar between both stents.

Restenosis outcomes appear to be associated with the pattern of the stenosis, with the highest repeat restenosis rates observed in patients with diffuse patterns.[135,136] Although the strategy of repeat DES has been largely used, the long-term safety of exposing the vessel wall to another potent antiproliferative therapy, such as radiation or a second DES, remains to be determined, and the potential exists for markedly aberrant vascular healing and higher rates of late and very late stent thrombosis. The use of IVUS or OCT may be helpful to define the mechanism associated with DES restenosis and should be considered. If mechanical failures are encountered and the stenosis is discrete, properly sized balloon angioplasty may suffice. If the disease is diffuse or mostly outside the stent, such as with edge restenosis, another DES could be effective. However, a safe and effective strategy for the rare cases of diffuse or proliferative DES restenosis remains to be established. The use of drug-eluting balloons, which usually elute paclitaxel, to treat in-stent restenosis appears to be a very promising alternative.[137]

NEWER GENERATION DRUG-ELUTING STENTS AND BEYOND

First-generation DES technology convincingly demonstrated that local cell-cycle inhibition could lead to a dramatic reduction in restenosis rates. However, this was accompanied by low but significantly elevated rates of late and very late stent thrombosis (ST) compared with the BMS. The extent to which very late ST is a "necessary evil" of DES use, implying overlapping mechansims responsible for restenosis and reendothelialization, is still unknown. However, studies that have tested newer-generation stents suggest that ST rates can indeed be diminished without significantly altering the antiproliferative agent or giving up efficacy against restenosis.

The Clinical Evaluation of the XIENCE V Everolimus-Eluting Coronary Stent System (SPIRIT IV) trial compared the Xience V everolimus-eluting stent (X-EES) to the first-generation PES in 3687 patients with stable CAD.[138] Target-lesion failure (TLF) rates at 1 year were significantly lower with the X-EES (4.2% vs. 6.8%, relative risk [RR] 0.62; 95% confidence interval [CI], 0.46 to 0.82). Individual end points of MI (1.9% vs. 3.1%, $P = .02$) and ST (0.17% vs. 0.85%, $P = .004$) also favored X-EES over PES at 1 year. The results held at 2 years, and EES was still associated with superior outcomes[139] for TLF (6.9% vs. 9.9%, $P = .003$) and MI (2.5% vs. 3.9%, $P = .02$). ST rates at 2 years were still considerably lower for the newer-generation stent at 2 years (0.4% vs. 1.2%, $P = .008$). The Comparison of the Everolimus Eluting XIENCE-V Stent With the Paclitaxel Eluting TAXUS LIBERTÉ Stent in All-Comers: A Randomized Open Label Trial (COMPARE) tested the X-EES versus the PES in a broader population of 1800 patients (60% had ACS and 25% had STEMI) and involved more complex lesions (45% had type C lesions, with an average of 1.4 lesions per patient).[140] The primary end point—a composite of all-cause mortality, MI, and TVR at 12 months—was lower with the X-EES (6% vs. 9%, $P = .02$). TLR was also reduced with the X-EES (2% vs. 5%, $P = .0002$),

as was definite and probable ST (0.7% vs. 3%, $P = .002$). The advantages for the X-EES held up after 2 years for the primary end point (9.0% vs. 13.7%, $P = .0016$) and definite/probable ST (0.9% vs. 3.9%, $P < .0001$).[141] Rates of very late ST, between years 1 and 2, were also low with the X-EES (0.3% vs. 1.5%, $P = .02$) despite the fact that only 13% of this relatively high-risk population continued dual antiplatelet therapy beyond 1 year.

The Promus Element (Boston Scientific, Natick, MA) everolimus-eluting stent (P-EES) consists of the same antiproliferative and biopolymer as the EES mounted on a novel platinum-chromium scaffold. The scaffold compares favorably to cobalt-chromium in preclinical bench testing with increased radial strength, conformability, trackability, and radiopacity.[142] The Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System for the Treatment of Up to Two De Novo Coronary Artery Lesions (PLATINUM) randomized 1530 patients with CAD (24% had unstable angina) to either the X-EES or P-EES.[142] The primary end point of TLF—defined as the composite of target vessel–related cardiac death, target vessel–related MI, or ischemia-driven TLR—was similar for both stents (2.9% vs. 3.4% for P-EES), meeting the criteria for noninferiority ($P = .001$). No significant differences were reported in the 12-month rates of cardiac death or MI (2.5% vs. 2.0%, $P = .56$), TLR (1.9% vs. 1.9%, $P = .96$), or definite/probable ST (0.4% vs. 0.4%, $P = 1.00$).

The Resolute zotarolimus-eluting stent (R-ZES) system (Medtronic, Minneapolis, MN) uses a novel biopolymer designed to house the hydrophobic zotarolimus drug within a hydrophobic C10 compartment, coated with hydrophilic C19 for improved biocompatibility.[143] The Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention (RESOLUTE) All-Comers trial[144] compared R-ZES to X-EES in 2292 patients, over 50% of whom presented with ACS; this trial was powered for clinical events with a noninferiority design. Rates of TLF were similar for both stents (8.2% for R-ZES vs. 8.3%, $P < .001$ for noninferiority). In-stent late lumen loss was not statistically different between the two stents (0.27 ± 0.43 mm for R-ZES vs. 0.19 ± 0.40 for X-EES, $P = .08$). Rates of definite, probable, or possible ST were similar for both stents (2.3% vs. 1.5% X-EES, $P = .17$). These findings were confirmed in TWENTE, the Real-World Endeavor Resolute Versus Xience V Drug-Eluting Stent Study in Twente, a second head-to-head comparison of the R-ZES with the X-EES designed to test these two stent designs across broad patient populations, including those with ACS and higher risk, "off-label" lesion subsets.[145] Patients treated with the R-ZES had a TVF rate of 8.2% compared with 8.1% in patients treated with the X-EES (difference 0.1%; 95% CI, −2.8% to 3.0%, $P = .001$ for noninferiority). Rates of definite or probable ST were similar for both stents (0.9% and 1.2% for X-EES, $P = .59$).

These trials of newer-generation DESs have shown both improved efficacy in terms of TLR and improved safety with reduced ST rates compared with first-generation designs. Final judgement about the efficacy and safety of newer generation devices will require further long-term follow-up. However, the signals to date should be both reassuring and a cause for optimism. In contemporary trials using newer generation DESs, adverse events following PCI with newer generation stents are driven as much by progression of CAD in untreated sites (de novo disease) as by TLF,[146] with very low rates of ST after year one (~0.4% at 4 years).

Predictors of restenosis after newer-generation DES placement appear similar to first-generation DESs[105,110] and include diabetes mellitus, previous PCI, angiographic complexity, vein graft disease, ostial lesions, and prior restenosis.[146] It is also notable that predictors of DES restenosis, including angiographic complexity, also predict future need for revascularization at de novo sites.[146] This suggests that in the current era, mechanisms that drive DES restenosis may overlap with those that drive the progression of de novo atherosclerosis, and vice versa. Thus innovation is urgently needed to address these challenging patient subsets who remain at high risk for adverse events.

SUMMARY

Restenosis is a major drawback to PCI and limits its durability. The development of first-generation and newer-generation DESs have drastically reduced, but not eradicated, restenosis. As a result of this, and in combination with improved deliverability of these newer designs, PCI is a feasible treatment option in the great majority of patients with CAD. Given the increased utilization of PCI, restenosis remains a significant problem requiring individualized treatment strategies.

Our experiences from Grüntzig to the present have consistently highlighted that coronary atherosclerosis is a formidable adversary. Thus this generation of devices, no matter how much improved, is unlikely to be the last. It is notable that the same predictors of restenosis after bare-metal stenting are relevant even after newer-generation drug-eluting stenting, predicting both failure at the stented segment and progression elsewhere. Thus important biologic mechansims remain untapped. The current challenge is to improve the efficacy of PCI by developing new strategies that treat complex obstructive atherosclerosis, prevent restenosis, and restore arterial healing.

REFERENCES

1. Grüntzig AR, Senning A, Siegenthaler WE: Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med* 301:61–68, 1979.
2. Welt FG, Rogers C: Inflammation and restenosis in the stent era. *Arterioscler Thromb Vasc Biol* 22:1769–1776, 2002.
3. Forrester JS, Fishbein M, Helfant R, Fagin J: A paradigm for restenosis based on cell biology: clues for the development of new preventive therapies. *J Am Coll Cardiol* 17:758–769, 1991.
4. Koskinas KC, Chatzizisis YS, Antoniadis AP, Giannoglou GD: Role of endothelial shear stress in stent restenosis and thrombosis: pathophysiologic mechanisms and implications for clinical translation. *J Am Coll Cardiol* 59:1337–1349, 2012.
5. Palumbo R, Gaetano C, Antonini A, et al: Different effects of high and low shear stress on platelet-derived growth factor isoform release by endothelial cells: consequences for smooth muscle cell migration. *Arterioscler Thromb Vasc Biol* 22:405–411, 2002.
6. Massberg S, Enders G, Leiderer R, et al: Platelet-endothelial cell interactions during ischemia/reperfusion: the role of P-Selectin. *Blood* 92:507–515, 1998.
7. Massberg S, Gawaz M, Grüner S, et al: A crucial role of glycoprotein VI for platelet recruitment to the injured arterial wall in vivo. *J Exp Med* 197:41–49, 2003.
8. Bach R, Jung F, Kohsiek I, et al: Factors affecting the restenosis rate after percutaneous transluminal coronary angioplasty. *Thromb Res* 74(Suppl 1):S55–S67, 1994.
9. Libby P, Schwartz D, Brogi E, et al: A cascade model for restenosis. A special case of atherosclerosis progression. *Circulation* 86:III47–III52, 1992.
10. Welt FG, Tso C, Edelman ER, et al: Leukocyte recruitment and expression of chemokines following different forms of vascular injury. *Vasc Med* 8:1–7, 2003.
11. Horvath C, Welt FG, Nedelman M, et al: Targeting CCR2 or CD18 inhibits experimental in-stent restenosis in primates: inhibitory potential depends on type of injury and leukocytes targeted. *Circ Res* 90:488–494, 2002.
12. Byrne RA, Joner M, Kastrati A: Polymer coatings and delayed arterial healing following drug-eluting stent implantation. *Minerva Cardioangiol* 57:567–584, 2009.
13. Pallero MA, Talbert Roden M, Chen YF, et al: Stainless steel ions stimulate increased thrombospondin-1-dependent TGF-beta activation by vascular smooth muscle cells: implications for in-stent restenosis. *J Vasc Res* 47:309–322, 2010.
14. Danenberg HD, Golomb G, Groothuis A, et al: Liposomal alendronate inhibits systemic innate immunity and reduces in-stent neointimal hyperplasia in rabbits. *Circulation* 108:2798–2804, 2003.
15. Versaci F, Gaspardone A, Tomai F, et al: Immunosuppressive Therapy for the Prevention of Restenosis after Coronary Artery Stent Implantation (IMPRESS Study). *J Am Coll Cardiol* 40: 1935–1942, 2002.
16. Rogers C, Edelman ER, Simon DI: A mAb to the beta2-leukocyte integrin Mac-1 (CD11b/CD18) reduces intimal thickening after angioplasty or stent implantation in rabbits. *Proc Natl Acad Sci U S A* 95:10134–10139, 1998.
17. Wang Y, Sakuma M, Chen Z, et al: Leukocyte engagement of platelet glycoprotein Ib-alpha via the integrin Mac-1 is critical for the biological response to vascular injury. *Circulation* 112: 2993–3000, 2005.
18. Simon DI, Dhen Z, Seifert P, et al: Decreased neointimal formation in Mac-1(-/-) mice reveals a role for inflammation in vascular repair after angioplasty. *J Clin Invest* 105:293–300, 2000.
19. Berk BC, Gordon JB, Alexander RW: Pharmacologic roles of heparin and glucocorticoids to prevent restenosis after coronary angioplasty. *J Am Coll Cardiol* 17:111B–117B, 1991.
20. Holmes DR, Jr, Savage M, LaBlanche JM, et al: Results of Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) trial. *Circulation* 106:1243–1250, 2002.
21. Murray M, Schrodt GR, Berg HG: Role of smooth muscle cells in healing of injured arteries. *Arch Pathol* 82:138–146, 1966.
22. Thyberg J, Hedin U, Sjölund M, et al: Regulation of differentiated properties and proliferation of arterial smooth muscle cells. *Arteriosclerosis* 10:966–990, 1990.
23. Libby P, Warner SJ, Salomon RN, Birinyi LK: Production of platelet-derived growth factor-like mitogen by smooth-muscle cells from human atheroma. *N Engl J Med* 318:1493–1498, 1988.
24. Scott NA, Cipolla GD, Ross CE, et al: Identification of a potential role for the adventitia in vascular lesion formation after balloon overstretch injury of porcine coronary arteries. *Circulation* 93:2178–2187, 1996.
25. Riessen R, Isner JM, Blessing E, et al: Regional differences in the distribution of the proteoglycans biglycan and decorin in the extracellular matrix of atherosclerotic and restenotic human coronary arteries. *Am J Pathol* 144:962–974, 1994.
26. Schwartz RS, Huber KC, Murphy JG, et al: Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. *J Am Coll Cardiol* 19:267–274, 1992.

27. Nabel EG, Boehm M, Akyurek LM, et al: Cell cycle signaling and cardiovascular disease. *Cold Spring Harb Symp Quant Biol* 67:163–170, 2002.
28. Tanner FC, Yang ZY, Duckers E, et al: Expression of cyclin-dependent kinase inhibitors in vascular disease. *Circ Res* 82:396–403, 1998.
29. Polyak K, Kato JY, Solomon MJ, et al: p27Kip1, a cyclin-Cdk inhibitor, links transforming growth factor-beta and contact inhibition to cell cycle arrest. *Genes Dev* 8:9–22, 1994.
30. Sherr CJ, Roberts JM: CDK inhibitors: positive and negative regulators of G1-phase progression. *Genes Dev* 13:1501–1512, 1999.
31. Coats S, Flanagan WM, Nourse J, Roberts JM: Requirement of p27Kip1 for restriction point control of the fibroblast cell cycle. *Science* 272:877–880, 1996.
32. Koyama H, Raines EW, Bornfeldt KE, et al: Fibrillar collagen inhibits arterial smooth muscle proliferation through regulation of Cdk2 inhibitors. *Cell* 87:1069–1078, 1996.
33. van Tiel CM, Bonta PI, Rittersma SZ, et al: p27kip1-838C>A single nucleotide polymorphism is associated with restenosis risk after coronary stenting and modulates p27kip1 promoter activity. *Circulation* 120:669–676, 2009.
34. Vézina C, Kudelski A, Sehgal SN: Rapamycin (AY-22,989), a new antifungal antibiotic. I. Taxonomy of the producing streptomycete and isolation of the active principle. *J Antibiot (Tokyo)* 28:721–726, 1975.
35. Sehgal SN: Rapamune (RAPA, rapamycin, sirolimus): mechanism of action immunosuppressive effect results from blockade of signal transduction and inhibition of cell cycle progression. *Clin Biochem* 31:335–340, 1998.
36. Sehgal SN: Sirolimus: its discovery, biological properties, and mechanism of action. *Transplant Proc* 35:S7–S14, 2003.
37. Marx SO, Jayaraman T, Go LO, Marks AR: Rapamycin-FKBP inhibits cell-cycle regulators of proliferation in vascular smooth-muscle cells. *Circ Res* 76:412–417, 1995.
38. Powell JD, Lerner LC, Schwartz RH: Inhibition of cell cycle progression by rapamycin induces T cell clonal anergy even in the presence of costimulation. *J Immunol* 162:2775–2784, 1999.
39. Zeiser R, Leveson-Gower DB, Zambricki EA, et al: Differential impact of mammalian target of rapamycin inhibition on CD4+CD25+Foxp3+ regulatory T cells compared with conventional CD4+ T cells. *Blood* 111:453–462, 2008.
40. Chen YW, Smith ML, Sheets M, et al: Zotarolimus, a novel sirolimus analogue with potent anti-proliferative activity on coronary smooth muscle cells and reduced potential for systemic immunosuppression. *J Cardiovasc Pharmacol* 49:228–235, 2007.
41. Schuler W, Sedrani R, Cottens S, et al: SDZ RAD, A new rapamycin derivative: pharmacological properties in vitro and in vivo. *Transplantation* 64:36–42, 1997.
42. Sedrani R, Cottens S, Kallen J, Schuler W: Chemical modification of rapamycin: the discovery of SDZ RAD. *Transplant Proc* 30:2192–2194, 1998.
43. Sollott SJ, Cheng L, Pauly RR, et al: Taxol inhibits neointimal smooth muscle cell accumulation after angioplasty in the rat. *J Clin Invest* 95:1869–1876, 1995.
44. Roberts RL, Nath J, Friedman MM, Gallin JI: Effects of taxol on human neutrophils. *J Immunol* 129:2134–2141, 1982.
45. Roy C, Chaly N, Brown DL: Taxol-induced reorganization of the microtubule system in murine splenic lymphocytes inhibits response to allogeneic cells but not to concanavalin A. *Biochem Cell Biol* 66:389–395, 1988.
46. Byrd-Leifer CA, Block EF, Takeda K, et al: The role of MyD88 and TLR4 in the LPS-mimetic activity of Taxol. *Euro J Immunol* 31:2448–2457, 2001.
47. Carboni JM, Singh C, Tepper MA: Taxol and lipopolysaccharide activation of a murine macrophage cell line and induction of similar tyrosine phosphoproteins. *J Natl Cancer Inst Monogr* 95–101, 1993.
48. Roubin GS, King SB, 3rd, Douglas JS, Jr: Restenosis after percutaneous transluminal coronary angioplasty: the Emory University Hospital experience. *Am J Cardiol* 60:39B–43B, 1987.
49. Gould KL, Lipscomb K, Hamilton GW: Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol* 33:87–94, 1974.
50. Kuntz RE, Baim DS: Defining coronary restenosis. Newer clinical and angiographic paradigms. *Circulation* 88:1310–1323, 1993.
51. Rensing BJ, Hermans WR, Deckers JW, et al: Which angiographic variable best describes functional status 6 months after successful single-vessel coronary balloon angioplasty? *J Am Coll Cardiol* 21:317–324, 1993.
52. Costa MA, Simon DI: Molecular basis of restenosis and drug-eluting stents. *Circulation* 111:2257–2273, 2005.
53. Sousa JE, Costa MA, Tuzcu EM, et al: New frontiers in interventional cardiology. *Circulation* 111:671–681, 2005.
54. Costa MA, Sabaté M, Angiolillo DJ, et al: Relocation of minimal luminal diameter after bare metal and drug-eluting stent implantation: incidence and impact on angiographic late loss. *Catheter Cardiovasc Interv* 69:181–188, 2007.
55. Garcia-Garcia HM, Shen Z, Piazza N: Study of restenosis in drug eluting stents: new insights from greyscale intravascular ultrasound and virtual histology. *EuroIntervention* 5(Suppl D):D84–D92, 2009.
56. Yamamoto M, Takano M, Murakami D, et al: Optical coherence tomography analysis for restenosis of drug-eluting stents. *Int J Cardiol* 146:100–103, 2010.
57. Bezerra HG, Costa MA, Guagliumi G, et al: Intracoronary optical coherence tomography: a comprehensive review clinical and research applications. *JACC Cardiovasc Interv* 2:1035–1046, 2009.
58. Mehilli J, Kastrati A, Wessely R, et al: Randomized trial of a nonpolymer-based rapamycin-eluting stent versus a polymer-based paclitaxel-eluting stent for the reduction of late lumen loss. *Circulation* 113:273–279, 2006.
59. Morice MC, Serruys PW, Sousa JE, et al: A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 346:1773–1780, 2002.
60. Strauss BH, Serruys PW, de Scheerder IK, et al: Relative risk analysis of angiographic predictors of restenosis within the coronary Wallstent. *Circulation* 84:1636–1643, 1991.
61. Sabaté M, Costa MA, Kozuma K, et al: Methodological and clinical implications of the relocation of the minimal luminal diameter after intracoronary radiation therapy. Dose Finding Study Group. *J Am Coll Cardiol* 36:1536–1541, 2000.
62. Takano M, Inami S, Jang IK, et al: Evaluation by optical coherence tomography of neointimal coverage of sirolimus-eluting stent three months after implantation. *Am J Cardiol* 99:1033–1038, 2007.
63. Bouma BE, Tearney GJ, Yabushita H, et al: Evaluation of intracoronary stenting by intravascular optical coherence tomography. *Heart* 89:317–320, 2003.
64. Gonzalo N, Garcia-Garcia HM, Serruys PW, et al: Reproducibility of quantitative optical coherence tomography for stent analysis. *EuroIntervention* 5:224–232, 2009.
65. Finn AV, Kolodgie FD, Harnek J, et al: Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation* 112:270–278, 2005.
66. Hassan AK, Bergheanu SC, Stijnen T, et al: Late stent malapposition risk is higher after drug-eluting stent compared with bare-metal stent implantation and associates with late stent thrombosis. *Eur Heart J* 31:1172–1180, 2010.
67. Ruygrok PN, Webster MW, de Valk V, et al: Clinical and angiographic factors associated with asymptomatic restenosis after percutaneous coronary intervention. *Circulation* 104:2289–2294, 2001.
68. Andersen K, Steinthorsdottir SD, Haraldsdottir S, Gudnason T: Clinical evaluation and stress test have limited value in the diagnosis of in-stent restenosis. *Scand Cardiovasc J* 43:402–407, 2009.
69. Kumbhani DJ, Ingelmo CP, Schoenhagen P, et al: Meta-analysis of diagnostic efficacy of 64-slice computed tomography in the evaluation of coronary in-stent restenosis. *Am J Cardiol* 103:1675–1681, 2009.
70. de Graaf FR, Schuijf JD, van Velzen JE, et al: Diagnostic accuracy of 320-row multidetector computed tomography coronary angiography to noninvasively assess in-stent restenosis. *Invest Radiol* 45:331–340, 2010.
71. Wijns W, Serruys PW, Simoons ML, et al: Predictive value of early maximal exercise test and thallium scintigraphy after successful percutaneous transluminal coronary angioplasty. *Br Heart J* 53:194–200, 1985.
72. Chen MS, John JM, Chew DP, et al: Bare metal stent restenosis is not a benign clinical entity. *Am Heart J* 151:1260–1264, 2006.
73. Rathore S, Kinoshita Y, Terashima M, et al: A comparison of clinical presentations, angiographic patterns and outcomes of in-stent restenosis between bare metal stents and drug eluting stents. *EuroIntervention* 5:841–846, 2010.
74. Popma JJ, van den Berg EK, Dehmer GJ: Long-term outcome of patients with asymptomatic restenosis after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 62:1298–1299, 1988.
75. Ruygrok PN, Melkert R, Morel MA, et al: Does angiography six months after coronary intervention influence management and outcome? Benestent II Investigators. *J Am Coll Cardiol* 34:1507–1511, 1999.
76. Krüger S, Koch KC, Kaumanns I, et al: Clinical significance of fractional flow reserve for evaluation of functional lesion severity in stent restenosis and native coronary arteries. *Chest* 128:1645–1649, 2005.
77. Serruys PW, de Jaegere P, Kiemeneij F, et al: A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med* 331:489–495, 1994.
78. Fischman DL, Leon MD, Baim DS, et al: A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med* 331:496–501, 1994.
79. de Jaegere P, Mudra H, Figulla H, et al: Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic results from the Multicenter Ultrasound Stenting in Coronaries Study (MUSIC Study). *Eur Heart J* 19:1214–1223, 1998.
80. Moses JW, Leon MB, Popma JJ, et al: Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 349:1315–1323, 2003.
81. Stone GW, Ellis SG, Cox DA, et al: A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 350:221–231, 2004.
82. Fajadet J, Wijns W, Laarman GJ, et al: Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation* 114:798–806, 2006.
83. DIABETES Investigators: Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the diabetes and sirolimus-eluting stent (DIABETES) trial. *Circulation* 112:2175–2183, 2005.
84. Kastrati A, Dibra A, Eberle S, et al: Sirolimus-eluting stents vs paclitaxel-eluting stents in patients with coronary artery disease: meta-analysis of randomized trials. *JAMA* 294:819–825, 2005.
85. Colombo A, Drzewiecki J, Banning A, et al: Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 108:788–794, 2003.
86. Windecker S, Remondino A, Eberli FR, et al: Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med* 353:653–662, 2005.
87. Morice MC, Columbo A, Meier B, et al: Sirolimus- vs paclitaxel-eluting stents in de novo coronary artery lesions: the REALITY trial: a randomized controlled trial. *JAMA* 295:895–904, 2006.
88. Stone GW, Midei M, Newman W, et al: Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. *JAMA* 299:1903–1913, 2008.
89. Mehran R, Dangas G, Abazaid AS, et al: Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation* 100:1872–1878, 1999.
90. Alfonso F, Cequier A, Angel J, et al: Value of the American College of Cardiology/American Heart Association angiographic classification of coronary lesion morphology in patients with in-stent restenosis. Insights from the Restenosis Intra-stent Balloon angioplasty versus elective Stenting (RIBS) randomized trial. *Am Heart J* 151:681.e1–681.e9, 2006.
91. Lemos PA, Saia F, Ligthart JM, et al: Coronary restenosis after sirolimus-eluting stent implantation: morphological description and mechanistic analysis from a consecutive series of cases. *Circulation* 108:257–260, 2003.
92. Colombo A, Orlic D, Stankovic G, et al: Preliminary observations regarding angiographic pattern of restenosis after rapamycin-eluting stent implantation. *Circulation* 107:2178–2180, 2003.
93. Corbett SJ, Cosgrave J, Melzi G, et al: Patterns of restenosis after drug-eluting stent implantation: insights from a contemporary and comparative analysis of sirolimus- and paclitaxel-eluting stents. *Eur Heart J* 27:2330–2337, 2006.
94. Steigen TK, Maeng M, Wiseth R, et al: Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. *Circulation* 114:1955–1961, 2006.
95. Abizaid A, Kornowski R, Mintz GS, et al: The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. *J Am Coll Cardiol* 32:584–589, 1998.
96. Hirshfeld JW, Jr, Schwartz JS, Jugo R, et al: Restenosis after coronary angioplasty: a multivariate statistical model to relate lesion and procedure variables to restenosis. The M-HEART Investigators. *J Am Coll Cardiol* 18:647–656, 1991.
97. Foley DP, Melkert R, Serruys PW: Influence of coronary vessel size on renarrowing process and late angiographic outcome after successful balloon angioplasty. *Circulation* 90:1239–1251, 1994.
98. Violaris AG, Melkert R, Serruys PW: Long-term luminal renarrowing after successful elective coronary angioplasty of total occlusions. A quantitative angiographic analysis. *Circulation* 91:2140–2150, 1995.
99. Kastrati A, Schömig A, Elezi S, et al: Predictive factors of restenosis after coronary stent placement. *J Am Coll Cardiol* 30:1428–1436, 1997.
100. Kastrati A, Elezi S, Dirschinger J, et al: Influence of lesion length on restenosis after coronary stent placement. *Am J Cardiol* 83:1617–1622, 1999.
101. de Feyter PJ, Kay P, Disco C, Serruys PW: Reference chart derived from post-stent-implantation intravascular ultrasound predictors of 6-month expected restenosis on quantitative coronary angiography. *Circulation* 100:1777–1783, 1999.
102. Serruys PW, Kay IP, Disco C, et al: Periprocedural quantitative coronary angiography after Palmaz-Schatz stent implantation predicts the restenosis rate at six months: results of a meta-analysis of the BElgian NEtherlands Stent study (BENESTENT) I, BENESTENT II Pilot, BENESTENT II and MUSIC trials. Multicenter Ultrasound Stent In Coronaries. *J Am Coll Cardiol* 34:1067–1074, 1999.
103. Lemos PA, Hoye A, Serruys PW: Recurrent angina after revascularization: an emerging problem for the clinician. *Coron Artery Dis* (15 Suppl 1):S11–S15, 2004.
104. Costa M, Angiolillo DJ, Teirstein P, et al: Sirolimus-eluting stents for treatment of complex bypass graft disease: insights from the SECURE registry. *J Invasive Cardiol* 17:396–398, 2005.
105. Lemos PA, Hoye A, Goedhart D, et al: Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) Study. *Circulation* 109:1366–1370, 2004.
106. Kuntz RE, Safian RD, Carrozza JP, et al: The importance of acute luminal diameter in determining restenosis after coronary atherectomy or stenting. *Circulation* 86:1827–1835, 1992.
107. Costa MA, Angiolillo DJ, Tannenbaum M, et al: Impact of stent deployment procedural factors on long-term effectiveness and

safety of sirolimus-eluting stents (final results of the multicenter prospective STLLR trial). *Am J Cardiol* 101:1704–1711, 2008.
108. Castagna MT, Mintz GS, Leiboff BO, et al: The contribution of "mechanical" problems to in-stent restenosis: an intravascular ultrasonographic analysis of 1090 consecutive in-stent restenosis lesions. *Am Heart J* 142:970–974, 2001.
109. Popma JJ, Tiroch K, Almonacid A, et al: A qualitative and quantitative angiographic analysis of stent fracture late following sirolimus-eluting stent implantation. *Am J Cardiol* 103:923–929, 2009.
110. Kastrati A, Dibra A, Mehilli J, et al: Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. *Circulation* 113:2293–2300, 2006.
111. Kang SJ, Mintz GS, Park DW, et al: Mechanisms of in-stent restenosis after drug-eluting stent implantation: intravascular ultrasound analysis. *Circ Cardiovasc Interv* 4:9–14, 2011.
112. Nebeker JR, Virmani R, Bennett CL, et al: Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol* 47:175–181, 2006.
113. Virmani R, Guagliumi G, Farb A, et al: Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: Should we be cautious? *Circulation* 109:701–705, 2004.
114. Fuke S, Maekawa K, Kawamoto K, et al: Impaired endothelial vasomotor function after sirolimus-eluting stent implantation. *Circ J* 71:220–225, 2007.
115. Shin DI, Kim PJ, Seung KB, et al: Drug-eluting stent implantation could be associated with long-term coronary endothelial dysfunction. *Int Heart J* 48:553–567, 2007.
116. Maekawa K, Kawamoto K, Fuke S, et al: Images in cardiovascular medicine: severe endothelial dysfunction after sirolimus-eluting stent implantation. *Circulation* 113:e850–e851, 2006.
117. Togni M, Windecker S, Cocchia R, et al: Sirolimus-eluting stents associated with paradoxic coronary vasoconstriction. *J Am Coll Cardiol* 46:231–236, 2005.
118. Hofma SH, van der Giessen WJ, van Dalen BM, et al: Indication of long-term endothelial dysfunction after sirolimus-eluting stent implantation. *Eur Heart J* 27:166–170, 2006.
119. Tesfamariam B: Drug release kinetics from stent device-based delivery systems. *J Cardiovasc Pharmacol* 51:118–125, 2008.
120. Kamath KR, Barry JJ, Miller KM: The Taxus drug-eluting stent: a new paradigm in controlled drug delivery. *Adv Drug Deliv Rev* 58:412–436, 2006.
121. Waugh J, Wagstaff AJ: The paclitaxel (TAXUS)-eluting stent: a review of its use in the management of de novo coronary artery lesions. *Am J Cardiovasc Drugs* 4:257–268, 2004.
122. McKeage K, Murdoch D, Goa KL: The sirolimus-eluting stent: a review of its use in the treatment of coronary artery disease. *Am J Cardiovasc Drugs* 3:211–230, 2003.
123. Raman VK, Edelman ER: Coated stents: local pharmacology. *Semin Interv Cardiol* 3:133–137, 1998.
124. Shin DI, Seung KB, Kim PJ, et al: Long-term coronary endothelial function after zotarolimus-eluting stent implantation. A 9 month comparison between zotarolimus-eluting and sirolimus-eluting stents. *Int Heart J* 49:639–652, 2008.
125. Kim JW, Suh SY, Choi CU, et al: Six-month comparison of coronary endothelial dysfunction associated with sirolimus-eluting stent versus paclitaxel-eluting stent. *JACC Cardiovasc Interv* 1:65–71, 2008.
126. Hamilos MI, Ostojic M, Beleslin B, et al: Differential effects of drug-eluting stents on local endothelium-dependent coronary vasomotion. *J Am Coll Cardiol* 51:2123–2129, 2008.
127. Thanyasiri P, Kathir K, Celermajer DS, Adams MR: Endothelial dysfunction and restenosis following percutaneous coronary intervention. *Int J Cardiol* 119:362–367, 2007.
128. Erbel R, Haude M, Höpp HW, et al: Coronary-artery stenting compared with balloon angioplasty for restenosis after initial balloon angioplasty. Restenosis Stent Study Group. *N Engl J Med* 339:1672–1678, 1998.
129. Alfonso F, Zueco J, Cequier A, et al: A randomized comparison of repeat stenting with balloon angioplasty in patients with in-stent restenosis. *J Am Coll Cardiol* 42:796–805, 2003.
130. Alfonso F, Augé JM, Zueco J, et al: Long-term results (three to five years) of the Restenosis Intrastent: Balloon angioplasty versus elective Stenting (RIBS) randomized study. *J Am Coll Cardiol* 46:756–760, 2005.
131. Waksman R, Ajani AE, White RL, et al: Five-year follow-up after intracoronary gamma radiation therapy for in-stent restenosis. *Circulation* 109:340–344, 2004.
132. Sousa JE, Costa MA, Abizaid A, et al: Sirolimus-eluting stent for the treatment of in-stent restenosis: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation* 107:24–27, 2003.
133. Holmes DR, Jr, Teirstein P, Satler L, et al: Sirolimus-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the SISR randomized trial. *JAMA* 295:1264–1273, 2006.
134. TAXUS V ISR Investigators: Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the TAXUS V ISR randomized trial. *JAMA* 295:1253–1263, 2006.
135. Lemos PA, van Mieghem CA, Arampatzis CA, et al: Post-sirolimus-eluting stent restenosis treated with repeat percutaneous intervention: late angiographic and clinical outcomes. *Circulation* 109:2500–2502, 2004.
136. Cosgrave J, Melzi G, Biodi-Zoccai GG, et al: Drug-eluting stent restenosis the pattern predicts the outcome. *J Am Coll Cardiol* 47:2399–2404, 2006.
137. ISAR-DESIRE 3 Investigators: Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. *Lancet* 381:461–467, 2013.
138. SPIRIT III Investigators: Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. *JAMA* 299:1903–1913, 2008.
139. Stone GW, Rizvi A, Sudhir K, et al: Randomized comparison of everolimus- and paclitaxel-eluting stents: 2-year follow-up from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) IV trial. *J Am Coll Cardiol* 58: 19–25, 2011.
140. Kedhi E, Joesoef KS, McFadden E, et al: Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *Lancet* 375:201–209, 2010.
141. Smits PC, Kedhi E, Royaards KJ, et al: 2-year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice. COMPARE (Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTÉ stent in all-comers: a randomized open label trial). *J Am Coll Cardiol* 58: 11–18, 2011.
142. Stone GW, Teirstein PS, Meredith IT, et al: A prospective, randomized evaluation of a novel everolimus-eluting coronary stent: the PLATINUM (a Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of Up to Two de Novo Coronary Artery Lesions) Trial. *J Am Coll Cardiol* 57:1700–1708, 2011.
143. Hezi-Yamit A, Sullivan C, Wong J, et al: Novel high throughput polymer biocompatibility screening designed for SAR (structure-activity relationship): application for evaluating polymer coatings for cardiovascular drug-eluting stents. *Comb Chem High Throughput Screen* 12:664–676, 2009.
144. Serruys PW, Silber S, Garg S, et al: Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med* 363:136–146, 2010.
145. von Birgelen C, Basalus MW, Tandjung K, et al: A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: The TWENTE Trial. *J Am Coll Cardiol* 59: 1350–1361, 2012.
146. Taniwaki M, Stefanini GG, Silber S, et al: 4-Year clinical outcomes and predictors of repeat revascularization in patients treated with new-generation drug-eluting stents: a report from the RESOLUTE All-Comers Trial (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention). *J Am Coll Cardiol* 63:1617–1625, 2014.

34 Bioresorbable Coronary Scaffolds

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KEY POINTS

- Bioresorbable scaffold (BRS) has the potential to overcome the limitations of permanent metallic stents because it provides temporary scaffolding and then disappears, liberating the treated vessel from its cage and restoring pulsatility, cyclical strain, physiologic shear stress, and mechanotransduction. After bioresorption of BRS, repeat percutaneous or surgical revascularization may easily be accomplished if needed.
- Bioresorbable metallic scaffolds and polymeric scaffolds are the two main types of BRS. The latter are predominantly composed of polylactic acids (PLAs). Magnesium-based scaffolds represent the main metallic scaffolding option, although iron-based scaffolds have also been tested in preclinical models.
- Initial data on the use of BRS comes from small-scale registries or trials in stable patients with simple lesions. However, studies are ongoing to evaluate use of BRS in complex lesions and acute coronary syndromes.
- Two BRS devices have received CE mark approval and are increasingly used in clinical practice. However, long-term safety and efficacy data from adequately powered clinical trials are required before routine use of these devices can be recommended in all-comer patients.

Andreas Grüntzig first performed balloon angioplasty in man in 1977 and revolutionized the treatment of coronary artery disease; however, the outcomes were compromised by acute vessel closure as a result of dissection or elastic recoil, late vascular remodeling, and neointimal proliferation.[1] Coronary stents were developed to overcome these limitations.[2,3] The two landmark trials, Belgian Netherlands Stent study (BENESTENT) and the Stent Restenosis Study (STRESS), reported superiority of bare-metal stents (BMSs) over balloon angioplasty and established bare-metal stenting as a second revolution in coronary intervention.[2,3] The clinical outcomes of bare-metal stenting were, however, compromised by a high incidence of in-stent restenosis.[4,5] Drug-eluting stents (DESs) were developed by coating BMSs with polymers containing antiproliferative drugs such as sirolimus and paclitaxel to overcome neointimal proliferation within the stents. DESs have significantly reduced in-stent restenosis and target-lesion revascularization (TLR) compared with BMSs,[6,7] and hence DESs are being hailed as a "third revolution" in coronary intervention. The first-generation DESs were associated with an increased risk of stent thrombosis (ST), which was largely attributed to a chronic inflammatory response to the durable polymers.[8,9] However, the newer-generation DESs, with biocompatible or biodegradable polymers, have a considerably improved safety profile.[10-12] The vast majority of percutaneous coronary intervention (PCI) procedures performed involve balloon angioplasty and stent deployment. However, these stents still leave a permanent metal implant inside the vessel, along with all its potential future problems. Bioresorbable stents, commonly referred to as *scaffolds*, can provide support to the vessel wall for a defined period after angioplasty but are subsequently resorbed.[13] Bioresorbable scaffolds herald a significant step forward in the advancement of coronary intervention and are considered a potential fourth revolution in coronary intervention.[14]

TERMINOLOGY

Stent or Scaffold?

The intravascular devices we now call *stents* were initially described as "endovascular prostheses." The word *stent* was popularized by Sigwart and colleagues during a stent-angioplasty course in 1986, and this term gained acceptance and approval in the cardiology community. In the interventional world, *scaffold* is a relatively newer term for *bioresorbable stent*, whether metallic or polymeric. The word *scaffold* has been widely used in peer-reviewed medical literature to describe these devices over the last few years and therefore should be preferred to distinguish these devices from permanent stents.

Biodegradation, Bioabsorption, and Bioresorption

Surgical sutures made from glycolic and lactic acids were the first commercial application of polymers in medicine and were called *absorbable sutures*. The term *bioabsorbable* generally reflects the disappearance of the compound into another substance. However, *bioabsorption* does not necessarily equate to degradation and, even less, to elimination of the polymer from the body. For example, even if the bioabsorbable polymeric suture thread is not visible as a result of dissolution (bioabsorption), high-molecular-mass molecules can still be trapped between skin and mucosa without passing through physiologic barriers and being eliminated. The term *bioabsorption* does not mean complete cleavage of macromolecules into small molecules that can be eliminated from the body via natural routes like kidney, liver, or lungs. To indicate the total elimination of polymers by dissolution, assimilation, and excretion, the term *bioresorption* was introduced.[15,16] The term *biodegradation* may also be confusing and should be restricted to cell-mediated in-vivo mechanisms.[15,16] We therefore recommend the term *bioresorbable scaffolding* to describe these novel devices.

RATIONALE FOR BIORESORBABLE SCAFFOLDING

BRS may preserve vessel geometry and tissue biomechanics because of better flexibility and conformability than that of conventional stents.[17] BRS may help in restoration of physiologic vasomotion, vascular mechanotransduction (conversion of hemodynamic forces to chemical stimuli or signaling pathways), adaptive shear stress, late luminal gain, plaque media regression, and late expansive remodeling once bioresorption is complete and the vessel is liberated from its "cage."[18] The metallic stents can alter vessel geometry and biomechanics, and resultant chronic irritation and flow disturbances may contribute to neointimal proliferation and adverse events.[19,20] BRS offers the potential to preserve vascular geometry, producing less alteration in vessel angulation and curvature.[17] It has also been shown that at 6 to 12 months after BRS implantation, coronary geometry tends to revert to its preimplant level, whereas it remains permanently altered after implantation of conventional metallic stents.[21] The absence of any residual foreign material and restoration of functional endothelial coverage can also potentially reduce the risk of very late ST and the need for long-term dual-antiplatelet therapy (DAPT). Additionally, a BRS can overcome

some other problems associated with the use of permanent metallic stents such as "jailing" of the side branches, overhang at ostial lesions, and inability to graft the stented segment.[22] The potential advantages of a BRS over other technologies are shown in Table 34-1.

BIORESORBABLE MATERIALS FOR CORONARY STENTS

The conventional permanent stents are typically made of stainless steel, nitinol, cobalt-chromium, or platinum-chromium. The current generation BRSs are composed of either a metallic (iron- or magnesium-based) alloy[23] or polymers (usually polylactides).[16] Various physical and biochemical factors determine the suitability of a material for a BRS.

Physical Properties

The physical properties of different materials used for stent and scaffold manufacturing are compared in Table 34-2. Metallic BRS is intuitively attractive because it has the potential to perform much the same as the conventional metallic stents in the early phase and also has the advantage of subsequent bioresorption. An ideal metallic BRS should therefore offer mechanical properties similar to a conventional stent: a nonthrombogenic surface, predictable and steerable bioresorption kinetics, and minimal or no inflammatory response on resorption. Magnesium and iron meet most of these criteria and have been further evaluated.

To manufacture a polymeric scaffold, a polymer should have high tensile strength, high modulus, and optimal elongation to allow the creation of a low-profile, balloon-expandable device. Furthermore, chemical and thermal properties of the polymer determine the bioresorption time, the type of degradation products, and the type of processing and sterilization methods that can be used. Polyglycolic acid (PGA), the polymer of glycolic acid, is the simplest linear aliphatic polyester. PGA is highly crystalline with a high melting point and a degradation period of 6 to 12 months. Polylactic acid (PLA) has two optical isomers, L- and D-lactic acid. Poly-D,L-lactic acid (PDLLA) contains both D-lactic acid and L-lactic acid. Poly-L-lactic acid (PLLA) is the homopolymer of L-lactide. PDLLA is amorphous with low tensile strength, higher elongation time, and a rapid degradation rate. In contrast, PLLA is semicrystalline and has a slower degradation rate and higher tensile strength. In a scaffold, usually the semicrystalline PLLA polymer made of crystal lamellae (regions with high concentrations of polymer with crystalline structure) is interconnected by amorphous tie chains that bind the crystallites (Fig. 34-1). Because the amorphous regions are less packed and therefore are more accessible to water, the amorphous polymer is more susceptible to hydration than the semicrystalline polymer. Figure 34-1 describes the initial reduction in molecular weight, the decrease in radial support at about 6 months, the loss in mass starting at 12 months, and subsequent completion at 24 months.

TABLE 34-1 Comparison of Bioresorbable Scaffolds With Other Angioplasty Techniques/Devices

	BA	BMS	DES	BRS
Acute occlusion	–	+	+	+
Acute recoil	–	+	+	+
Acute thrombosis	–	–	–	–
Subacute thrombosis	±	–	–	–
Late thrombosis	+	–	–	±
Very late thrombosis	+	±	–/±	+/±
Neointimal hyperplasia	–	–	+	+
Constrictive remodeling	–	+	+	+
Adaptive (expansive) remodeling	+	–	–	+
Restoration of vasomotion	+	–	–	+
Late luminal enlargement	+	–	–	+
Potential for future bypass graft	+	–	–	+

BA, Balloon angioplasty; *BMS,* bare-metal stent; *DES,* drug-eluting stent; *BRS,* bioresorbable scaffold.
+, Positive/beneficial effect; –, negative/no effect; ±, neutral or uncertain effect.

Bioresorption

The ability to control bioresorption to a predictable and desirable level is important in the success of BRS technology. The mechanism, speed, and byproducts of the resorption process are also important determinants of material suitability. Lactide- and glycolide-based polymers undergo gradual hydrolysis, which leads to the formation of water-soluble, low-molecular-weight components that are metabolized into carbon dioxide and water (Fig. 34-2). PLLA-based BRS usually has a combination of semicrystalline polymers to provide mechanical strength and amorphous polymers to allow uniform dispersion of the drug and loss of integrity at the desired time.[16] The duration of the degradation process depends on the crystallization of the polymer and varies from 2 to 4 years.[16]

The process of iron bioresorption is quite slow and involves the oxidation of ferrous ion to ferric ion or interaction with nearby cells. Magnesium bioresorption occurs via corrosion, which is accelerated in an acidic milieu. The corrosion rate of the magnesium alloy varies from 2 to 12 months by amalgamating the alloy with other rare metals.[24,25] Lu and colleagues[26] reported a novel approach to control the degradation of the magnesium-based alloys, allowing drug release by the fabrication of a composite two-layer coating film, one for control of the biocorrosion rate of the magnesium alloy and one for the control of the drug-release rate. The magnesium scaffolds are metabolized to their chloride, oxide, sulfate, or phosphate salts. The byproduct in the vessel is hydroxyapatite, which is eventually digested by macrophages.

HISTORIC DEVELOPMENT OF BIORESORBABLE SCAFFOLDING TECHNOLOGY

The first bioresorbable scaffold, made of a polymer of PLLA, was developed in the early 1980s by Stack and coworkers[27] and implanted in

TABLE 34-2 Physical Properties of Materials for Coronary Stents/Scaffolds

Material	Tensile Strength (MPa)	Tensile Elasticity (GPa)	Elongation at Break (%)	Degradation Time (Mo)
Nitinol	700	45	10 to 20	Biostable
Stainless steel 316L	668	193	>40	Biostable
Cobalt-chromium	1449	210 to 235	40	Biostable
Magnesium alloy	220 to 330	40 to 45	2 to 20	1 to 3
Poly-L-lactide	60 to 70	3.1 to 3.7	2 to 6	>24
Poly-D,L-lactide	45 to 55	3.1 to 3.7	2 to 6	6 to 12
Polyglycolide	90 to 110	6.5 to 7.0	1 to 2	6 to 12

MPa, Megapascal; *GPa,* gigapascal.

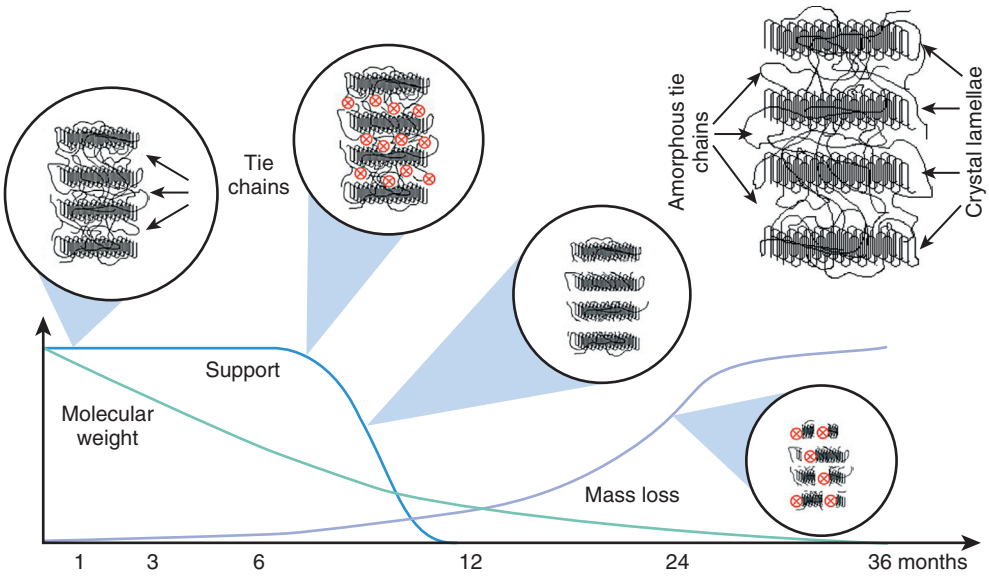

FIGURE 34-1 Mechanical disintegration of a bioresorbable scaffold, which first undergoes reduction in molecular weight, then loss of strength, and finally mass loss.

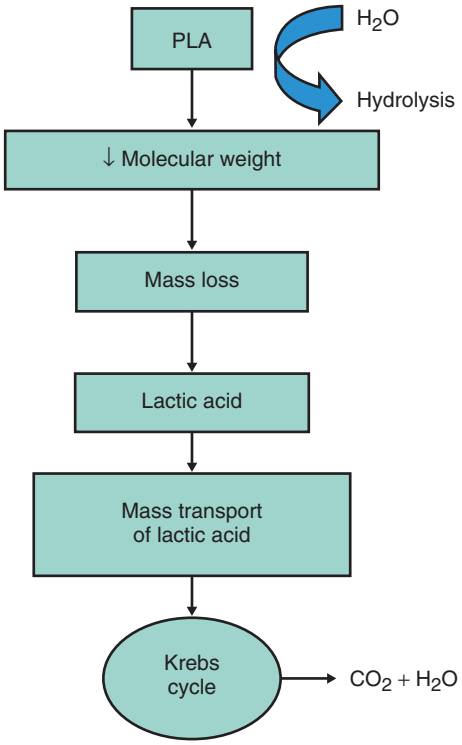

FIGURE 34-2 Metabolic bioresorption of polymeric scaffolds. Hydrolysis process eventually converts bioresorbable polymers into carbon dioxide and water. *PLA,* Polylactic acid.

animal models at Duke University in the 1990s. Subsequent work at Kyoto University, the Thorax Centre, and Mayo and Cleveland Clinics has elucidated different properties of the various polymers. However, the technology failed to develop for the lack of an ideal polymer at that stage (low-molecular-weight polylactides were associated with an intense inflammatory neointimal response)[28] and for the advent of metallic DESs.[16]

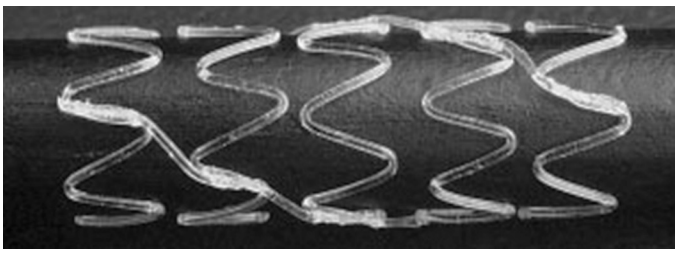

FIGURE 34-3 Igaki-Tamai scaffold. The Igaki-Tamai is a poly-L-lactic acid scaffold with a helical zigzag design.

Igaki-Tamai (Igaki Medical Planning Company, Kyoto, Japan), a monofilamentous 183-kDa PLLA-based fully bioresorbable scaffold without any drug coating, was the first device of its kind to be evaluated in man (Fig. 34-3). This system was self-expanding but also required contrast heated at 70° to 80° C and 30-second balloon inflation. A first-in-man (FIM) trial ($n = 15$) was reported in 2000 and showed no stent thrombosis (ST) or major adverse cardiac events (MACEs) at 30 days and only one case of TLR at a 6-month follow-up.[29] Angiographic restenosis rates of 5.3% and 10.5% were reported, with a loss index of 0.44 and 0.48 mm at 3 and 6 months, respectively.[29] The study reported no deaths, myocardial infarction (MI), or coronary artery bypass grafting (CABG). Long-term follow-up of the Igaki-Tamai scaffold has demonstrated a good safety profile.[30,31] Over 10 years of follow-up of the first 50 patients (63 lesions) treated with 84 Igaki-Tamai scaffolds, TLR rates were 16% at 1 year, 18% at 5 years, and 28% at 10 years. Only two cases of definite ST were recorded. Survival rates free of death and cardiac death at 10 years were 87% and 98%, respectively.[31] Despite these promising results and the possibility to reduce restenosis by adding an antiproliferative drug,[32] this device failed to become a mainstream player because of concerns about use of the heated contrast in coronary arteries.

CURRENT LANDSCAPE OF POLYMERIC BIORESORBABLE SCAFFOLD DEVICES

The Absorb (Abbott Vascular, Temecula, CA) and DESolve (Elixir Medical, Sunnyvale, CA) devices have achieved CE mark. The

TABLE 34-3 Summary of Design and Structure of Clinically Tested Bioresorbable Scaffolds

Scaffold (Manufacturer)	Strut Material	Coating Material	Eluted Drug	Strut Thickness	Crossing Profile	Radiopacity	Radial Support	Resorp. (Months)	Current Status
				POLYMERIC					
Igaki-Tamai (Kyoto Medical)	PLLA	None	None	170	N/A	Gold markers	6 mo	24-36	CE mark for peripheral use
BVS 1.0 (Abbott Vascular)	PLLA	PDLLA	Everolimus	156	1.4 mm	Platinum markers	Weeks	18-24	Disc.
BVS 1.1 (Abbott Vascular)	PLLA	PDLLA	Everolimus	156	1.4 mm	Platinum markers	6 mo	24-48	CE mark
DESolve (Elixir)	PLLA	None	Myolimus	150	1.5 mm	Metallic markers	N/A	12-24	CE mark
REVA (Reva Medical)	PTD-PC	None	None	200	1.8 mm	Radiopaque scaffold	3-6 mo	24	Disc.
ReZolve (Reva Medical)	PTD-PC	None	Sirolimus	115-230	1.8 mm	Radiopaque scaffold	4-6 mo	4-6	Clinical trials
ReZolve2 (Reva Medical)		None	Sirolimus		1.5 mm	Radiopaque scaffold			
ART 18AZ (ART)	PDLLA	None	None	170	N/A 6-Fr compatible	None	3-6 mo	3-6	Clinical trials
Fortitude (Amaranth)	PLLA	None	None	150-200	N/A 6-Fr compatible	None	3-6 mo	3-6	Clinical trials
IDEAL BTI (Xenogenics)	Polylactide and salicylates	SA/AA	Sirolimus	200	1.5-1.7 mm	None	3 mo	6-9	Clinical trials
				METALLIC					
AMS-1 (Biotronik)	Mg alloy	None	None	165	1.2 mm	None	Weeks	<4	Disc.
DREAMS-1 (Biotronik)	Mg alloy with some rare metals	PLGA	Paclitaxel	125	N/A 6-Fr compatible	None	3-6 mo	9	Clinical trials
DREAMS-2 (Biotronik)	Mg alloy with some rare metals	PLLA	Sirolimus	150	N/A 6-Fr compatible	Metallic markers	3-6 mo	9	Clinical trials

BVS, Bioresorbable vascular scaffold; *Disc.,* discontinued; *Mg,* magnesium; *N/A,* not available; *PDLLA,* poly-DL-lactic acid; *PLGA,* poly(lactide-*co*-glycolide) polymer matrix; *PLLA,* poly-L-lactic acid; *SA/AA,* salicylic acid/adipic acid; *PTD-PC,* poly-tyrosine-derived polycarbonate; *Resorp.,* resorption.

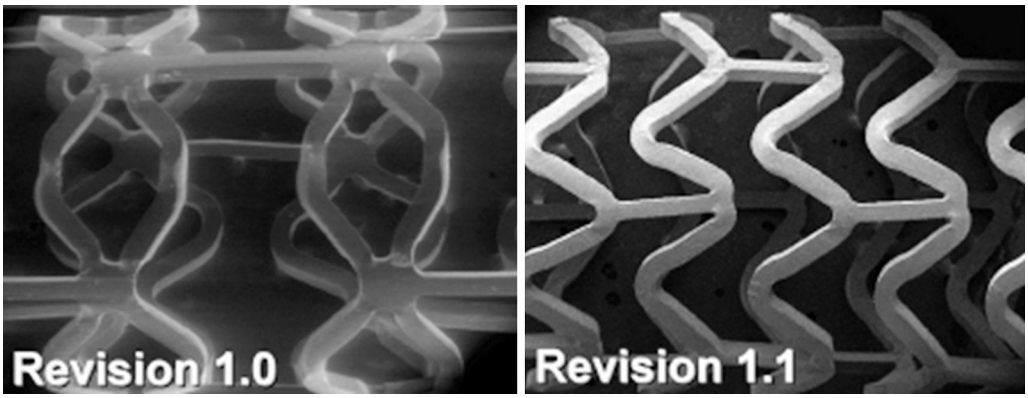

FIGURE 34-4 Bioresorbable vascular scaffold (BVS; Abbott Vascular, Santa Clara, California) system. The BVS is a balloon-expandable, everolimus-eluting bioresorbable scaffold. Revision 1.1 is commercially available.

structure and design of the BRS devices currently being evaluated in clinical studies are shown in Table 34-3.

Absorb Bioresorbable Vascular Scaffold

The Absorb bioresorbable vascular scaffold (BVS) is an everolimus-eluting BRS composed of PLLA and PDLLA. The first-generation scaffold, BVS 1.0, consisted of circumferential hoops of PLLA; the design was changed in the second-generation device, BVS 1.1, to in-phase zigzag hoops linked by bridges (Fig. 34-4) to give better radial strength. The manufacturing process for the polymer was also modified to achieve slower hydrolysis and thus preserve mechanical integrity for a longer period.[16]

The Absorb BVS 1.0 was tested in ABSORB Cohort A. This multicenter single-arm (n = 30) study demonstrated late lumen enlargement, feasibility of noninvasive imaging with computed tomography

TABLE 34-4 Summary of Clinical Trials With Bioresorbable Scaffolds

Scaffold	Clinical Study	*N*	Major End Points	Late Loss (mm)	TLR	MACE
			POLYMERIC			
Igaki-Tamai	Igaki-Tamai study	15	Acute recoil, late loss, and MACE at 6 mo	0.48 at 6 mo	6.7% at 6 mo	6.7% at 6 mo
BVS 1.0	ABSORB Cohort A	30	Acute success, MACE up to 5 yr	0.44 at 6 mo	0% at 6 mo, 0% at 5 yr	3.3% at 6 mo, 3.4% at 5 yr
BVS 1.1	ABSORB Cohort B	101	LLL, TLR, and MACE at 6 mo and at 1, 2, and 3 yr	0.19 at 6 mo 0.27 at 12 mo	3.6% at 12 mo	9% at 2 yr 10% at 3 yr
DESolve	DESolve 1 DESolve NX	15 120	LLL at 6 mo Procedural success, LLL at 6 mo, MACE up to 5 yr	0.19 at 6 mo 0.21 at mo	6.7 % at 12 mo 1.6% at 6 mo	20% at 12 mo 3.25% at 6 mo
REVA	RESORB	27	MACE	1.81 at 6 mo	66.7% at 6 mo	
ReZolve	RESTORE	50	TLR at 6 mo, LLL at 12 mo	0.20 at 12 mo for $n = 8$	2 out of 12 (16.7%) at 6 mo	2 out of 12 (16.7%) at 6 mo
			METALLIC			
AMS-1	PROGRESS-AMS	63	MACE at 4 mo	1.08 at 4 mo	24% at 4 mo	24% at 4 mo
DREAMS-1	BIOSOLVE-I	46	Target lesion failure at 6 and 12 mo	0.64 at 6 mo 0.52 at 12 mo	4.3% at 6 mo 6.5% at 12 mo	4.3% at 6 mo 6.5% at 12 mo

LLL, Late lumen loss; *MACE,* major adverse cardiac events; *TLR,* target lesion revascularization.

(CT) scanning, and restoration of vasomotion and endothelial function at 2 years.[33-35] Five-year clinical follow-up showed no ST, only one case of non–Q wave MI, and a MACE rate of 3.4% (Table 34-4).[36] The second-generation device, BVS 1.1, was tested in the ABSORB cohort B clinical investigation. This study was split into two parts: cohort B1 ($n = 45$) underwent invasive imaging with quantitative coronary angiography (QCA), intravascular ultrasound (IVUS), and optical coherence tomography (OCT) at the index procedure and then at 6- and 24-months follow-up, whereas cohort B2 underwent invasive imaging at the index procedure and then at 12- and 36-month follow-up. In the entire cohort B, the MACE rate was 9.0% (3 non–Q wave MIs, 6 ischemia-driven TLRs, and no cardiac deaths) at 2-year follow-up (see Table 34-4). The ABSORB cohort B has completed 3-year follow-up with no cardiac deaths or scaffold thrombosis but 3 MIs (all non–Q wave) and 7 ischemia-driven TLRs, with a MACE rate of 10%. A small head-to-head study to compare the BVS ($n = 31$ lesions) and the XIENCE DES ($n = 19$ lesions) has shown no significant differences in late lumen loss (LLL; 0.18 ± 0.20 mm vs. 0.29 ± 0.36 mm; $P = .42$), percentage of uncovered struts (5.3% vs. 4.5%; $P = .11$), mean neointimal thickness (120.6 ± 46.0 μm vs. 136.1 ± 71.4 μm; $P = .82$), and in-stent/scaffold-area obstruction (12.5% ± 7.1% vs. 13.6% ± 9.7%; $P = .91$) at 12 months.[37]

ABSORB EXTEND is an international, prospective, single-arm study that will recruit over 800 patients with more complex coronary disease than was previously studied in the ABSORB trial. The first patient was enrolled in January 2010. In this study, a 2.5 mm BRS is also introduced, thus allowing for examination of the feasibility of BRS use in small vessels. Additionally, patients with long lesions are not excluded; hence it will be possible to evaluate the potential safety of overlapping devices. At 1 year, for the first 512 patients enrolled in the study, the composite end points of ischemia-driven MACE and ischemia-driven target-vessel failure (TVF) were 4.3% and 4.9%, respectively. The cumulative rate of Academic Research Consortium (ARC)–defined definite and probable scaffold thrombosis for this population was 0.8% at 1 year.[38]

DESolve Bioresorbable Scaffold

The DESolve (Elixir Medical, Sunnyvale CA) drug-eluting BRS system is a PLLA-based scaffold (Fig. 34-5) coated with an antiproliferative drug, novolimus, mounted on a rapid-exchange balloon catheter delivery system. The scaffold incorporates two radiopaque markers at each end to aid in the angiographic assessment of scaffold placement, and it is coated with a matrix of polylactide-based polymer and novolimus at a 5 μg/mm dose. Most of the antiproliferative drug (85%) is released over 4 weeks. The system has a crossing profile of 1.47 mm and is 6-Fr guiding catheter compatible. The DESolve scaffold comes in a broad range of scaffold sizes to provide availability for most patients (diameters of 2.5, 3.0, and 3.5 mm and lengths of 14 and 18 mm).

The DESolve BRS was tested in the DESolve FIM trial, which showed an effective suppression of neointimal hyperplasia at 6 months (see Table 34-4); no significant change in vessel volume (148.0 ± 37.0 mm^3 at baseline and 150.03 ± 35.38 mm^3 at 6 months); and instead of "chronic recoil," a scaffold enlargement (scaffold area 5.35 ± 0.78 mm^2 at baseline and 5.61 ± 0.81 mm^2 at 6 months). At 12 months, no scaffold thrombosis was evident, and no MACEs were directly attributable to the scaffold.[39]

Presented in 2013, the Elixir Medical Clinical Evaluation of the DESolve Novolimus Eluting Bioresorbable Coronary Scaffold System, the DESolve Nx trial ($n = 126$), showed that the primary end point of in-stent LLL was 0.21 mm (± 0.34) at 6 months. IVUS assessment of the scaffolds and vessels at 6 months in a subset of 40 patients demonstrated a significant ($P < .001$) increase in vessel area (17%), mean scaffold area (16%), and mean lumen area (9%). Serial OCT analysis in 38 patients also demonstrated a 17% increase in mean scaffold area ($P < .001$) at 6 months. Nearly 99% of struts were covered by 6 months. The MACE rate was 3.35% and included one cardiac death, one non–Q wave MI, and two cases that required TLR (see Table 34-4).[40] The DESolve has rather rapid drug release (85% over 4 weeks); therefore some concerns exist about the long-term efficacy of the device. A subset of patients will undergo multislice CT assessment at 12 months and angiographic, IVUS, and OCT assessment at 24 months to provide longer-term assessment of the scaffold.

Reva Medical Bioresorbable Scaffolding

Reva Medical (San Diego, CA) makes scaffolding with tyrosine-derived polycarbonate and are both bioresorbable and radiopaque (Fig. 34-6). Reva polymer is based on an iodinated, tyrosine-derived polycarbonate. The polymer degrades into benign metabolites that are cleared from the body, and it was developed to allow the scaffold to maintain

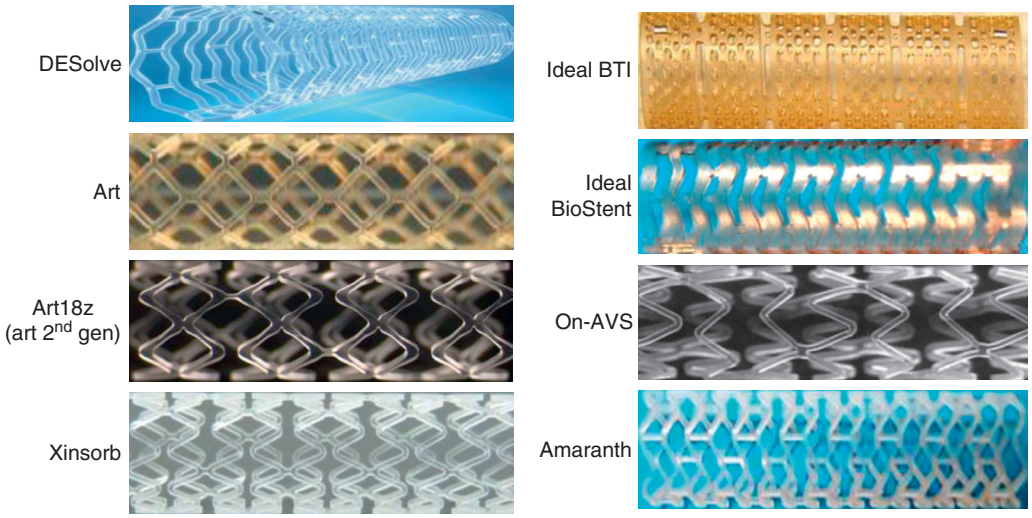

FIGURE 34-5 Design of various polymeric bioresorbable scaffolds in clinical or preclinical studies.

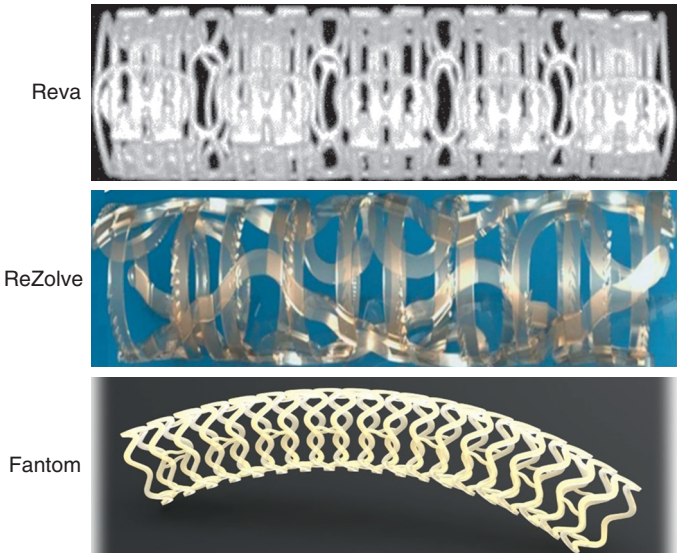

FIGURE 34-6 Designs of different versions of Reva bioresorbable scaffolds.

structural integrity and strength during the first 3 months. At 12 months, the stent no longer has significant mechanical strength, and the polymer continues to resorb and be eliminated from the body. After approximately 4 years, only tiny particles of the original polymer remain. The Reva's patented slide-and-lock mechanism is based on a ratchet system: each "tooth" on the sliding part passes through a bracket in the stent and locks into place as the stent is opened in an artery; this is accomplished by use of a balloon catheter, which prevents it from passing back through. The first-generation non–drug-eluting Reva BRS was evaluated in the Reva Endovascular Study of a Bioresorbable Coronary Stent (RESORB) FIM trial (see Table 34-4). The data showed no vessel recoil (vessel area 15.5 mm^2 post procedure and 15.3 mm^2 at 6 months) but a disappointingly high in-stent LLL and TLR rate.[41] To overcome these limitations, a sirolimus-eluting version, the ReZolve BRS, was developed (see Table 34-3) and is being evaluated in the RESTORE trial (see Table 34-4). Preliminary data on 26 patients with 6 months of follow-up has suggested reasonably good safety and efficacy.[42] However, the technical success rate of the ReZolve was only 85% because of its sheathed delivery system and high crossing profile.[42] Further improvements in design have resulted in Reva's current product, the ReZolve2, which has a sheathless delivery system. The ReZolve2 is being tested in the RESTORE-II study ($n = 125$) to get the data needed to apply for CE Mark. A newer design, the Fantom, is based on similar polymer formulation and elutes sirolimus (see Fig. 34-6); it is being evaluated in a FIM study.

The ART Bioresorbable Scaffold

The ART (Arterial Remodeling Technologies, Paris, France) BRS is made from amorphous semicrystalline PDLLA, so it resorbs relatively rapidly.[43,44] The design includes pairs of out-of-phase zigzag hoops directly joined at their crowns (see Fig. 34-5). The adjacent pairs are linked by two straight bridges. Struts are 170 µm thick, and the scaffold is compatible with a 6-Fr guidewire. The device comprises no antiproliferative drug, and it is hoped that outward vessel remodeling will accommodate intervention-induced intimal hyperplasia, as demonstrated in preclinical studies. Twenty-three BMS devices (3.0 by 12 mm) and 36 lactic acid–based BRSs (3.0 by 11 mm) were implanted in porcine coronary arteries. Acute recoil was comparable between the BRS and the BMS groups (4.6% ± 6.7% vs 4.6% ± 5.1%, $P = .98$).[45] BRS outer diameter increased significantly from 1 to 6 months, indicating positive scaffold remodeling, whereas BMS diameter remained unchanged. LLL decreased significantly from 1 to 6 months in the BRS group ($P = .003$) without any significant difference between BRS and BMS groups at 6 months ($P = .68$). Microcomputed tomography identified BRS dismantling starting at 3 months, and weight-averaged molar masses of scaffold parts were 20% and 14% of their initial values at 3 and 6 months.[45] The Arterial Remodeling Transient Dismantling Vascular Angioplasty (ARTDIVA) FIM trial ($n = 30$) was undertaken to assess the ART device in simple lesions.

Amaranth Bioresorbable Scaffold

The Amaranth Fortitude (Amaranth Medical, Mountain View, CA) is a non–drug-eluting PLLA device with proprietary tube fabrication. The structural integrity of the Amaranth scaffold lasts 3 to 6 months, and the resorption process requires 1 to 2 years. Preliminary experimental studies have shown that the scaffold has a high radial strength, prolonged mechanical stability, and exhibits minimal recoil. A recent report evaluated the performance of the scaffold in porcine models compared with the Liberté BMS (Boston Scientific, Natick, MA). A similar LLL was reported at 28- and 90-day follow-up. However,

thereafter the LLL started to decrease in the Amaranth group, whereas it increased in the Liberté BMS group, from 90-day to 180-day follow-up. OCT examination at the 90-day follow-up revealed a lower neointimal thickness in the Amaranth scaffold compared with that of the BMS. As a result, Amaranth Medical initiated the FIM study to recruit 30 patients in order to evaluate the safety and efficacy of the scaffold.[46] Amaranth has also developed a sirolimus-eluting version of the BRS, which is currently undergoing preclinical testing.

The Ideal Bioresorbable Scaffold

The Xenogenics Ideal BioStent (Xenogenics Corporation, Philadelphia) is a sirolimus-eluting device with a backbone of polylactide anhydride mixed with a polymer of salicylic acid and sebacic acid linker. The presence of salicylic acid provides antiinflammatory properties to the device.[47,48] The Ideal BioStent was tested in the WHISPER FIM trial (n = 11) in 2008. The first-generation device required an 8-Fr guide catheter, and it performed poorly at suppressing neointimal proliferation because of inadequate drug dosing and rapid release of the sirolimus. The second generation Ideal BioStent with a higher sirolimus dose, slower drug release, and a 6-Fr compatible delivery system is currently undergoing preclinical evaluation.[49]

Bioresorbable Scaffolds at Developmental Stages

The Xinsorb (Huaan Biotechnology, China) BRS is a sirolimus-eluting, balloon-expandable polymeric device with a strut thickness of 160 μm, and it has shown good acute performance in animal studies.[50] The MeRes (Meril Life Sciences, Gujarat, India) device is a sirolimus-eluting BRS consisting of a new PLA formulation; it has a hybrid scaffold geometry structure, which gives the scaffold a high radial strength and avoids overexpansion at the edges. The encouraging preliminary data warrant further preclinical studies to investigate the safety and efficacy of the scaffold. The ON-AVS (OrbusNeich, Fort Lauderdale, FL) is a tube-shaped lockable and balloon-expandable BRS. The device consists of three polymeric materials—poly-L-lactide-co-ε-caprolactone, PDLA, and PLLA—and it incorporates a partitioned coating technology that allows for the scaffold to be covered by abluminal sirolimus and luminal endothelial progenitor cell capture (+CD34) antibodies. Preliminary preclinical evaluation demonstrated an optimal device implantation without evidence of fracture.

Other BRS devices include the Fades (Zorion Medical, Indianapolis, IN), Sahajanand (Sahajanand Medical Technologies, Surat, India), Avatar (S3V, Hyderabad, India), and Arterius (Arterius Ltd, Bradford, United Kingdom).

THE CURRENT LANDSCAPE OF METALLIC BIORESORBABLE SCAFFOLD DEVICES

Iron-Based Bioresorbable Scaffolds

Iron is an essential nutrient required by the human body. It serves a vital role as a carrier of oxygen to the tissues from the lungs by red blood cell hemoglobin, as a transport medium for electrons within cells, and as a cofactor for many enzyme systems in various tissues. The slow degradation and small amount of iron in a stent (41 mg) in relation to the iron load of the whole body (400 to 500 mg/L) make any systemic toxicity unlikely. Peuster and colleagues[51] used corrodible iron (>99.8% iron) to produce iron scaffolds (NOR-I; Georg-August University, Goettingen, Germany) and implanted these in the descending aorta of New Zealand white rabbits. During 6 to 18 months of follow-up, no adverse events and no thromboembolic complications were reported, and all the scaffolds were patent at follow-up angiography at 6, 12, and 18 months. Moreover, these scaffolds produced no systemic iron toxicity, local inflammation, or excessive neointimal proliferation. In another study, Waksman and colleagues[52] deployed iron scaffolds and cobalt-chromium stents in the coronary arteries of juvenile domestic pigs. Animals were sacrificed at 28 days, and measured parameters such as intimal thickness, intimal area, and percentage occlusion showed a trend in favor of the iron scaffolds. Iron ions released from bioresorbable iron scaffolds have been shown to reduce proliferation of vascular smooth muscle cells and may therefore reduce in-stent restenosis.[53] Iron-based BRS appeared promising in short-term preclinical studies; however, long-term animal data have not been obtained, and clinical evaluation has yet to be performed, possibly because of concerns about slow degradation time and local or systemic iron-related toxicity.

Magnesium-Based Bioresorbable Scaffolds

Magnesium is preferred because of its biocompatibility in the human body; it is the fourth most common cation in the human body with a daily requirement of 350 mg, and it is essential for the synthesis of over 300 enzymes. The metabolic conversion of magnesium to its chloride, oxide, sulphate, or phosphate salts is well tolerated. The byproduct in the vessel is hydroxyapatite, which is eventually digested by macrophages (Fig. 34-7).

AMS-1 (Biotronik AG, Bülach, Switzerland) was the first magnesium-based BRS evaluated in man in the Clinical Performance and Angiographic Results of Coronary Stenting With Absorbable Metal Stents (PROGRESS-AMS) study (see Table 34-4). The immediate angiographic results were similar to those using metallic stents; however, the radial support was lost within a few weeks after implantation, which resulted in a high rate of recoil and constrictive remodeling.[25] In addition to the mechanical insufficiency, the device was not eluting any antiproliferative drug and hence was associated with a high incidence of late loss and TLR (see Table 34-4). However, no death, MI, or ST occurred. Long-term follow-up data from angiographic and IVUS examination performed in 8 patients who did not require repeat revascularization at 4 months have demonstrated no evidence of either late recoil or late neointimal growth.[54] These findings suggest that the magnesium scaffold was safe but lacked efficacy because of loss of scaffold support and uncontrolled neointimal proliferation. Therefore a drug-eluting version, Dreams, was developed using a refined, more slowly resorbable WE43 alloy with a six-crown three-link design (Fig. 34-8) and with a higher collapse pressure than the AMS-1 (1.5 vs. 0.8 bar). The cross-sectional profile of scaffold struts in Dreams was redesigned to be square as opposed to the rectangular shape of the AMS-1; thereby strut thickness was reduced from 165 to 120 μm. To reduce neointimal growth, the Dreams was coated with a bioresorbable poly(lactide-*co*-glycolide) polymer matrix (PLGA) containing the antiproliferative drug paclitaxel (0.07 μg/mm^2).[55] The Safety and Performance of the Drug-Eluting Absorbable Metal Scaffold (DREAMS) in Patients With de Novo Coronary Lesions (BIOSOLVE-1) FIM trial assessed the safety and performance of this first-generation drug-eluting magnesium-based BRS in 46 patients with 47 lesions at five European centers.[56] During the procedure, all devices were successfully delivered. At 12 months, 3 of 43 patients (7%; 95% confidence interval [CI], 1.7 to 19.3) had target-lesion failure (TLF) with no cardiac death or scaffold thrombosis. The in-scaffold LLL was reduced at 6 months 0.65 (± 0.5 mm) and at 12 months 0.52 (± 0.39 mm) compared with 1.08 mm (± 0.49) of the prior generation bare AMS-1 magnesium scaffold. However, the LLL with Dreams still did not match the excellent results of currently available drug-eluting stents.

The device has been further optimized. Dreams-2 is made of a WE43 alloy with a six-crown two-link design and a strut thickness of 150 μm with radiopaque markers at both ends (made from tantalum), resulting in a slower dismantling and resorption rate. To further reduce the neointimal proliferation, the Dreams 2 is coated with a bioresorbable PLA polymer carrier with sirolimus, which is known to have a more potent antiproliferative effect than paclitaxel.[57] Dreams 2 has completed preclinical assessment and is currently being evaluated in the First in Man Study of the Dreams Second-Generation Drug-Eluting Absorbable Metal Scaffold (BIOSOLVE-II) trial (n = 120) to get the data needed to apply for CE Mark.

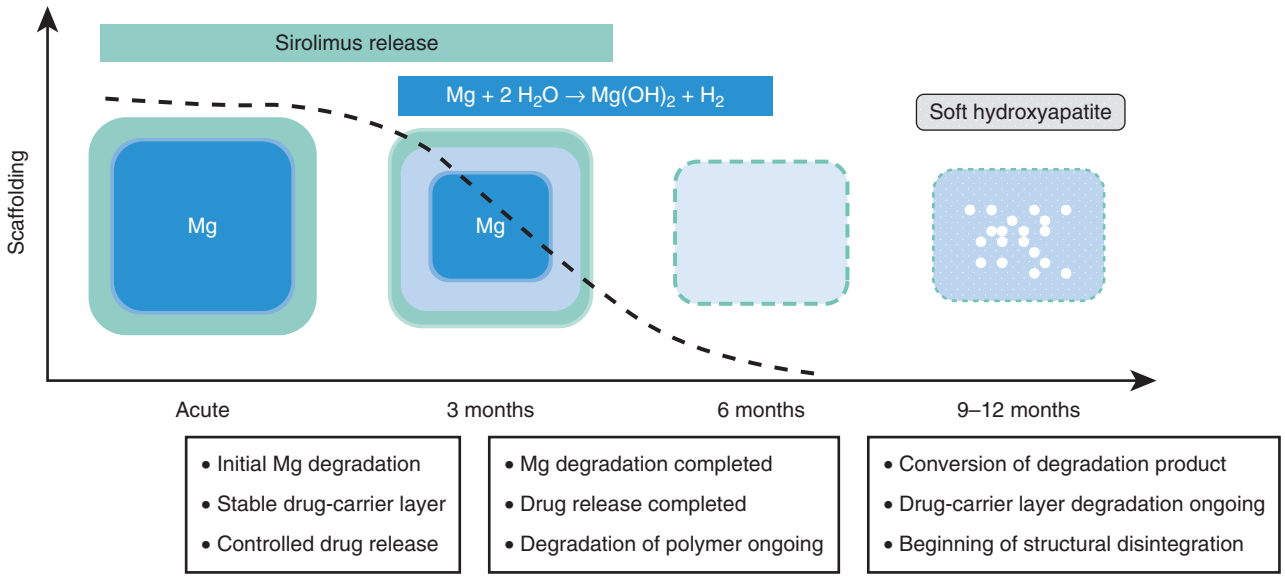

FIGURE 34-7 Designs of different versions of magnesium (Mg)-based bioresorbable scaffolds.

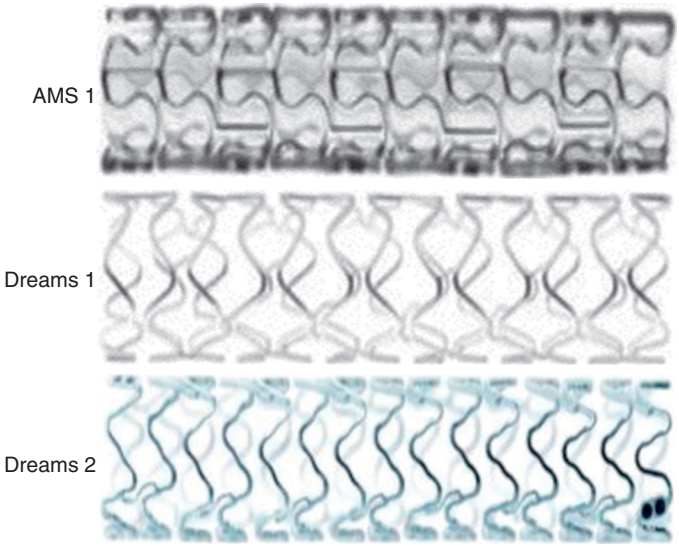

FIGURE 34-8 Device functionality of magnesium-based drug-eluting bioresorbable scaffolds (Biotronik AG, Bülach, Switzerland).

TABLE 34-5 Characteristics of an Ideal Bioresorbable Scaffold

- The scaffold material should have high tensile strength and strain-to-failure capacity before bioresorption to allow creation of a low-profile, balloon-expandable design for easy deliverability and flexibility.
- The scaffold should possess adequate radial strength to provide mechanical support to vessel wall during local healing.
- The scaffold material should have a moderate degradation rate in a predictable fashion over a defined period, leaving no residual matrices.
- The degradation products should be biocompatible and nontoxic and should not cause an excessive inflammatory reaction.
- The scaffold material should not be thrombogenic and should not release emboli that may cause watershed infarcts.
- The scaffold material should be easily processed and sterilizable.
- The scaffold should have an acceptable shelf life.
- The scaffold should be noninferior to conventional stents at early stages and superior at long-term follow-up for clinical outcomes.

CRITICAL EVALUATION OF WHAT A BIORESORBABLE SCAFFOLD CAN OFFER

Table 34-5 outlines the characteristics of an ideal BRS.

Acute Performance

Ideally, the scaffolding provided by BRS in the first few months should be as good as that provided by conventional metal stents. Metallic BRS has good radial strength and low recoil. In a simulated bench test, a magnesium-based AMS device matched the recoil characteristics and radial strength of permanent metal stents, but larger strut dimensions were required to achieve this.[58] However, concerns exist about acute stent recoil and radial strength of polymeric BRS devices. The DESolve scaffold has also been shown to maintain radial strength and vessel support for the first 3 to 4 months. For the Absorb BVS, a comparison of BVS 1.0 ($n = 27$) with XIENCE-V ($n = 27$) demonstrated no statistical difference in absolute acute recoil (BVS 0.20 ± 0.21 mm vs. XIENCE-V 0.13 ± 0.21 mm, $P = .32$) or percentage acute recoil (BVS 6.9% ± 7.0% vs. XIENCE-V 4.3% ± 7.1%, $P = .25$).[59] The newer-generation BVS 1.1 has acute recoil similar to the BVS 1.0.[60] Although these data show no statistical difference in acute recoil of polymeric and metallic stents, there is a numerical difference, and concerns about acute performance of polymeric devices persist. With a number of new devices being developed, it is important that these be tested for acute recoil in vivo.[50]

Bioresorption

In the ABSORB trial, multiple imaging modalities were used to assess the bioresorption of BVS devices. IVUS virtual histology (IVUS-VH) misinterprets polymeric struts as pseudodense calcium, so there was an increase in the mean pseudodense calcium (9.8% vs. 25.4%, $P <$ .001) immediately after implantation, which was reduced by 30% at the 6-month follow-up and remained stable between 6 months and 2 years.[34,61] On echogenicity analysis, both calcified plaques and polymeric struts appear as hyperechogenic tissue. There was a significant reduction in echogenicity from after the procedure to the 6-month

follow-up (18.5% ± 9.1% vs. 10.3% ± 7.6%, $P < .001$), and a further reduction occurred between 6 months and 2 years (10.3% ± 7.6% vs. 7.7% ± 6.5%, $P = .005$). By 2 years, echogenicity returned to the preprocedural level.[61] On serial OCT analysis, a 35% reduction was seen in the number of visible struts from baseline to the 2-year follow-up.[61] The complete bioresorption of the device has yet to be shown but is expected at the 5-year follow-up. For Reva devices, it has been shown that by 4 years, only tiny particles of the original polymer remain. For Dreams, OCT demonstrated that at 6 months, 86% of the scaffold struts were discernible, which decreased to 61% at 12 months, reflecting continuing resorption. Furthermore, serial IVUS-VH analysis done in nine patients showed a significant decrease in dense calcium at 6 months (15.4% reduction) and at 12 months (12.9% reduction) compared with postprocedure levels, without significant changes in necrotic core area over time. The decrease in dense calcium was therefore interpreted as a surrogate marker for the bioabsorption of the scaffold.[56]

Restoration of Vascular Physiology

In ABSORB cohort A, evaluation of the scaffolded segment following intraluminal administration of acetylcholine suggested that at 2 years, the scaffolding function of the polymeric struts had completely disappeared, and the scaffolded segment could exhibit vasomotion.[62] A positive acetylcholine test with vasodilatation of the scaffold also provided an indirect proof that the endothelial lining was intact and functional, so that the biochemical process of nitric oxide release was working efficiently. This observation corroborates with transmission electron microscopy findings in a porcine model, which showed maturation of endothelial junctions between 1 and 36 months with dense intercellular desmosomes at 3 years.[61] It has also been shown that implantation of the Absorb BVS leads to a significant decrease in vascular compliance, measured on palpography and described as Rotterdam Classification score /mm, at the scaffolded segment (from 0.37 [interquartile range 0.24 to 0.45] to 0.14 [interquartile range 0.09 to 0.23], $P < .001$) with mismatch in compliance in a paired analysis between the scaffolded and adjacent segments (proximal 0.23 [95% CI, 0.12 to 0.34], scaffold 0.12 [95% CI, 0.07 to 0.19], distal 0.15 [95% CI, 0.05 to 0.26], $P = .042$). This compliance mismatch disappears at short- and mid-term follow-up.[63] Magnesium BRS devices have also demonstrated the recovery of the responsiveness of the treated vessel to vasoactive agents.[64]

Prevention of Very Late Thrombotic Events

After bioresorption of the BRS, the treated segment of the vessel will return to normal function and will be free of a permanent foreign body, thus potentially minimizing the risk of very late thrombotic events and the need for long-term DAPT. BRS can potentially eliminate certain factors that contribute to the late ST including delayed endothelialization, chronic inflammatory response, and localized hypersensitivity reaction.[65] It has been shown that the incidence of very late ST is significantly lower using a DES with a biodegradable polymer compared with a DES with a durable polymer (0.4% vs. 1.8%, $P = .004$).[11] It is notable that a recently reported study has shown that even balloon angioplasty has a risk of very late thrombosis, suggesting that a BRS may not be able to eliminate this complication,[66] and indeed cases of late scaffold thrombosis have been reported after BVS implantation.[67] Long-term follow-up data will prove whether a BRS can reduce this potentially fatal complication.

Passivation of Vulnerable Plaques

In theory, BRS implantation may provide a symmetric, uniform, fibrous neointimal layer, which along with late lumen enlargement and lack of any permanent vascular prosthesis may help to stabilize and passivate vulnerable plaques and thus prevent future cardiovascular events.[63] The idea is appealing and is indirectly supported by studies on the concept of plaque passivation by stents[68] and BRS providing a symmetric and circumferential thick fibrous cap with functional endothelium, late lumen enlargement, and normal shear stress distribution.[63] The uniform neointimal layer may work as a thick fibrous cap and may seal the underlying plaque.[69] IVUS analysis of the Absorb BVS between 6 months and 2 years also revealed a significant plaque media reduction (12.7%) without a significant change in the vessel wall area.[18,70] This potential transformation of vulnerable lesions to stable plaques is an interesting hypothesis that needs further validation. The PROSPECT-ABSORB substudy will prospectively evaluate the role of BVS for this indication.

CURRENT CHALLENGES

Optimizing Bioresorbable Scaffolding Technology

To achieve adequate radial strength, current BRS devices have thicker struts (typically 150 to 200 μm) than contemporary metallic stents (about 80 μm). However, newer devices with 100 to 120 μm are likely to appear soon. It would be important to demonstrate that these devices have comparable radial strength and acute recoil.

Polymeric devices also have inherent limit of expansion and can break as a result of overdilation. Although the radial strength of bioresorbable vascular scaffolding (BVS) has been reported to be comparable to metallic stents, this is true if the BVS is deployed within the limits of its size; if it is overstretched beyond its designed limits, it may lose some of its radial strength and may indeed fracture.[71] Currently, it is vital to have adequate lesion preparation, appropriately sizing the reference vessel and respecting the nominal size of the scaffolding. However, it is essential to further improve this technology to allow a degree of stretchability without compromising device performance.

Use in All-Comer Populations

The initial clinical studies have obviously restricted the use of BRS devices to simple lesions. Hence, concerns exist for their use in patients with complex lesions and tortuous or calcified vessels. There are small case series for use of BRS for PCI of the left main stem,[72] small diameter (≤2.5 mm) vessels,[73] calcific lesions, long lesions with overlapping stents, in-stent restenosis, bifurcations,[74] and chronic total occlusions (Fig. 34-9). Early data for use of BRS in all-comer patients appear promising,[75] but further data with larger sample sizes and long-term follow-up are needed.

Use in Acute Coronary Syndromes

Safety and efficacy data for BRS use in acute coronary syndromes (ACSs) are not yet widely available. A recent small registry has suggested that a BVS device may be used safely and effectively in patients with STEMI undergoing primary PCI.[76] Gori and colleagues[77] deployed BVS for 150 consecutive patients with ACS (194 lesions) and compared outcomes with a control group composed of 103 consecutive patients (129 lesions) who underwent everolimus drug-eluting stent (DES) implantation around the same time. Procedural success was obtained in all but two patients in the BVS group. In-hospital 30-day and 6-month MACE rates (of death, nonfatal MI, or reintervention) were similar between both groups. Definite or probable in-stent/scaffold thrombosis occurred in two BVS patients and one DES patient during the index admission, and it occurred in another patient in each group in the first month after BVS/DES implantation. Diletti and colleagues[78] evaluated the feasibility and acute performance of BVS for the treatment of patients presenting with ST-segment elevation myocardial infarction (STEMI) in a prospective, single-arm, single-center study ($n = 49$). The procedural success was 97.9%. Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow was achieved in 91.7% of patients, and the postprocedure percentage diameter stenosis (DS) was 14.7% (± 8.2%). No patients had angiographically visible residual thrombus at the end of the procedure. OCT analysis performed in 31

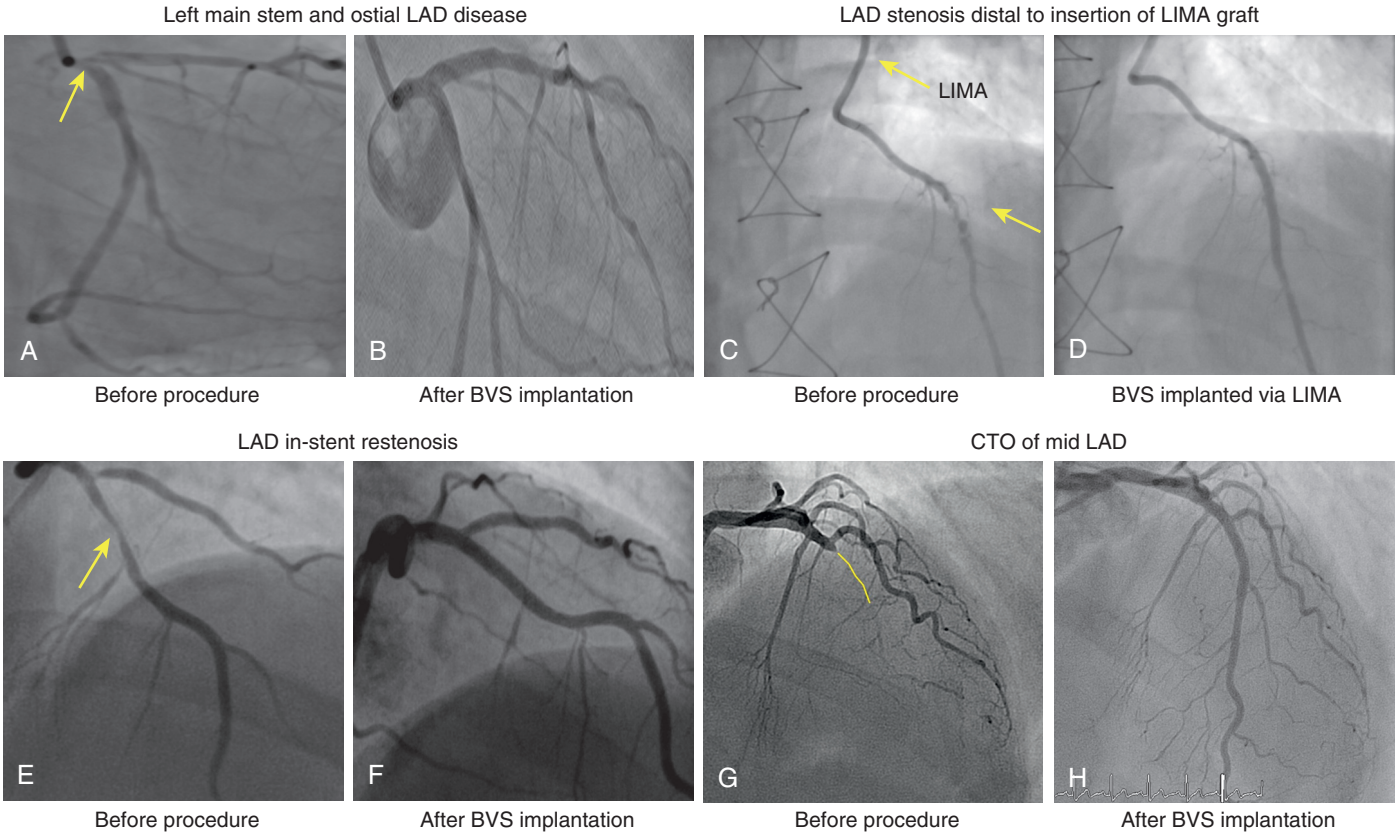

FIGURE 34-9 Absorb biovascular scaffold (BVS) use in complex coronary artery disease. Left main stem and ostial left anterior descending (LAD) coronary artery disease (**A**) treated with provisional strategy using a BVS (**B**). Patient with severe native coronary artery disease and previous coronary artery bypass grafting (CABG) developed stenosis of the LAD just distal to the insertion of a left internal mammary artery (LIMA) graft (**C**), which was successfully treated by placing a BVS device from the LIMA into the LAD (**D**). A patient with in-stent restenosis of a previously deployed mid-LAD stent (**E**) was successfully treated by implantation of a BVS within the previous stent (**F**). Chronic total occlusion (CTO) of the LAD (**G**) was treated with BVS implantation (**H**) with good angiographic results.

patients showed that the postprocedure mean lumen area was 8.02 mm^2 (± 1.92), minimum lumen area was 5.95 mm^2 (± 1.61), mean incomplete scaffold apposition area was 0.118 mm^2 (± 0.162), and mean intraluminal defect area was 0.013 mm^2 (± 0.017). At the 30-day follow-up, no TLF, cardiac death, or scaffold thrombosis was reported. However, no randomized data are yet available.

Need for Long-Term Outcomes Data

Limited data from 10-year follow-up of Igaki-Tamai and 5-year follow-up of ABSORB cohort A appear promising. However, most of the data for BRS use are derived from small, nonrandomized studies with short- or midterm follow-up, and further studies are warranted. ABSORB-II is a prospective, randomized controlled trial that aims to compare the safety and efficacy of the BVS 1.1 versus the Xience stent in 501 patients with stable angina and one- or two-vessel disease randomized on a 2:1 basis.[79] Clinical follow-up is planned at 30- and 180-days and at 1, 2, and 3 years. All subjects will undergo coronary angiography and IVUS at baseline (before and after device implantation) and at 2-year follow-up. The primary end points are the superiority of the Absorb BVS for vasomotion of the treated segment at 2 years and noninferiority for angiographic minimum lumen diameter at 2 years. An interim analysis at 1-year follow-up showed a smaller postprocedural lumen diameter or area in the ABSORB BVS group (1.15 mm vs. 1.46 mm, $P < .0001$; 2.85 mm^2 vs. 3.60 mm^2, $P < .0001$; respectively). BVS-treated patients were less likely to have angina at 1 year (ABSORB BVS 22% vs. XIENCE 30%, $P = .04$). One definite acute, one definite subacute, and one probable late scaffold thrombosis were found in the ABSORB BVS group as opposed to no stent thrombosis in the XIENCE group. There was 5% of MACE in the ABSORB BVS group compared with 3% events in the XIENCE group (MI: 4% vs. 1%; clinical-driven TLR: 1% vs. 2%; for ABSORB BVS vs. XIENCE, respectively). The final report of the ABSORB II trial regarding the primary and secondary endpoint is expected in coming years. Another study, ABSORB Physiology, is planned to assess the acute and long-term effect of BVS compared with conventional metallic drug-eluting stents in terms of impact on vascular compliance, distensibility, endothelial responsiveness, and changes in the shear stress distribution after device/stent implantation and at 2 years follow-up. ABSORB-III is a prospective, randomized, single-blind, multicenter trial to compare the Absorb BVS ($n = 1267$) with the Xience DES ($n = 633$). The primary end point is noninferiority for TLF at 1 year. ABSORB-IV will include an additional 3000 patients randomized 1:1 with Xience, and combined with subjects in ABSORB-III, it will evaluate patient-reported angina at the end of 1 year and a reduction in TLF between 1 and 5 years.

CONCLUSION AND FUTURE DIRECTIONS

The concept of a bioresorbable scaffold to treat coronary stenosis is inherently appealing with a multitude of potential benefits. Further refinement in the structure and design of the scaffolds may be

required to overcome the current limitations. It remains to be proven whether BRS devices can be used safely and effectively in an all-comers population, including those with acute coronary syndromes and complex coronary artery disease. Furthermore, superiority of BRS devices over current-generation DESs for clinical outcomes at long-term follow-up need to be proved in adequately powered, randomized controlled trials. However, the data from clinical studies to date appear promising, and we remain optimistic about the future of bioresorbable scaffolds.

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REFERENCES

1. Iqbal J, Gunn J, Serruys PW: Coronary stents: historical development, current status and future directions. *Br Med Bull* 106:193–211, 2013.
2. Serruys PW, de Jaegere P, Kiemeneij F, et al: A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med* 331(8):489–495, 1994.
3. Fischman DL, Leon MB, Baim DS, et al: A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med* 331(8):496–501, 1994.
4. Hoffmann R, Mintz GS, Dussaillant GR, et al: Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. *Circulation* 94(6):1247–1254, 1996.
5. Gordon PC, Gibson CM, Cohen DJ, et al: Mechanisms of restenosis and redilation within coronary stents–quantitative angiographic assessment. *J Am Coll Cardiol* 21(5):1166–1174, 1993.
6. Stone GW, Ellis SG, Cox DA, et al: A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 350(3):221–231, 2004.
7. Morice MC, Serruys PW, Sousa JE, et al: A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 346(23):1773–1780, 2002.
8. McFadden EP, Stabile E, Regar E, et al: Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 364(9444):1519–1521, 2004.
9. Lagerqvist B, James SK, Stenestrand U, et al: Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med* 356(10):1009–1019, 2007.
10. Stone GW, Rizvi A, Newman W, et al: Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med* 362(18):1663–1674, 2010.
11. Stefanini GG, Kalesan B, Serruys PW, et al: Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4-year follow-up of a randomised non-inferiority trial. *Lancet* 378(9807):1940–1948, 2011.
12. Iqbal J, Sumaya W, Tatman V, et al: Incidence and predictors of stent thrombosis: a single-centre study of 5,833 consecutive patients undergoing coronary artery stenting. *EuroIntervention* 9(1):62–69, 2013.
13. Waksman R: Biodegradable stents: they do their job and disappear. *J Invasive Cardiol* 18(2):70–74, 2006.
14. Wykrzykowska JJ, Onuma Y, Serruys PW: Vascular restoration therapy: the fourth revolution in interventional cardiology and the ultimate "rosy" prophecy. *EuroIntervention* 5(Suppl F):F7–F8, 2009.
15. Vert M: Bioabsorbable polymers in medicine: an overview. *EuroIntervention* 5(Suppl F):F9–F14, 2009.
16. Onuma Y, Serruys PW: Bioresorbable scaffold: the advent of a new era in percutaneous coronary and peripheral revascularization? *Circulation* 123(7):779–797, 2011.
17. Gomez-Lara J, Garcia-Garcia HM, Onuma Y, et al: A comparison of the conformability of everolimus-eluting bioresorbable vascular scaffolds to metal platform coronary stents. *JACC Cardiovasc Interv* 3(11):1190–1198, 2010.
18. Serruys PW, Garcia-Garcia HM, Onuma Y: From metallic cages to transient bioresorbable scaffolds: change in paradigm of coronary revascularization in the upcoming decade? *Eur Heart J* 33(1):16–25b, 2012.
19. Wentzel JJ, Whelan DM, van der Giessen WJ, et al: Coronary stent implantation changes 3-D vessel geometry and 3-D shear stress distribution. *J Biomech* 33(10):1287–1295, 2000.
20. Gyongyosi M, Yang P, Khorsand A, Glogar D: Longitudinal straightening effect of stents is an additional predictor for major adverse cardiac events. Austrian Wiktor Stent Study Group and European Paragon Stent Investigators. *J Am Coll Cardiol* 35(6):1580–1589, 2000.
21. Gomez-Lara J, Brugaletta S, Farooq V, et al: Angiographic geometric changes of the lumen arterial wall after bioresorbable vascular scaffolds and metallic platform stents at 1-year follow-up. *JACC Cardiovasc Interv* 4(7):789–799, 2011.
22. Okamura T, Serruys PW, Regar E: Cardiovascular flashlight: the fate of bioresorbable struts located at a side branch ostium: serial three-dimensional optical coherence tomography assessment. *Eur Heart J* 31(17):2179, 2010.
23. Moravej M, Mantovani D: Biodegradable metals for cardiovascular stent application: interests and new opportunities. *Int J Mol Sci* 12(7):4250–4270, 2011.
24. Waksman R, Pakala R, Kuchulakanti PK, et al: Safety and efficacy of bioabsorbable magnesium alloy stents in porcine coronary arteries. *Catheter Cardiovasc Interv* 68(4):607–617, discussion 618–609, 2006.
25. Erbel R, Di Mario C, Bartunek J, et al: Temporary scaffolding of coronary arteries with bioabsorbable magnesium stents: a prospective, non-randomised multicentre trial. *Lancet* 369(9576):1869–1875, 2007.
26. Lu P, Cao L, Liu Y, et al: Evaluation of magnesium ions release, biocorrosion, and hemocompatibility of MAO/PLLA-modified magnesium alloy WE42. *J Biomed Mater Res B Appl Biomater* 96(1):101–109, 2011.
27. Stack RS, Califf RM, Phillips HR, et al: Interventional cardiac catheterization at Duke Medical Center. *Am J Cardiol* 62(10 Pt 2):3f–24f, 1988.
28. Lincoff AM, Furst JG, Ellis SG, et al: Sustained local delivery of dexamethasone by a novel intravascular eluting stent to prevent restenosis in the porcine coronary injury model. *J Am Coll Cardiol* 29(4):808–816, 1997.
29. Tamai H, Igaki K, Kyo E, et al: Initial and 6-month results of biodegradable poly-l-lactic acid coronary stents in humans. *Circulation* 102(4):399–404, 2000.
30. Onuma Y, Garg S, Okamura T, et al: Ten-year follow-up of the IGAKI-TAMAI stent. A posthumous tribute to the scientific work of Dr. Hideo Tamai. *EuroIntervention* 5(Suppl F):F109–F111, 2009.
31. Nishio S, Kosuga K, Igaki K, et al: Long-Term (>10 years) clinical outcomes of first-in-human biodegradable poly-l-lactic acid coronary stents: Igaki-Tamai stents. *Circulation* 125(19):2343–2353, 2012.
32. Yamawaki T, Shimokawa H, Kozai T, et al: Intramural delivery of a specific tyrosine kinase inhibitor with biodegradable stent suppresses the restenotic changes of the coronary artery in pigs in vivo. *J Am Coll Cardiol* 32(3):780–786, 1998.
33. Serruys PW, Ormiston JA, Onuma Y, et al: A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. *Lancet* 373(9667):897–910, 2009.
34. Bruining N, Tanimoto S, Otsuka M, et al: Quantitative multimodality imaging analysis of a bioabsorbable poly-L-lactic acid stent design in the acute phase: a comparison between 2- and 3D-QCA, QCU and QMSCT-CA. *EuroIntervention* 4(2):285–291, 2008.
35. Garcia-Garcia HM, Gonzalo N, Pawar R, et al: Assessment of the absorption process following bioabsorbable everolimus-eluting stent implantation: temporal changes in strain values and tissue composition using intravascular ultrasound radiofrequency data analysis. A substudy of the ABSORB clinical trial. *EuroIntervention* 4(4):443–448, 2009.
36. Onuma Y, Dudek D, Thuesen L, et al: Five-year clinical and functional multislice computed tomography angiographic results after coronary implantation of the fully resorbable polymeric everolimus-eluting scaffold in patients with de novo coronary artery disease: the ABSORB cohort A trial. *JACC Cardiovasc Interv* 6(10):999–1009, 2013.
37. Gomez-Lara J, Brugaletta S, Farooq V, et al: Head-to-head comparison of the neointimal response between metallic and bioresorbable everolimus-eluting scaffolds using optical coherence tomography. *JACC Cardiovasc Interv* 4(12):1271–1280, 2011.
38. Abizaid A, Costa JR, Jr, Bartorelli AL, et al: The ABSORB EXTEND study: preliminary report of the twelve-month clinical outcomes in the first 512 patients enrolled. *EuroIntervention* 2014; pii: 20130827-06. [Epub ahead of print].
39. Verheye S, Ormiston JA, Stewart J, et al: A next-generation bioresorbable coronary scaffold system: from bench to first clinical evaluation: 6- and 12-month clinical and multimodality imaging results. *JACC Cardiovasc Interv* 7(1):89–99, 2014.
40. Abizaid A: *First report on the Pivotal DESolve Nx Trial: 6-month clinical and multi-modality imaging results*, Paris, France, 2013, EuroPCR.
41. Grube E: Bioabsorbable stent. *The Boston Scientific and REVA technology*, Barcelona, 2009, EuroPCR.
42. Costa RA: *REVA ReZolve clinical program update*, Miami Beach, 2012, Transcatheter Cardiovascular Therapeutics.
43. Lafont A, Durand E: A.R.T.: concept of a bioresorbable stent without drug elution. *EuroIntervention* 5(Suppl F):F83–F87, 2009.
44. Durand E, Lemitre M, Couty L, et al: Adjusting a polymer formulation for an optimal bioresorbable stent: a 6-month follow-up study. *EuroIntervention* 8(2):242–249, 2012.
45. Durand E, Sharkawi T, Leclerc G, et al: Head-to-head comparison of a drug-free early programmed dismantling polylactic acid bioresorbable scaffold and a metallic stent in the porcine coronary artery: six-month angiography and optical coherence tomographic follow-up study. *Circ Cardiovasc Interv* 7(1):70–79, 2014.
46. Iqbal J: *A non–drug-eluting PLLA scaffold with high flexibility and strength*, Paris, France, 2013, EuroPCR.
47. Jabara R, Chronos N, Robinson K: Novel bioabsorbable salicylate-based polymer as a drug-eluting stent coating. *Catheter Cardiovasc Interv* 72(2):186–194, 2008.
48. Jabara R, Pendyala L, Geva S, et al: Novel fully bioabsorbable salicylate-based sirolimus-eluting stent. *EuroIntervention* 5(Suppl F):F58–F64, 2009.
49. Jabara R: Bio-mechanical properties and ABC of bioresorption of adipic acid. *PCR focus group on bioresorbable vascular scaffolds*, The Netherlands, 2012, Rotterdam.
50. Wu Y, Shen L, Wang Q, et al: Comparison of acute recoil between bioabsorbable poly-L-lactic acid XINSORB stent and metallic stent in porcine model. *J Biomed Biotechnol* 2012:413956, 2012.
51. Peuster M, Wohlsein P, Brugmann M, et al: A novel approach to temporary stenting: degradable cardiovascular stents produced from corrodible metal-results 6-18 months after implantation into New Zealand white rabbits. *Heart* 86(5):563–569, 2001.
52. Waksman R, Pakala R, Baffour R, et al: Short-term effects of biocorrodible iron stents in porcine coronary arteries. *J Interv Cardiol* 21(1):15–20, 2008.
53. Mueller PP, May T, Perz A, et al: Control of smooth muscle cell proliferation by ferrous iron. *Biomaterials* 27(10):2193–2200, 2006.
54. Waksman R, Erbel R, Di Mario C, et al: Early- and long-term intravascular ultrasound and angiographic findings after bioabsorbable magnesium stent implantation in human coronary arteries. *JACC Cardiovasc Interv* 2(4):312–320, 2009.
55. Wittchow E, Adden N, Riedmuller J, et al: Bioresorbable drug-eluting magnesium-alloy scaffold: design and feasibility in a porcine coronary model. *EuroIntervention* 8(12):1441–1450, 2013.
56. Haude M, Erbel R, Erne P, et al: Safety and performance of the drug-eluting absorbable metal scaffold (DREAMS) in patients with de-novo coronary lesions: 12 month results of the prospective, multicentre, first-in-man BIOSOLVE-I trial. *Lancet* 381(9869):836–844, 2013.
57. Kollum M, Heitzer T, Schmoor C, et al: Intra-individual head-to-head comparison of Sirolimus®- and Paclitaxel®-eluting stents for coronary revascularization. A randomized, multi-center trial. *Int J Cardiol* 167(4):1552–1559, 2013.
58. Grogan JA, Leen SB, McHugh PE: Comparing coronary stent material performance on a common geometric platform through simulated bench testing. *J Mech Behav Biomed Mater* 12:129–138, 2012.
59. Tanimoto S, Serruys PW, Thuesen L, et al: Comparison of in vivo acute stent recoil between the bioabsorbable everolimus-eluting coronary stent and the everolimus-eluting cobalt chromium coronary stent: insights from the ABSORB and SPIRIT trials. *Catheter Cardiovasc Interv* 70(4):515–523, 2007.
60. Onuma Y, Serruys PW, Gomez J, et al: Comparison of in vivo acute stent recoil between the bioresorbable everolimus-eluting coronary scaffolds (revision 1.0 and 1.1) and the metallic everolimus-eluting stent. *Catheter Cardiovasc Interv* 78(1):3–12, 2011.
61. Onuma Y, Serruys PW, Perkins LE, et al: Intracoronary optical coherence tomography and histology at 1 month and 2, 3, and 4 years after implantation of everolimus-eluting bioresorbable vascular scaffolds in a porcine coronary artery model: an attempt to decipher the human optical coherence tomography images in the ABSORB trial. *Circulation* 122(22):2288–2300, 2010.
62. Brugaletta S, Heo JH, Garcia-Garcia HM, et al: Endothelial-dependent vasomotion in a coronary segment treated by ABSORB everolimus-eluting bioresorbable vascular scaffold system is related to plaque composition at the time of bioresorption of the polymer: indirect finding of vascular reparative therapy? *Eur Heart J* 33(11):1325–1333, 2012.
63. Brugaletta S, Gogas BD, Garcia-Garcia HM, et al: Vascular compliance changes of the coronary vessel wall after bioresorbable vascular scaffold implantation in the treated and adjacent segments. *Circ J* 76(7):1616–1623, 2012.
64. Ghimire G, Spiro J, Kharbanda R, et al: Initial evidence for the return of coronary vasoreactivity following the absorption of bioabsorbable magnesium alloy coronary stents. *EuroIntervention* 4(4):481–484, 2009.
65. Di Mario C, Borgia F: Assimilating the current clinical data of fully bioabsorbable stents. *EuroIntervention* 5(Suppl F):F103–F108, 2009.

66. Yamaji K, Kimura T, Morimoto T, et al: Very long-term (15 to 23 years) outcomes of successful balloon angioplasty compared with bare metal coronary stenting. *J Am Heart Assoc* 1(5):e004085, 2012.
67. ABSORB EXTEND Investigators: Lessons learned from acute and late scaffold failures in the ABSORB EXTEND trial. *EuroIntervention* 10(4):449–457, 2014.
68. Wykrzykowska JJ, Diletti R, Gutierrez-Chico JL, et al: Plaque sealing and passivation with a mechanical self-expanding low outward force nitinol vShield device for the treatment of IVUS and OCT-derived thin cap fibroatheromas (TCFAs) in native coronary arteries: report of the pilot study vShield Evaluated at Cardiac hospital in Rotterdam for Investigation and Treatment of TCFA (SECRITT). *EuroIntervention* 8(8):945–954, 2012.
69. Brugaletta S, Radu MD, Garcia-Garcia HM, et al: Circumferential evaluation of the neointima by optical coherence tomography after ABSORB bioresorbable vascular scaffold implantation: can the scaffold cap the plaque? *Atherosclerosis* 221(1):106–112, 2012.
70. Ormiston JA, Serruys PW, Onuma Y, et al: First serial assessment at 6 months and 2 years of the second generation of absorb everolimus-eluting bioresorbable vascular scaffold: a multi-imaging modality study. *Circ Cardiovasc Interv* 5(5):620–632, 2012.
71. Ormiston JA, De Vroey F, Serruys PW, Webster MW: Bioresorbable polymeric vascular scaffolds: a cautionary tale. *Circ Cardiovasc Interv* 4(5):535–538, 2011.
72. Fernández D, Brugaletta S, Martin-Yuste V, et al: First experience of a bioresorbable vascular scaffold implantation in left main stenosis. *Int J Cardiol* 168(2):1566–1568, 2013.
73. Diletti R, Farooq V, Girasis C, et al: Clinical and intravascular imaging outcomes at 1 and 2 years after implantation of absorb everolimus eluting bioresorbable vascular scaffolds in small vessels. Late lumen enlargement: does bioresorption matter with small vessel size? Insight from the ABSORB cohort B trial. *Heart* 99(2):98–105, 2013.
74. Capranzano P, Gargiulo G, Capodanno D, et al: Treatment of coronary bifurcation lesions with bioresorbable vascular scaffolds. *Minerva Cardioangiol* 62(3):229–234, 2014.
75. Costopoulos C, Latib A, Naganuma T, et al: Comparison of early clinical outcomes between ABSORB bioresorbable vascular scaffold and everolimus-eluting stent implantation in a real-world population. *Catheter Cardiovasc Interv* 85(1):E10–E15, 2015.
76. Kajiya T, Liang M, Sharma RK, et al: Everolimus-eluting bioresorbable vascular scaffold (BVS) implantation in patients with ST-segment elevation myocardial infarction (STEMI). *EuroIntervention* 9(4):501–504, 2013.
77. Gori T, Schulz E, Hink U, et al: Early outcome after implantation of Absorb bioresorbable drug-eluting scaffolds in patients with acute coronary syndromes. *EuroIntervention* 9(9):1036–1041, 2014.
78. Diletti R, Karanasos A, Muramatsu T, et al: Everolimus-eluting bioresorbable vascular scaffolds for treatment of patients presenting with ST-segment elevation myocardial infarction: BVS STEMI first study. *Eur Heart J* 35(12):777–786, 2014.
79. Diletti R, Serruys PW, Farooq V, et al: ABSORB II randomized controlled trial: A clinical evaluation to compare the safety, efficacy, and performance of the Absorb everolimus-eluting bioresorbable vascular scaffold system against the XIENCE everolimus-eluting coronary stent system in the treatment of subjects with ischemic heart disease caused by de novo native coronary artery lesions: rationale and study design. *Am Heart J* 164(5):654–663, 2012.

35 The Role of Adjunct Devices: Atherectomy, Cutting Balloon, and Laser

JOHN A. BITTL

KEY POINTS

- Rotational and orbital atherectomy have useful roles in the facilitation of stent implantation in undilatable, rigid, or heavily calcified lesions.
- Cutting and scoring balloons slip less often within restenotic or ostial lesions than do conventional balloons.
- Laser angioplasty uses a thermomechanical mechanism, not photodissociation, to modify rigid or undilatable lesions for stent implantation.
- Atheroablative procedures do not lower complications or reduce restenosis when compared with percutaneous transluminal coronary angioplasty (PTCA) in randomized controlled trials.
- Atheroablative devices cause more coronary perforations than do conventional balloons.
- The use of most atheroablative devices requires advanced technical skills.

The past 25 years have seen several mechanical approaches that ablate or section atheromatous plaque during percutaneous coronary intervention (PCI) to optimize acute results and reduce restenosis. Although hundreds of small mechanistic studies have reported promising findings, dozens of clinical trials have failed to demonstrate that a strategy of plaque ablation achieves better clinical outcomes than PTCA alone,[1] and thus the routine use of atheroablative approaches during PCI has not found support.[2] In specific circumstances, however, the use of atheroablative devices is beneficial, and in selected cases, such devices are the only means of achieving procedural and clinical success.[3] This chapter analyzes the results of clinical trials and illustrates the complementary but essential role that atheroablative devices play in the current practice of interventional cardiology.

HISTORICAL BACKGROUND

Before the modern era of coronary stenting, the search for treatments to overcome the shortcomings of PTCA was based on experimental studies, which showed that the healing response of treated coronary arteries was directly proportional to the degree of imposed injury.[4] This was supported by angiographic analyses, which suggested that the degree of late restenosis was directly proportional to the gain achieved acutely during treatment and that a constant ratio defined the relation between late loss and acute gain for a broad range of interventional devices.[5] The decades-long search for a mechanical approach to excise or section atheromatous plaque emerged from the hypothesis that plaque excision improves clinical outcomes and lowers the rate of restenosis after PCI. Directional coronary atherectomy (DCA) entered clinical trials in 1987. Excimer laser coronary angioplasty (ELCA) and percutaneous transluminal rotational atherectomy (PTRA) appeared in 1988. Holmium laser angioplasty (HLA) premiered in 1990, cutting balloon angioplasty (CBA) debuted in 1991, and the newest ablative device, orbital atherectomy (OA), entered investigation in 2008.

Although each device used a different mechanism for modifying atheromatous plaque, the common goal was to obtain larger lumens, higher success rates, and lower restenosis rates than could be achieved with balloon PTCA alone. However, evidence from randomized trials (Table 35-1)[1,6-32] challenged the ablation hypothesis, and the introduction of coronary stenting (Chapter 16) rapidly replaced atheroablative therapies. Clinical guidelines now specify that no atheroablative device should be used routinely during PCI.[2] The guidelines add the provision that rotational atherectomy is reasonable for fibrotic or heavily calcified lesions that might not be crossed by a balloon catheter or adequately dilated with high-pressure balloons before stent implantation (class IIa).[2] Cutting and scoring balloons might be considered to reduce slippage and trauma during PCI for in-stent restenosis (ISR) or ostial lesions in side branches (class IIb).[2] Laser angioplasty might be considered for fibrotic or moderately calcified lesions that cannot be crossed or dilated with high-pressure balloons before stent implantation (class IIb).[2] Each of the ablative approaches in current practice is reviewed in the following sections.

PERCUTANEOUS TRANSLUMINAL ROTATIONAL ATHERECTOMY

Mechanism of Action

Percutaneous transluminal rotational atherectomy (PTRA) excavates tissue and reduces lesion rigidity by attacking calcified atherosclerotic plaque like a dental drill, which bores into enamel but leaves pulp unharmed. Based on the theory of differential cutting, rotary ablation pulverizes rigid atherosclerotic plaque, which is not able to deflect, and yet preserves the integrity of the flexible artery wall. The hard plaque is abraded into small particles that average 5 µm in diameter and are taken up by the reticuloendothelial system.

Equipment

The Rotablator system (SciMed/Boston Scientific, Natick, MA) contains: (1) the RotaLink preconnected, exchangeable burr and advancing device that houses an air turbine, drive shaft, and burr; (2) a console that regulates the air supply and monitors the rotation of the burr; and (3) a DynaGlide foot pedal to activate the device. The burr has an abrasive tip that is welded to a long flexible drive shaft covered by a plastic sheath, and it tracks over a central coaxial RotaWire (0.009-inch diameter, 3.3-m length) that has a flexible radiopaque platinum distal part (20 mm-length) that does not rotate during abrasion. The wire and the burr can be advanced independently.

The nickel-coated brass burr is elliptical with 2000 to 3000 microscopic diamond crystals on the leading face (Fig. 35-1). The diamond crystals are 20 µm in size with only 5 µm protruding from the nickel coating, and the trailing edge of the burr is smooth. Burrs are available in various diameters that range from 1.25 to 2.50 mm in 0.25-mm increments.

During rotation, saline solution irrigates the catheter sheath to lubricate and cool the rotating parts. The number of revolutions per minute (rpm) is measured by a fiberoptic light probe and is displayed on a control panel. The Advancer has preset delimiters for retraction and advancement. The wireClip Torquer and guidewires are critical components of the system. RotaGlide lubricant may be useful for crossing resistant lesions.

TABLE 35–1 Randomized Trials Comparing Atheroablative or Thrombectomy Devices

Acronym	Definition	Primary End Point*	Patients (*N*)	Year†	Indications	Comparison
AMIGO[6]	Atherectomy Before Multi-Link Improves Luminal Gain and Clinical Outcomes	Binary restenosis	753	2002	Native vessel	DCA vs. PTCA
AMRO[7]	Amsterdam Rotterdam Randomized Trial	6-month MACE	308	1993	Native vessel	ELCA vs. PTCA
ARTIST[8]	Angioplasty/Rotational Atherectomy for Treatment of Diffuse In-Stent Restenosis Trial	6-month MACE	298	2002	ISR in native vessel	PTRA vs. PTCA
BETACUT[10]	Beta Radiation Assisted by Cutting Balloon Angioplasty for In-Stent Restenosis	Binary restenosis	100	2002	ISR in native vessel	CBA vs. PTCA before BT
BOAT[11]	Balloon/Optimal Atherectomy Trial	Binary restenosis	989	1995	Native vessel	DCA vs. PTCA
CAPAS[12]	Cutting Balloon Atherotomy Versus Plain Old Balloon Angioplasty Study	Binary restenosis	232	1997	Native vessel	CBA vs. PTCA
CARAT[13]	Coronary Angioplasty and Rotablator Atherectomy Trial	Postprocedure diameter stenosis	222	2000	Native vessel	PTRA vs. PTRA
CAVEAT-I[14]	Coronary Angioplasty Versus Excisional Atherectomy Trial I	Binary restenosis	1012	1992	Native vessel	DCA vs. PTCA
CAVEAT-II[15]	Coronary Angioplasty Versus Excisional Atherectomy Trial II	Binary restenosis	305	1993	SVG	DCA vs. PTCA
CBASS[18]	Cutting Balloon for Small-Size Vessels‡	Binary restenosis	99	1999	Native vessels <2.6 mm	CBA vs. PTCA
CCAT[16]	Canadian Coronary Atherectomy Trial	Binary restenosis	274	1992	LAD	DCA vs. PTCA
COBRA[17]	Comparison of Balloon Angioplasty/Rotational Atherectomy	Binary restenosis	502	1996	Native vessel	PTRA vs. PTCA
CUBA[18]	Cutting Balloon Versus Conventional Balloon Angioplasty Trial‡	Binary restenosis	306	1997	Native vessel	CBA vs. PTCA
DART[19]	Dilation/Ablation Revascularization Trial	Binary restenosis	446	1998	Small vessel	PTRA vs. PTCA
ERBAC[21]	Excimer Rotablator Balloon Angioplasty Comparison	Procedural success	454	1996	Native vessel	ELCA vs. PTCA
ERBAC[21]	Excimer Rotablator Balloon Angioplasty Comparison	Procedural success	453	1996	Native vessel	PTRA vs. PTCA
GRT[23]	Global Randomized Trial	Binary restenosis	1238	1997	Native vessel	CBA vs. PTCA
LAVA[26]	Laser Angioplasty/ Coronary Angioplasty	6-month MACE	215	1997	Native vessel	HLA vs. PTCA
REDUCE 1[1]	Restenosis Reduction by Cutting Balloon Evaluation 1‡	Binary restenosis	802	2001	Native vessel	CBA vs. PTCA
REDUCE 2[18]	Restenosis Reduction by Cutting Balloon Evaluation 2‡	Binary restenosis	492	2002	ISR	CBA vs. PTCA
REDUCE 3[27]	Restenosis Reduction by Cutting Balloon Evaluation 3	Binary restenosis	521	2003	Stenting	CBA vs. PTCA
RESCUT[28]	Restenosis Cutting Balloon Evaluation	Binary restenosis	428	2002	ISR	CBA vs. PTCA
ROSTER[29]	Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-Stent Restenosis	Target lesion revascularization	200	2001	ISR	PTRA vs. PTCA
ROTAXUS[32]	Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease	In-stent late lumen loss	120	2013	Native vessel calcified lesions	PTRA vs. PTCA
SPORT[1]	Stenting Post Rotational Atherectomy Trial‡	30-day MACE	735	1999	Native vessel calcified lesions	PTRA vs. PTCA
STRATAS[30]	Study to Determine Rotablator System and Transluminal Angioplasty Strategy	Acute success	497	2000	Native vessel	PTRA vs. PTRA

BT, Brachytherapy; *CBA,* cutting balloon atherotomy; *DCA,* directional coronary atherectomy; *ELCA,* excimer laser coronary angioplasty; *HLA,* holmium laser angioplasty; *ISR,* in-stent restenosis; *PTCA,* percutaneous transluminal coronary angioplasty; *LAD,* proximal segment of the left anterior descending artery; *MACE,* major adverse cardiac event (death, myocardial infarction, or revascularization); *PTRA,* percutaneous transluminal rotational atherectomy; *SVG,* saphenous vein graft.
*If the primary end point was not stated or if multiple primary end points were listed, the end point used in power calculations for sample size estimation was used.
†Year that patient recruitment was completed. Otherwise, the year the study was reported or published.
‡Unpublished, with data approved by investigators where cited.[1]

Procedure

All patients are pretreated with aspirin and usually with a calcium antagonist. The size of the guide catheter depends on the size of the burr. A 6-Fr Runway Guide (Boston Scientific) with a 0.070-inch inner lumen accommodates a 1.25-mm burr, allowing conversion to PTRA if an undilatable or uncrossable lesion is encountered during PTCA.

Rotary ablation is preceded by administering an anticoagulant, placing the RotaWire across the lesion, and parking the unfolded wire tip in a straight segment of the distal vessel, not in a side branch. When treating large coronary arteries, particularly the right coronary artery, many cardiologists insert a prophylactic temporary pacemaker because of the possibility of bradyarrhythmias. Before advancing the burr into the guide catheter, the rotational speed of the burr is checked outside

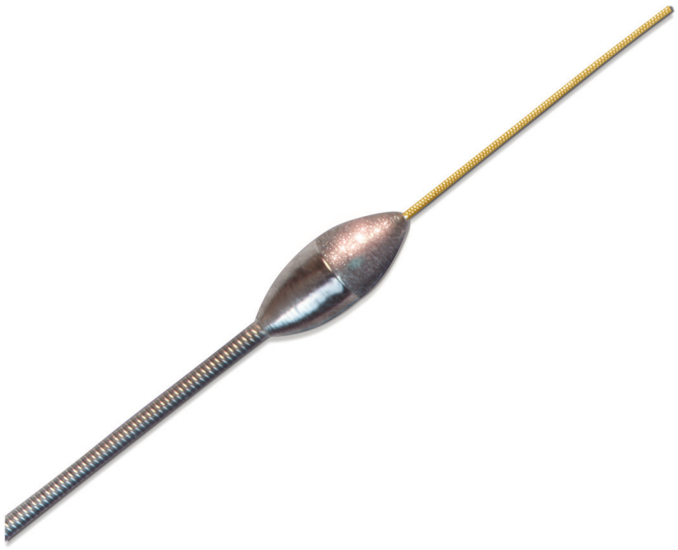

FIGURE 35-1 Rotablator burr. (Courtesy Boston Scientific, Natick, MA.)

the body at the Y-adaptor with flush running. An outside-body speed of 155,000 rpm translates to an unimpeded speed of 140,000 rpm within the coronary artery.

The burr and the drive shaft are manually advanced over the guidewire to a proximal segment of the target vessel. Before rotablation, a three-point checklist is completed to prevent abrupt burr advancement and vessel dissection: (1) the advancer knob is loosened and moved back and forth approximately 5 mm to unload stored tension on the drive cable; (2) the Y-adaptor is loosened to unload stored tension in the Rotablator sheath; and (3) the DynaGlide mode is activated at lower rotational speeds to unload any residual tension within the system. After the operator confirms that the burr moves freely, the device is advanced into the target lesion at therapeutic rotational speeds of 140,000 rpm. Compared with speeds of 190,000 rpm that were commonly used in the past, lower rotational speeds are associated with less platelet activation and aggregation. The burr is moved into the target lesion with a pecking motion that maintains a high speed of rotation. Decelerations of greater than 5000 rpm are avoided to reduce the risk of vessel trauma, heat formation, and large particle generation. Ablation runs are limited to 15 to 20 seconds each. If the lesion cannot be crossed after five attempts, the rotational speed may be increased to 160,000 rpm. If the procedure is unsuccessful because the lesion cannot be crossed, downsizing of the burr may be required. After successful crossing, a polishing run completes lesion preparation for definitive treatment, most commonly using a stent.

Clinical Results

Several trials have defined the optimal use of PTRA. The Study to Determine Rotablator and Transluminal Angioplasty Strategy (STRATAS) trial[30] compared an aggressive debulking strategy (burr/artery ratio of 0.7 to 0.9 followed by balloon inflation of less than 1 atm or no inflation) with a moderate debulking strategy (burr/artery ratio of less than 0.7 followed by conventional balloon angioplasty). The clinical success was similar, but the aggressive strategy caused more myocardial infarctions (11% vs. 7%) and a higher rate of restenosis (58% vs. 52%). The Coronary Angioplasty and Rotablator Atherectomy Trial (CARAT)[13] compared a large-burr strategy (burr/artery ratio >0.7) with a small-burr strategy (burr/artery ratio <0.7). The large-burr strategy achieved similar immediate lumen enlargement and rate of target-vessel revascularization (TVR) as the small-burr strategy but caused more angiographic complications (12.7% vs. 5.2%, $P < .05$). These two trials are the basis for recommending a single burr for each procedure, with sizing based on a burr/artery ratio of 0.5 to 0.6.

In a series of multicenter randomized trials,[1,8,17,19,21,32] rates of major adverse cardiac events (MACEs) at 30 days and rates of angiographic restenosis were higher after PTRA than after balloon PTCA alone (Fig. 35-2).

Lesion Selection

Because PTRA confers a slightly increased risk, it should be used selectively.[3] Most interventional laboratories find that they must maintain expertise with PTRA, because approximately 1% to 3% of lesions that can be crossed with a guidewire are uncrossable with balloon catheters or are undilatable at pressures higher than 20 atm. Rotational atherectomy successfully improves the compliance of most of these rigid lesions, allowing balloon dilation and stent implantation to be completed successfully (Fig. 35-3). For long calcified lesions, small burrs are recommended to alter the compliance of the vessel to allow balloon angioplasty and spot stenting of the segments with dissection (Fig. 35-4). Rotational atherectomy continues to fill an important role in contemporary practice to facilitate the dilation or stenting of lesions that cannot be crossed or expanded with balloon angioplasty.[3]

Certain precautions need emphasis. Angulated lesions located in a bend of more than 60 degrees are a relative contraindication to the use of PTRA, and lesions in a bend greater than 90 degrees are a strong contraindication because of the risk of dissection or perforation. When PTRA is performed in nonangulated lesions, the rotating burr should never be advanced to the point of contact with the spring tip of the RotaWire. The rotating burr should not be allowed to remain in one location within the artery; a gentle retraction and readvancement motion is needed to avoid dissection formation and welding. The rotating burr should not be advanced within the guide catheter. Rotational atherectomy should be avoided in dissected segments after balloon angioplasty, in lesions with visible thrombus, and in degenerated saphenous vein grafts (SVGs).

ORBITAL ATHERECTOMY

Mechanism of Action

Although orbital atherectomy (OA) shares common features with PTRA, it has a different mechanism of action that is based on the principle of elliptical burr movement, in which rotational speed determines the effective burr size.[3] The OA device uses an eccentrically mounted, diamond-coated crown (Fig. 35-5) that orbits over an atherectomy wire at speeds of 80,000 to 120,000 rpm.[33] Repeated passes of the crown across a calcified lesion "sands" away rigid plaque but allows elastic tissue to flex away from the crown. The orbital diameter of the crown expands radially via centrifugal force. The elliptical orbit may allow blood to flow around the crown during treatment, theoretically dispersing heat more efficiently and generating smaller particles than PTRA.[33]

Equipment

The Diamondback 360° Orbital Atherectomy System (Cardiovascular Systems, St. Paul, MN) works on a 0.012-inch, 325-cm ViperWire. The system is composed of a handheld device and an atherectomy controller.

Procedure

Several technical aspects of the OA procedure (Fig. 35-6) are similar to those used during PTRA, but some differences are highlighted. The procedure is initiated by crossing the coronary lesion with the ViperWire. Orbital atherectomy is performed with devices having crown

	Rotational atherectomy (PTRA)		PTCA	
30-Day mortality	**N**	**%**	**N**	**%**
ARTIST[8]	0/152	(0.0)	1/146	(0.7)
COBRA[17]	1/252	(0.4)	4/250	(1.6)
DART[19]	1/227	(0.4)	0/219	(0.0)
ERBAC[21]	2/231	(0.9)	2/222	(0.9)
ROTAXUS[32]	2/120	(1.7)	0/120	(0.0)
Total (OR 0.8 [0.3, 2.5])	**6/982**	**(0.6)**	**7/957**	**(0.7)**
30-Day MI				
ARTIST[8]	7/152	(4.6)	2/146	(1.4)
COBRA[17]	10/252	(4.0)	5/250	(2.0)
DART[19]	5/227	(2.2)	3/219	(1.4)
ERBAC[21]	8/231	(3.5)	8/222	(3.6)
Total (OR 1.6 [0.9, 3.0])	**30/862**	**(3.5)**	**18/837**	**(2.2)**
30-Day MACE				
ARTIST[8]	13/152	(8.6)	7/146	(4.8)
COBRA[17]	25/252	(9.9)	19/250	(7.6)
DART[19]	12/227	(5.3)	5/219	(2.3)
ERBAC[21]	7/231	(3.0)	6/222	(2.7)
ROTAXUS[32]	5/120	(4.2)	5/120	(4.2)
SPORT[1]	9/360	(2.5)	5/375	(1.3)
Total (OR 1.5 [1.1, 2.2])	**71/1342**	**(5.3)**	**47/1332**	**(3.5)**
Angiographic restenosis				
ARTIST[8]	80/124	(64.5)	62/121	(51.2)
COBRA[17]	80/163	(49.1)	87/170	(51.2)
DART[19]	55/108	(50.9)	56/111	(50.5)
ERBAC[21]	86/145	(59.3)	51/109	(46.8)
ROTAXUS[32]	15/124	(12.1)	17/123	(13.8)
SPORT[1]	82/269	(30.5)	73/263	(27.8)
Total (OR 1.2 [1.0, 1.5])	**398/932**	**(42.7)**	**346/906**	**(38.2)**
Cumulative revascularization				
ARTIST[8]	60/152	(39.5)	46/146	(31.5)
COBRA[17]	54/252	(21.4)	60/250	(24.0)
DART[19]	64/227	(28.2)	61/219	(27.9)
ERBAC[21]	90/205	(43.9)	64/191	(33.5)
ROSTER[29]	28/100	(28.0)	40/100	(40.0)
SPORT[1]	53/360	(14.7)	61/375	(16.3)
Total (OR 1.0 [0.9, 1.2])	**349/1296**	**(26.9)**	**333/1281**	**(26.0)**
Cumulative MACE				
ARTIST[8]	31/152	(20.4)	13/146	(8.9)
COBRA[17]	75/210	(35.7)	75/213	(35.2)
DART[19]	59/227	(26.0)	54/219	(24.7)
ERBAC[21]	94/205	(45.9)	70/191	(36.6)
ROSTER[29]	40/100	(40.0)	53/100	(53.0)
SPORT[1]	63/360	(17.5)	51/375	(13.6)
Total (OR 1.2 [1.0, 1.4])	**362/1254**	**(28.9)**	**316/1244**	**(25.4)**

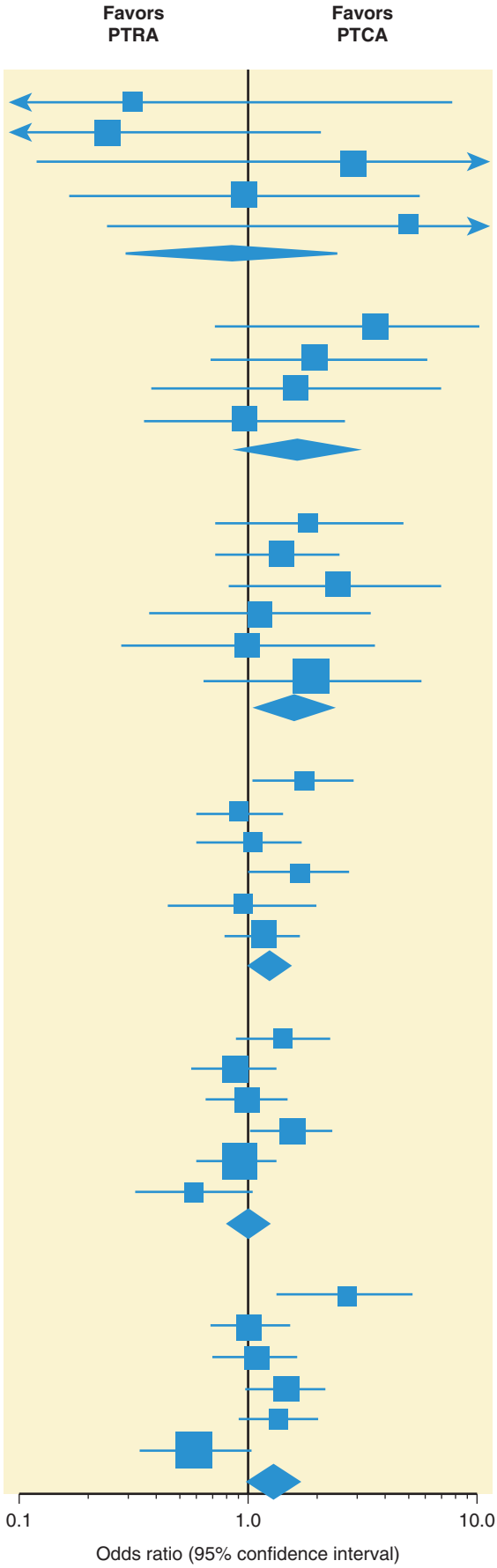

FIGURE 35-2 Systematic overview of randomized trials of percutaneous transluminal rotational atherectomy (PTRA) versus percutaneous transluminal coronary angioplasty (PTCA). Pooled odds ratios (ORs) and 95% confidence intervals are presented, and trial abbreviations are given in Table 35-1. *MACE,* Major adverse cardiovascular event; *MI,* myocardial infarction. (Updated and reprinted from Bittl JA, Chew DP, Topol EJ, et al: Meta-analysis of randomized trials of percutaneous transluminal coronary angioplasty versus atherectomy, cutting balloon atherotomy, or laser angioplasty. *J Am Coll Cardiol* 43:936-942, 2004.)

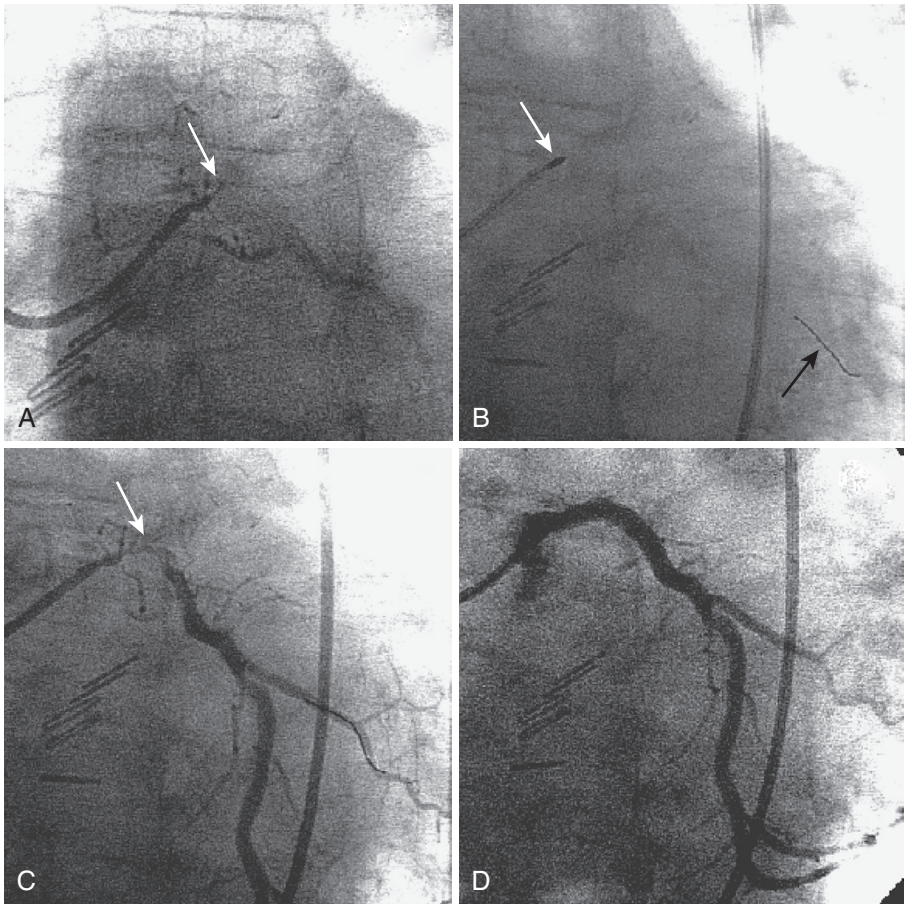

FIGURE 35-3 Rotational atherectomy for uncrossable left main stenosis. **A,** The left main occlusion jeopardized a large, unbypassed left circumflex coronary artery; it could be crossed with a guidewire but not with a balloon a catheter (*arrow*). **B,** After placement of a RotaWire with tip positioned distally (*black arrow*), a 1.25-mm burr was advanced through the left main occlusion (*white arrow*). **C,** The residual stenosis (*arrow*) was successfully treated with a sirolimus-eluting stent and was dilated to 4 mm. **D,** The final result.

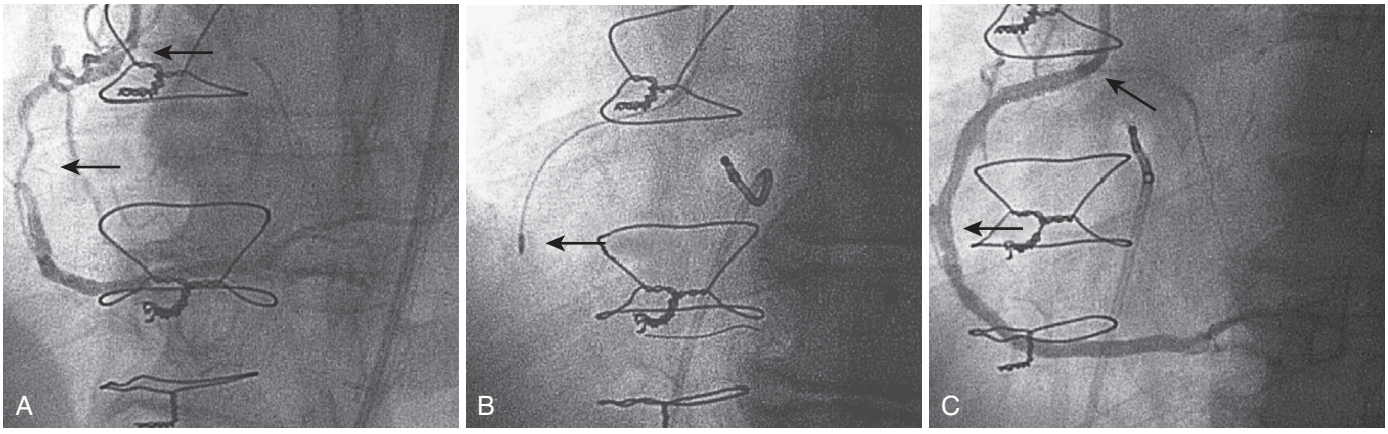

FIGURE 35-4 Rotational atherectomy for uncrossable lesions in the right coronary artery. Proximal and midportion stenoses (**A,** *arrows*) could not be crossed with low-profile balloon catheters but were successfully treated with a 1.25-mm burr (**B**), leaving dissections that were successfully treated with stents (**C**).

FIGURE 35-5 Orbital atherectomy crown. (Courtesy Cardiovascular Systems, St. Paul, MN.)

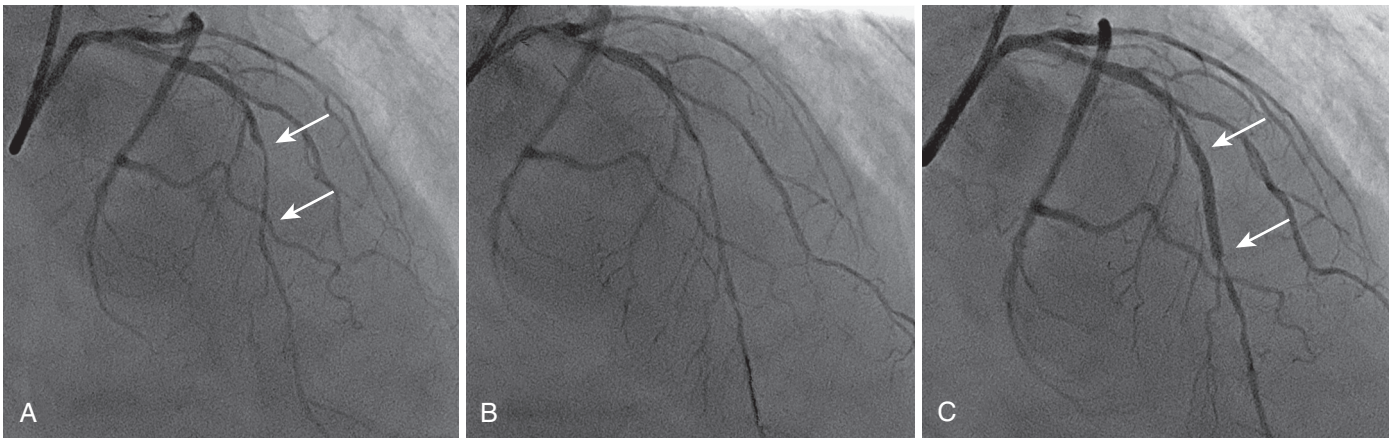

FIGURE 35-6 Orbital atherectomy of left anterior descending (LAD) artery. A heavily calcified lesion in the mid portion of the LAD artery (**A,** *arrows*) is treated with a 1.25-mm orbital atherectomy crown (**B**) and a drug-eluting stent (**C,** *arrows*).

diameters of 1.25, 1.50, 1.75, or 2.00 mm. The leading tip of the atherectomy device is never advanced within 5 mm of the distal opaque portion of the ViperWire, and ablation runs are limited to 30 seconds each. Although multiple atherectomy crowns can be used to treat each lesion, in clinical trials the average number of crowns has ranged from 1.1 to 1.3.[33]

Lesion Selection

Orbital atherectomy (OA) is recommended for severely calcified coronary lesions, defined in the pivotal clinical trial (see below) as severe calcification detected fluoroscopically in both sides of the arterial wall for at least 15 mm when viewed longitudinally or the presence of at least a 270-degree arc of calcium viewed in cross section using intravascular ultrasound (IVUS).[34]

Clinical Results

In the Safety and Feasibility of Orbital Atherectomy for the Treatment of Calcified Coronary Lesions (ORBIT I) study,[33] a registry of 50 patients with severely calcified lesions treated with OA followed by stent placement, procedural success was achieved in 47 patients (94%), and MACEs were reported in 2 patients (4%). Angiographic complications included dissections in 6 patients (12%) and a coronary perforation in 1 patient (2%).

In the Pivotal Trial to Evaluate the Safety and Efficacy of the Orbital Atherectomy System in Treating De Novo, Severely Calcified Coronary Lesions (ORBIT II),[34] a registry of 443 patients with severely calcified coronary lesions treated at 49 U.S. sites, the primary safety end point of freedom from 30-day MACE was achieved in 89.6% of patients. Stent delivery was successful in 97.7% of cases with less than 50% diameter stenosis (DS) achieved in 98.6% of subjects. Low rates of in-hospital Q-wave myocardial infarction (0.7%), cardiac death (0.2%), and TVR (0.7%) were reported. Angiographic complications included severe dissections in 15 patients (3.4%) and perforations in 8 patients (1.8%).

The role of OA vis-à-vis PTRA for the treatment of patients with severe calcified coronary lesions will likely depend on several factors, including local expertise and the relative cost of the two devices.

DIRECTIONAL CORONARY ATHERECTOMY

After approval of a directional coronary atherectomy (DCA) device by the U.S. Food and Drug Administration (FDA) in 1990 using registry data, several randomized trials comparing DCA with PTCA with and without stenting failed to demonstrate a clinical benefit of DCA (Fig. 35-7). At the current time, no DCA devices are marketed in the United States for coronary indications.

CUTTING BALLOON ANGIOPLASTY

Cutting balloon angioplasty (CBA), or atherotomy, is a variation of conventional PTCA (Chapter 15). In CBA, three or four sharp metal microtome blades mounted on a noncompliant balloon incise and score coronary atheroma during balloon inflation.

Mechanism of Action

The purpose of using cutting balloon atherotomy is to reduce the risk of uncontrolled longitudinal tears in the vessel wall caused by conventional balloon dilation. Compared with conventional PTCA, CBA makes controlled microincisions in the atheromatous plaque at lower pressures. Small mechanistic studies have confirmed that lesions can be dilated at lower pressure with cutting balloons than with conventional balloons.[22] In one study of 180 lesions, lumen enlargement was achieved at lower balloon pressures after CBA than after PTCA, and the increase in the cross-sectional area of plaque plus media measured by IVUS was larger after CBA.[35] In calcified lesions, CBA achieved larger lumen gains than did PTCA.[35]

Equipment

The Cutting Balloon Ultra-2 (Boston Scientific) is a monorail device, while the Flextome Cutting Balloon (Boston Scientific) has two configurations (Fig. 35-8). The Flextome device contains a flex point every 5 mm along the length of the atherotomes for greater flexibility and deliverability. It is available in over-the-wire and monorail configurations. Cutting balloons are available in balloon lengths of 6, 10, and 15 mm. The cutting blades, or atherotomes, are mounted longitudinally along the balloon surface. The atherotomes are not directly affixed to the balloon but rather are bonded to a pad mounted on the balloon. The double bond allows flexibility but ensures that atherotomes remain firmly fixed in place. The number of atherotomes depends on balloon diameter. Three atherotomes are on 2.0- and 3.25-mm balloons, and four are on 3.5- and 4.0-mm balloons.

Technique

The guidewires, catheters, and techniques used for CBA are similar to those used for conventional PTCA (Chapter 15). However, the cutting balloons are less compliant and may not track as well as conventional PTCA catheters. The risk of blade fracture or retention is reduced by

	Directional atherectomy		PTCA	
30-Day mortality	**N**	**%**	**N**	**%**
AMIGO[6]	0/381	(0.0)	0/372	(0.0)
BOAT[11]	0/497	(0.0)	2/492	(0.4)
CAVEAT-I[14]	0/512	(0.0)	2/500	(0.4)
CAVEAT-II[15]	3/149	(2.0)	3/156	(1.9)
CCAT[16]	0/138	(0.0)	0/136	(0.0)
Total (OR 0.42 [0.11, 1.64])	**3/1677**	**(0.2)**	**7/1656**	**(0.4)**
30-Day MI				
AMIGO[6]	18/381	(4.7)	9/372	(2.4)
BOAT[11]	30/497	(6.0)	12/492	(2.4)
CAVEAT-I[14]	31/512	(6.1)	14/500	(2.8)
CAVEAT-II[15]	26/149	(17.4)	18/156	(11.5)
CCAT[16]	6/138	(4.3)	5/136	(3.7)
Total (OR 1.95 [1.41, 2.70])	**111/1677**	**(6.6)**	**58/1656**	**(3.5)**
30-Day MACE				
AMIGO[6]	6/381	(1.6)	4/372	(1.1)
BOAT[11]	14/497	(2.8)	16/492	(3.3)
CAVEAT-I[14]	57/512	(11.1)	27/500	(5.4)
CAVEAT-II[15]	30/149	(20.1)	19/156	(12.2)
CCAT[16]	7/138	(5.1)	8/136	(5.9)
Total (OR 1.56 [1.15, 2.11])	**114/1677**	**(6.8)**	**74/1656**	**(4.5)**
Angiographic restenosis				
AMIGO[6]	103/381	(27.0)	83/372	(22.3)
BOAT[11]	126/401	(31.4)	145/364	(39.8)
CAVEAT-I[14]	184/371	(49.6)	186/328	(56.7)
CAVEAT-II[15]	47/103	(45.6)	48/95	(50.5)
CCAT[16]	61/133	(45.9)	53/124	(42.7)
Total (OR 0.90 [0.77, 1.05])	**559/1639**	**(34.1)**	**555/1533**	**(36.2)**
Cumulative revascularization				
BOAT[11]	126/497	(25.4)	138/492	(28.0)
CAVEAT-I[14]	170/512	(33.2)	174/500	(34.8)
CAVEAT-II[15]	37/149	(24.8)	49/156	(31.4)
Total (OR 0.90 [0.76, 1.06])	**372/1296**	**(28.7)**	**397/1284**	**(30.9)**
Longterm death				
AMIGO[6]	5/381	(1.3)	3/372	(0.8)
BOAT[11]	3/497	(0.6)	8/492	(1.6)
CAVEAT-I[14]	11/512	(2.1)	3/500	(0.6)
CAVEAT-II[15]	7/149	(4.7)	12/156	(7.7)
CCAT[16]	1/138	(0.7)	0/136	(0.0)
Total (OR 1.03 [0.60, 1.77])	**27/1677**	**(1.6)**	**26/1656**	**(1.6)**
Cumulative MACE				
BOAT[11]	115/497	(23.1)	153/492	(31.1)
CAVEAT-I[14]	216/512	(42.2)	193/500	(38.6)
CAVEAT-II[15]	60/149	(40.3)	69/156	(44.2)
Total (OR 0.91 [0.77, 1.07])	**431/1296**	**(33.3)**	**454/1284**	**(35.4)**

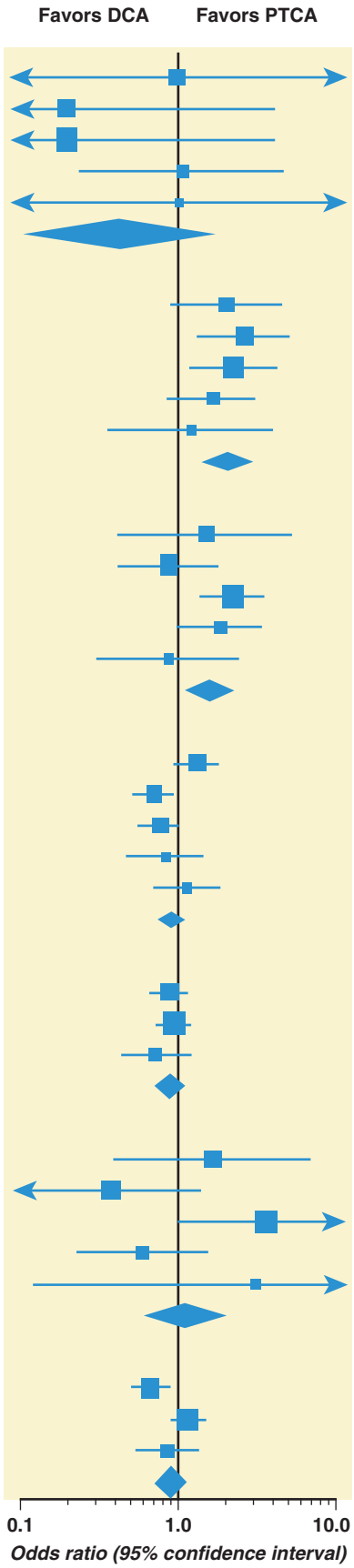

FIGURE 35-7 Systematic overview of randomized trials of directional coronary atherectomy (DCA) versus percutaneous transluminal coronary angioplasty (PTCA). Pooled odds ratios (ORs) and 95% confidence intervals are presented. Trial abbreviations are given in Table 35-1. *MACE,* Major adverse cardiovascular event; *MI,* myocardial infarction. (Updated and reprinted from Bittl JA, Chew DP, Topol EJ, et al: Meta-analysis of randomized trials of percutaneous transluminal coronary angioplasty versus atherectomy, cutting balloon atherotomy, or laser angioplasty. *J Am Coll Cardiol* 43:936-942, 2004.)

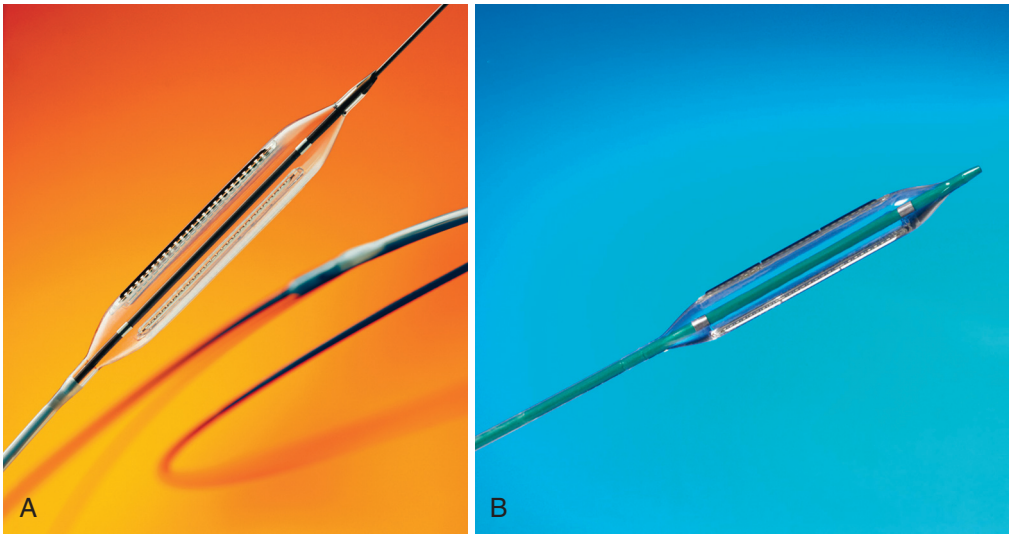

FIGURE 35-8 The Cutting Balloon Ultra 2 (**A**) is a monorail device, and the Flextome Cutting Balloon (**B**) is an over-the-wire catheter. (Courtesy Boston Scientific, Natick, MA.)

slowly inflating and deflating the balloon and by avoiding balloon pressures at or above rated burst pressures.

Clinical Results

Several small trials, all enrolling fewer than 200 patients, compared CBA with PTCA and reported that CBA reduced restenosis by 41% to 69% (Fig. 35-9).[12,18,22,24,25] However, other small studies that compared CBA with PTRA[31] or balloon PTCA[10] as pretreatment before brachytherapy for ISR found no difference in restenosis, and several large trials that compared CBA with PTCA generally found no difference in restenosis (see Fig. 35-9). The Global Randomized Trial (GRT)[23] randomized 1238 patients and reported no difference in angiographic restenosis between CBA and balloon PTCA (31.4% vs. 30.4%). The Restenosis Cutting Balloon Evaluation Trial (RESCUT)[28] enrolled 428 patients with ISR and reported no difference in restenosis between CBA and balloon PTCA (29.8% vs. 31.4%). The Restenosis Reduction by Cutting Balloon Evaluation (REDUCE 1) study[1] enrolled 802 patients and reported slightly higher restenosis rates with CBA than with PTCA (32.7% vs. 25.5%). The REDUCE 2 study[18] enrolled 416 patients and also observed a trend toward higher restenosis rates after CBA than after PTCA (52.1% vs. 44.2%). The REDUCE 3 study[27] randomized 453 patients undergoing coronary stenting and reported lower restenosis rates after the use of CBA than after PTCA (11.8% vs. 19.6%).

Lesion Selection

Bifurcation lesions are a challenge for conventional balloon angioplasty because of plaque shift and high restenosis rates, and in a small, nonrandomized series of 87 patients with bifurcation lesions, the use of CBA was associated lower restenosis rates than PTCA (40% vs. 67%).[36] Many interventional cardiologists use CBA for ostial lesions or for in-stent restenosis because cutting balloons appear to slip less often than conventional balloons.[23,27,28]

Complications

The risk of coronary perforation (Fig. 35-10) is slightly higher after the use of CBA than after conventional PTCA, as reported in the GRT (0.8% vs. 0.0%).[23]

SCORING BALLOON ANGIOPLASTY

The AngioSculpt scoring balloon catheter (AngioScore, Fremont, CA) is an alternative to the cutting balloon. The scoring balloon contains a flexible nitinol scoring ribbon with three rectangular spiral struts to incise the atheromatous plaque at pressures up to 18 atm. The system, which has a low crossing profile (2.7 F), is promoted as a more flexible alternative to the cutting balloon, but no multicenter randomized trials of the device have been reported.[37]

LASER ANGIOPLASTY

The use of lasers has broad appeal. Most people assume that medical lasers vaporize tissue through the mechanism of photochemical dissociation.

Mechanism of Action

The predominant mechanism of all medical lasers involves a thermomechanical process. In the case of the excimer laser, protein and nucleic acid chromophores absorb laser light at 308 nm and transfer heat to water. Intracellular water vaporizes and generates bubbles twice the diameter of the laser catheter (Fig. 35-11). The explosive increase in volume lyses cells and generates stress waves up to tens of kilobars that propagate away from the irradiated tissue.[38] The resulting barotrauma can be exploited to prepare rigid and undilatable lesions for stent implantation.[39]

Technique

The size of laser catheters used for angioplasty should be no more than two thirds the reference diameter of the target vessel. For severe stenoses, the smallest laser catheters are recommended to increase the likelihood of successful crossing. The elimination of blood and contrast from the coronary artery during excimer laser coronary angioplasty (ELCA) reduces collateral damage.[40] This is achieved by flushing all lines with saline and by injecting saline through the guide catheter at a rate of 2 to 3 mL per second during laser activation (Fig. 35-12). However, if lesions are found to be undilatable or uncrossable, using ELCA in a blood field without saline flush will enhance the photomechanical effects and may increase successful crossing.[39,41,42]

	Cutting balloon (CBA)		PTCA	
30-Day mortality	**N**	**%**	**N**	**%**
CAPAS[12]	0/114	(0.0)	1/118	(0.8)
GRT[23]	4/617	(0.6)	0/621	(0.0)
REDUCE 1[1]	0/399	(0.0)	0/403	(0.0)
REDUCE 2[18]	0/217	(0.0)	0/199	(0.0)
REDUCE 3[27]	0/260	(0.0)	0/261	(0.0)
RESCUT[28]	0/214	(0.0)	0/214	(0.0)
Total (OR 4.00 [0.45, 35.78])	**4/1821**	**(0.2)**	**1/1816**	**(0.1)**
30-Day MI				
CUBA[18]	3/153	(2.0)	3/153	(2.0)
GRT[23]	26/617	(4.2)	14/621	(2.3)
REDUCE 1[1]	1/399	(0.3)	3/403	(0.7)
RESCUT[28]	1/214	(0.5)	0/214	(0.0)
Total (OR 1.57 [0.89, 2.77])	**31/1383**	**(2.2)**	**20/1391**	**(1.4)**
30-Day MACE				
GRT[23]	23/617	(3.7)	17/621	(2.7)
REDUCE 1[1]	1/399	(0.3)	4/403	(1.0)
RESCUT[28]	2/214	(0.9)	1/214	(0.5)
Total (OR 1.19 [0.67, 2.12])	**26/1230**	**(2.1)**	**22/1238**	**(1.8)**
Angiographic restenosis				
CAPAS[12]	28/111	(25.2)	49/118	(41.5)
CBASS[18]	13/50	(26.0)	24/49	(48.8)
CUBA[18]	44/147	(29.9)	62/147	(42.2)
Ergene[22]	10/36	(27.8)	16/35	(45.7)
GRT[23]	173/551	(31.4)	170/559	(30.4)
Molstad[24]	5/30	(16.7)	7/27	(25.9)
REDUCE 1[1]	99/303	(32.7)	73/286	(25.5)
REDUCE 2[18]	113/217	(52.1)	88/199	(44.2)
REDUCE 3[27]	27/228	(11.8)	44/225	(19.6)
RESCUT[28]	56/188	(29.8)	61/194	(31.4)
Total (OR 0.92 [0.80, 1.06])	**568/1861**	**(30.5)**	**594/1839**	**(32.3)**
Cumulative revascularization				
CAPAS[12]	28/114	(24.6)	43/118	(36.4)
GRT[23]	72/617	(11.7)	92/621	(14.8)
Montorsi[25]	3/25	(12.0)	10/25	(40.0)
REDUCE 1[1]	87/399	(21.8)	77/403	(19.1)
RESCUT[28]	29/214	(13.6)	28/214	(13.1)
Total (OR 0.86 [0.71, 1.05])	**219/1369**	**(16.0)**	**250/1381**	**(18.1)**
Cumulative MACE				
CAPAS[12]	31/114	(27.2)	46/118	(39.0)
GRT[23]	84/617	(13.6)	94/621	(15.1)
REDUCE 1[1]	92/399	(23.1)	84/403	(20.8)
REDUCE 3[27]	30/260	(11.5)	44/261	(16.9)
RESCUT[28]	35/214	(16.4)	33/214	(15.4)
Total (OR 0.90 [0.75, 1.08])	**272/1604**	**(17.0)**	**298/1617**	**(18.4)**

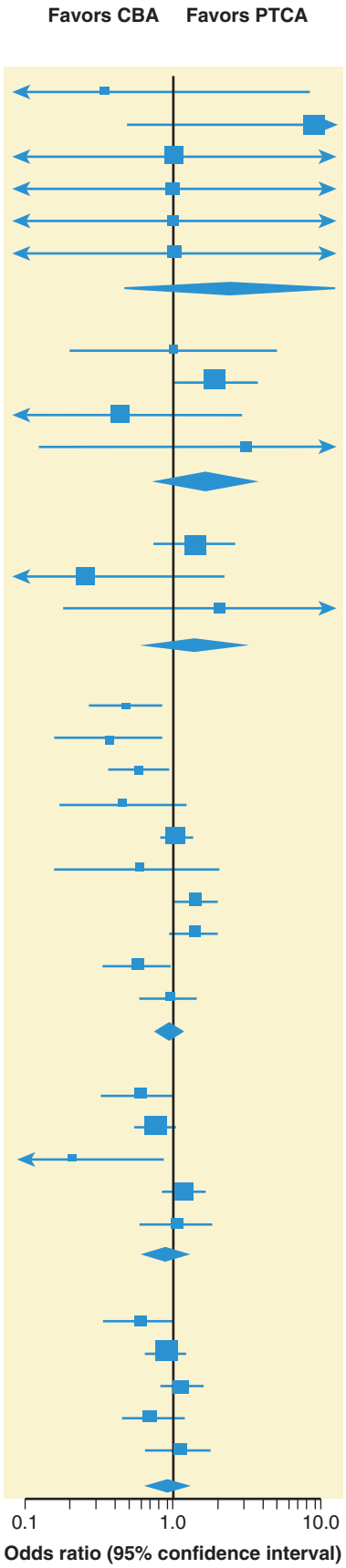

FIGURE 35-9 Systematic overview of randomized trials of cutting balloon angioplasty (CBA) versus percutaneous transluminal coronary angioplasty (PTCA). Pooled odds ratios (ORs) and 95% confidence intervals (CIs) are presented. Trial abbreviations are given in Table 35-1. *MACE,* Major adverse cardiovascular event; *MI,* myocardial infarction. (Updated and reprinted from Bittl JA, Chew DP, Topol EJ, et al: Meta-analysis of randomized trials of percutaneous transluminal coronary angioplasty versus atherectomy, cutting balloon atherotomy, or laser angioplasty. *J Am Coll Cardiol* 43:936-942, 2004.)

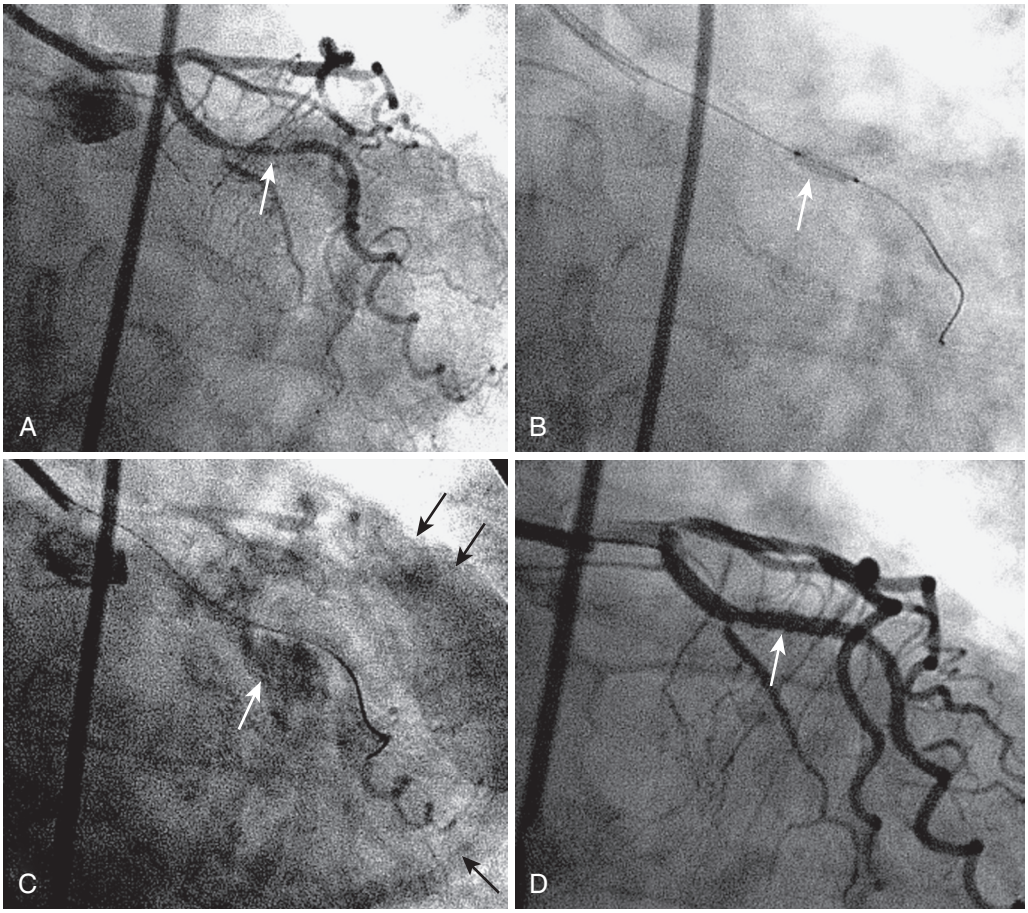

FIGURE 35-10 Perforation after cutting balloon angioplasty. The first marginal branch had been treated with a 3.0-mm bare-metal stent and showed moderate restenosis 7 months later (**A,** *arrow*), causing angina. A 3.0-mm cutting balloon was positioned within the stented segment (**B,** *arrow*), but inflation was complicated by free perforation (**C,** *white arrow*), circumferential hemopericardium (**C,** *black arrows*), and cardiac tamponade. The patient was rapidly stabilized with pericardiocentesis and placement of a polytetrafluoroethylene-covered stent to seal the coronary perforation (**D**).

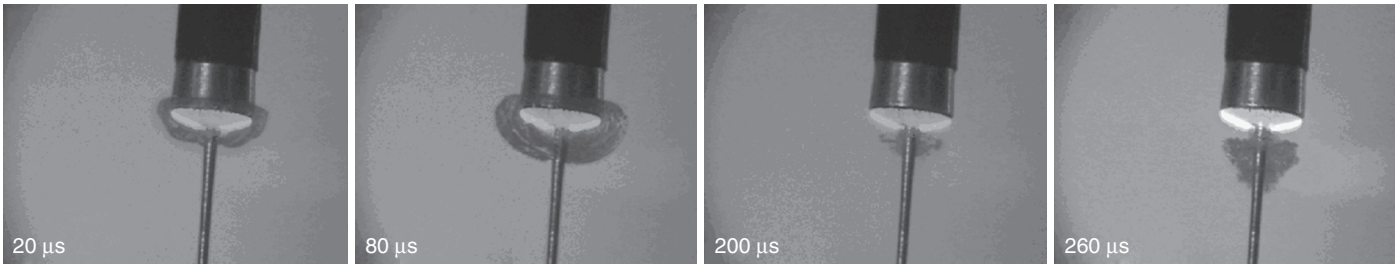

FIGURE 35-11 Laser-tissue interaction. Excimer laser light penetrates about 100 µm deep into tissue and rapidly converts cellular water into steam, causing a rapidly expanding vapor bubble to implode at the catheter tip.

Clinical Results

Several randomized studies have compared pulsed-wave lasers with other treatment modalities,[7,21,26] but none have shown a benefit over conventional PTCA (Fig. 35-13).

Lesion Selection

Although ELCA has been approved for seven lesion types—(1) long lesions, (2) moderately calcified lesions, (3) ISR before brachytherapy, (4) saphenous vein graft lesions, (5) ostial lesions, (6) total occlusions, and (7) undilatable lesions—some interventional cardiologists reserve its use for nondilatable lesions (Fig. 35-14).[2]

CONCLUSION

Originally explored as an alternative to PTCA, the use of atheroablative devices has found a complementary or facilitative role in the treatment of heavily calcified lesions, ostial disease, bifurcation stenoses, and undilatable lesions.

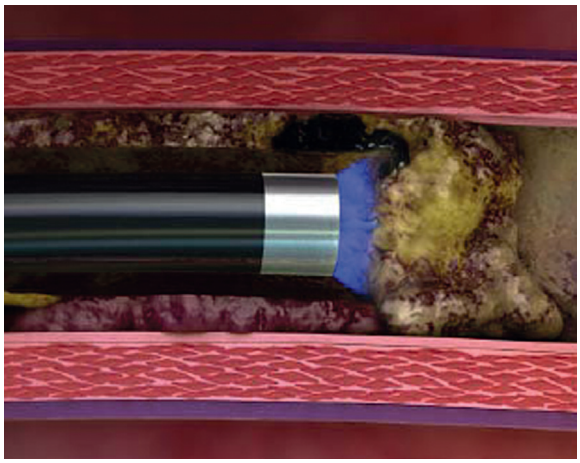

FIGURE 35-12 Schematic rendition of excimer laser angioplasty procedure. (Courtesy Spectranetics, Colorado Springs, CO).

	Laser angioplasty		PTCA	
30-Day mortality	**N**	**%**	**N**	**%**
AMRO[7]	0/151	(0.0)	0/157	(0.0)
ERBAC[21]	2/232	(0.9)	2/222	(0.9)
LAVA[26]	2/117	(1.7)	0/98	(0.0)
Total (OR 1.9 [0.3, 10.5])	**4/500**	**(0.8)**	2/477	**(0.4)**
30-Day MI				
AMRO[7]	5/151	(3.3)	5/157	(3.2)
ERBAC[21]	9/232	(3.9)	8/222	(3.6)
LAVA[26]	5/117	(4.3)	0/98	(0.0)
Total (OR 1.4 [0.7, 2.9])	**19/500**	**(3.8)**	**13/477**	**(2.7)**
30-Day MACE				
AMRO[7]	9/151	(6.0)	6/157	(3.8)
ERBAC[21]	10/232	(4.3)	6/222	(2.7)
LAVA[26]	12/117	(10.3)	4/98	(4.1)
Total (OR 1.9 [1.0, 3.5])	**31/500**	**(6.2)**	**16/477**	**(3.4)**
Angiographic restenosis				
AMRO[7]	64/124	(51.6)	52/126	(41.3)
ERBAC[21]	82/143	(57.3)	51/109	(46.8)
Total (OR 1.5 [1.1, 2.2])	**146/267**	**(54.7)**	**103/235**	**(43.8)**
Cumulative revascularization				
AMRO[7]	48/151	(31.8)	46/157	(29.3)
ERBAC[21]	100/211	(47.4)	64/191	(33.5)
Total (OR 1.5 [1.1, 2.0])	**148/362**	**(40.9)**	**110/348**	**(31.6)**
Cumulative MACE				
AMRO[7]	50/151	(33.1)	47/157	(29.9)
ERBAC[21]	101/211	(47.9)	70/191	(36.6)
LAVA[26]	41/117	(35.0)	33/98	(33.7)
Total (OR 1.3 [1.0, 1.7])	**192/479**	**(40.1)**	**150/446**	**(33.6)**

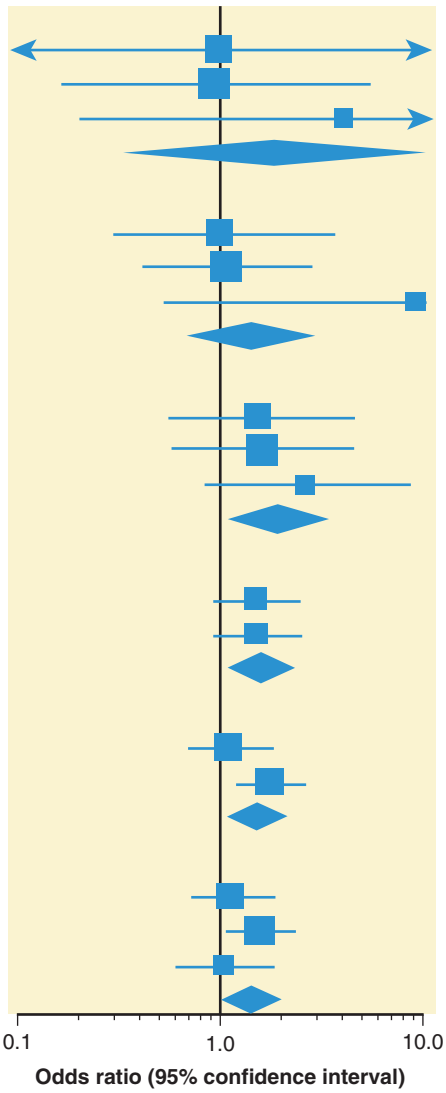

FIGURE 35-13 Systematic overview of randomized trials of laser angioplasty versus percutaneous transluminal coronary angioplasty (PTCA). Pooled odds ratios (ORs) and 95% confidence intervals (CIs) are presented, and trial abbreviations are given in Table 35-1. *MACE,* Major adverse cardiovascular event; *MI,* myocardial infarction. (Updated and reprinted from Bittl JA, Chew DP, Topol EJ, et al: Meta-analysis of randomized trials of percutaneous transluminal coronary angioplasty versus atherectomy, cutting balloon atherotomy, or laser angioplasty. *J Am Coll Cardiol* 43:936-942, 2004.)

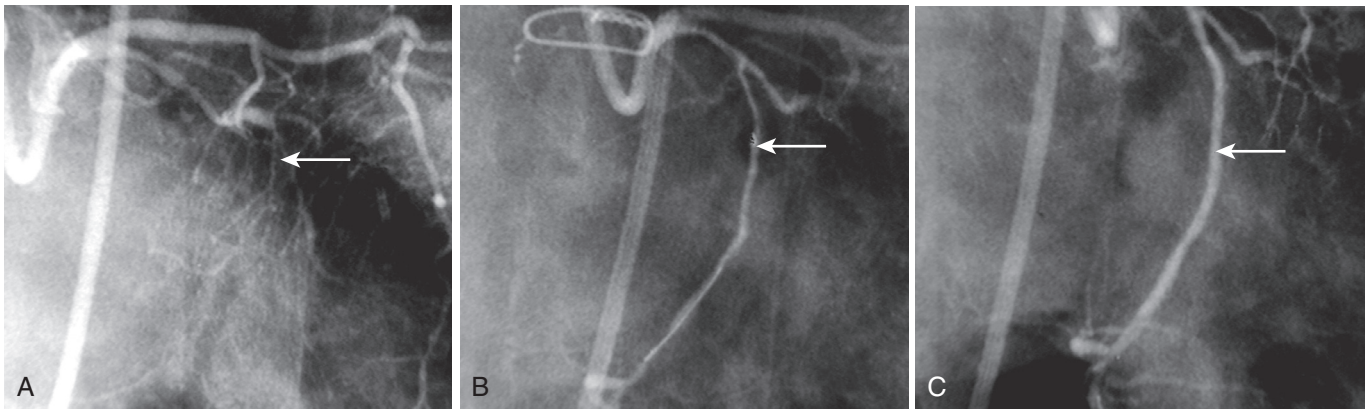

FIGURE 35-14 Long undilatable lesion treated with excimer laser angioplasty. The occluded left circumflex coronary artery (**A,** *arrow*) was crossed with a guidewire and treated with a 1.4-mm excimer laser catheter (**B,** *arrow*) followed by PTCA (**C,** *arrow*).

REFERENCES

1. Bittl JA, Chew DP, Topol EJ, et al: Meta-analysis of randomized trials of percutaneous transluminal coronary angioplasty versus atherectomy, cutting balloon atherotomy, or laser angioplasty. *J Am Coll Cardiol* 43:936–942, 2004.
2. Levine GN, Bates ER, Blankenship JC, et al: 2011 ACCF/AHA/SCAI guidelines for percutaneous coronary intervention: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 58:e44–e122, plus Data Supplements 123–124, 2011. <http://content.onlinejacc.org/cgi/content/full/j.jacc.2011.08.007>. Accessed 2011 December 27.
3. Tomey MI, Kini AS, Sharma SK: Current status of rotational atherecotmy. *JACC Cardiovasc Interv* 7:345–353, 2014.
4. Schwartz RS, Huber KC, Murphy JC, et al: Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. *J Am Coll Cardiol* 18:267–274, 1992.
5. Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS: A generalized model of restenosis following conventional balloon angioplasty, stenting, and directional atherectomy. *J Am Coll Cardiol* 21:15–25, 1993.
6. Stankovic G, Colombo A, Bersin R, et al: Comparison of directional coronary atherectomy and stenting versus stenting alone for the treatment of de novo and restenotic coronary artery narrowing. *Am J Cardiol* 93:953–958, 2004.
7. Appelman YE, Piek JJ, Strikwerda S, et al: Randomised trial of excimer laser angioplasty versus balloon angioplasty for treatment of obstructive coronary artery disease. *Lancet* 347:79–84, 1996.
8. vom Dahl J, Dietz U, Haager PK, et al: Rotational atherectomy does not reduce recurrent in-stent restenosis: results of the angioplasty versus rotational atherectomy for treatment of diffuse in-stent restenosis trial (ARTIST). *Circulation* 105:583–588, 2002.
9. Singh M, Rosenschein U, Ho KK, et al: Treatment of saphenous vein bypass grafts with ultrasound thrombolysis: a randomized study (ATLAS). *Circulation* 107:2331–2336, 2003.
10. Schlüter M, Tübler T, Lansky AJ, et al: Angiographic and clinical outcomes at 8 months of cutting balloon angioplasty and β-brachytherapy for native vessel in-stent restenosis (BETACUT): results from a stopped randomized controlled trial. *Catheter Cardiovasc Interv* 66:320–326, 2005.
11. Baim DS, Cutlip DE, Sharma SK, et al: Final results of the Balloon vs Optimal Atherectomy Trial. *Circulation* 97:322–331, 1998.
12. Izumi M, Tsuchikane E, Funamoto M, et al: Final results of the CAPAS trial. *Am Heart J* 142:782–789, 2001.
13. Safian RD, Feldman T, Muller DW, et al: Coronary angioplasty and Rotablator atherectomy trial (CARAT): immediate and late results of a prospective multicenter randomized trial. *Catheter Cardiovasc Interv* 53:213–220, 2001.
14. Topol EJ, Leya F, Pinkerton CA, et al: A comparison of balloon angioplasty with directional atherectomy in patients with coronary artery disease. *N Engl J Med* 329:221–227, 1993.
15. Holmes DR, Jr, Topol EJ, Califf RM, et al: A multicenter, randomized trial of coronary angioplasty versus directional atherectomy for patients with saphenous vein bypass graft lesions. CAVEAT-II Investigators. *Circulation* 91:1966–1974, 1995.
16. Adelman AG, Cohen EA, Kimball BP, et al: A comparison of coronary atherectomy with coronary angioplasty for lesions of the proximal left anterior descending coronary artery. *N Engl J Med* 329:228–233, 1993.
17. Dill T, Dietz U, Hamm CW, et al: A randomized comparison of balloon angioplasty versus rotational atherectomy in complex coronary lesion (COBRA study). *Eur Heart J* 21:1759–1766, 2000.
18. Chin K: Cutting balloons. In Ellis SG, Holmes DR, Jr, editors: *Strategic approaches in coronary intervention*, ed 3, Philadelphia, 2006, Lippincott Williams & Wilkins, pp 125–142.
19. Mauri L, Reisman M, Buchbinder M, et al: Comparison of rotational atherectomy with conventional balloon angioplasty in the prevention of restenosis of small coronary arteries: results of the Dilatation vs Ablation Revascularization Trial Targeting Restenosis (DART). *Am Heart J* 145:847–854, 2003.
20. Aizawa T: The debulking and stenting in restenosis elimination trial (DESIRE). *Circulation* 104:2954A, 2001.
21. Reifert N, Vandormael M, Krajcar M, et al: Randomized comparison of angioplasty of complex coronary lesions at a single center: Excimer Laser, Rotatational Atherectomy, and Balloon Angioplasty Comparison (ERBAC) Study. *Circulation* 96:91–98, 1997.
22. Ergene O, Seyithanoglu BY, Tastan A, et al: Comparison of angiographic and clinical outcome after cutting balloon and conventional balloon angioplasty in vessels smaller than 3 mm in diameter: a randomized trial. *J Invasive Cardiol* 10:70–75, 1998.
23. Mauri L, Bonan R, Weiner BH, et al: Cutting balloon angioplasty for the prevention of restenosis: results of the Cutting Balloon Global Randomized Trial. *Am J Cardiol* 90:1079–1083, 2002.
24. Molstad P, Myreng Y, Golf S, et al: The Barath Cutting Balloon versus conventional angioplasty. A randomized study comparing acute success rate and frequency of late restenosis. *Scand Cardiovasc J* 32:79–85, 1998.
25. Montorsi P, Galli S, Fabbiocchi F, et al: Randomized trial of conventional balloon angioplasty versus cutting balloon for in-stent restenosis. Acute and 24-hour angiographic and intravascular ultrasound changes and long-term follow-up. *Ital Heart J* 5:271–279, 2004.
26. Stone GW, de Marchena E, Dageforde D, et al: Prospective, randomized, multicenter comparison of laser-facilitated balloon angioplasty versus stand-alone balloon angioplasty in patients with obstructive coronary artery disease. The Laser Angioplasty Versus Angioplasty (LAVA) Trial Investigators. *J Am Coll Cardiol* 30:1714–1721, 1997.
27. Ozaki Y, Yamaguchi T, Suzuki T, et al: Impact of cutting balloon angioplasty (CBA) priot to bare metal stenting on restenosis: a prospective randomized multicenter trial comparing CBA with balloon angioplasty (BA) before stenting (Reduce III). *Circ J* 71:1–8, 2007.
28. Albiero R, Silber S, Di Mario C, et al: Cutting balloon versus conventional balloon angioplasty for the treatment of in-stent restenosis: results of the restenosis cutting balloon evaluation trial (RESCUT). *J Am Coll Cardiol* 43:943–949, 2004.
29. Sharma SK, Kini A, Mehran R, et al: Randomized trial of Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-stent Restenosis (ROSTER). *Am Heart J* 147:16–22, 2004.
30. Whitlow PL, Bass TA, Kipperman RM, et al: Results of the Study to Determine Rotablator and Transluminal Angioplasty Strategy (STRATAS). *Am J Cardiol* 87:699–705, 2001.
31. Lee S-W, Park S-W, Hong M-K, et al: Comparison of angiographic and clinical outcomes between rotational atherectomy and cutting balloon angioplasty followed by radiation therapy with a rhenium 188-mercaptoacetyltriglycine-filled balloon in the treatment of diffuse in-stent restenosis. *Am Heart J* 150:577–582, 2005.
32. Abdel-Wahab M, Richardt G, Joachim Büttner H, et al: High-speed rotational atherectomy before paclitaxel-eluting stent implantation in complex calcified coronary lesions: the randomized ROTAXUS (Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease) trial. *JACC Cardiovasc Interv* 6:10–19, 2013. Accessed January 1, 2013.
33. Parikh K, Chandra P, Choksi N, et al: Safety and feasibility of orbital atherectomy for the treatment of calcified coronary lesions: the ORBIT I Trial. *Cathet Cardiovasc Interv* 81:1134–1139, 2013.
34. Chambers JW, Feldman RL, Himmelstein SI, et al: Pivotal trial to evaluate the safety and efficacy of the orbital atherectomy system in treating de novo, severely calcified coronary lesions (ORBIT II). *J Am Coll Cardiol Interv* 7:510–518, 2014.
35. Okura H, Hayase M, Shimodozono S, et al: Mechanisms of acute lumen gain following cutting balloon angioplasty in calcified and noncalcified lesions: an intravascular ultrasound study. *Catheter Cardiovasc Interv* 57:429–436, 2002.
36. Takebayashi H, Haruta S, Kohno H, et al: Immediate and 3-month follow-up outcome after cutting balloon angioplasty for bifurcation lesions. *J Interv Cardiol* 17:1–7, 2004.
37. de Ribamar Costa J, Jr, Mintz GS, Carlier SG, et al: Nonrandomized comparison of coronary stenting under intravascular ultrasound guidance of direct stenting without predilation versus conventional predilation with a semi-compliant balloon versus predilation with a new scoring balloon. *Am J Cardiol* 100:812–817, 2007.
38. Bittl JA: Physical aspects of excimer laser angioplasty for undilatable lesions. *Catheter Cardiovasc Interv* 71:808–809, 2008.
39. Noble S, Bilodeau L: High energy excimer laser to treat coronary in-stent restenosis in an underexpanded stent. *Catheter Cardiovasc Intervent* 71:803–807, 2008.
40. Deckelbaum LI, Natarajan MK, Bittl JA, et al: Effect of intracoronary saline on dissection during excimer laser coronary angioplasty: a randomized trial. *J Am Coll Cardiol* 26:1264–1269, 1995.
41. Ahmed WH, Al-Anazi MM, Bittl JA: Excimer laser facilitated angioplasty for undilatable coronary narrowings. *Am J Cardiol* 78:1045–1047, 1996.
42. Goldberg SL, Colombo A, Akiyama T: Stent under-expansion refractory to balloon dilatation: a novel solution with excimer laser. *J Invasive Cardiol* 10:269–273, 1998.

36 Support Devices for High-Risk Percutaneous Coronary Interventions

SRIHARI S. NAIDU | HOWARD C. HERRMANN

KEY POINTS

- Clinical characteristics of the high-risk patient include older age, history of myocardial infarction (MI), low ejection fraction, congestive heart failure (CHF), recent hemodynamic instability, renal insufficiency, and peripheral vascular disease.
- High-risk angiographic characteristics include left main coronary artery (LMCA) disease, last patent conduit, multivessel coronary artery disease, complex lesions (calcified, tortuous, bifurcation), decreased preprocedure Thrombolysis in Myocardial Infarction (TIMI) flow, and thrombotic lesions.
- The decision to use a circulatory support device should be made within the context of the risk profile of the specific patient for periprocedural clinical decompensation when appropriate after obtaining surgical consultation. American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) clinical guidelines support hemodynamic devices in high-risk percutaneous coronary intervention (PCI) as a class IIb recommendation and as rescue therapy for cardiogenic shock as a class I recommendation.
- Intraaortic balloon pump (IABP) support provides up to 0.5 L/minute of cardiac output; this is supported by a large amount of experiential data in patients with stable cardiac rhythm undergoing high-risk PCI, although recently presented randomized data and meta-analyses question a benefit.
- Cardiopulmonary support (CPS) can completely support the circulation irrespective of cardiac rhythm and can be instituted quickly by experienced practitioners; however, it leads to high rates of vascular and access-site complications and does not unload the left ventricle (LV).
- The TandemHeart device (Cardiac Assist, Pittsburgh, PA) indirectly unloads the LV, provides an intermediate level of support that reaches flows of up to 3.5 L/minute, and can be used for an extended period, but it is limited by the complex insertion technique and is supported by relatively meager clinical data.
- The percutaneous Impella device (Abiomed, Danvers, MA) directly unloads the LV, can provide up to 2.5 L/minute (Impella 2.5), 3.5 to 4.0 L/minute (Impella CP), or 5.0 L/minute (Impella 5.0) of circulatory support, and it can also be used for an extended period. It has gained more widespread use because of the easier insertion technique and relatively robust observational and randomized trial data.
- Well-designed randomized controlled trials of the IABP versus no support (the Balloon Pump-Assisted Coronary Intervention Study [BCIS-1]) and the IABP versus Impella 2.5 (A Prospective Randomized Clinical Trial of Hemodynamic Support With Impella 2.5 Versus Intraaortic Balloon Pump in Patients Undergoing High-Risk Percutaneous Coronary Intervention [PROTECT II]) have been reported for the high-risk PCI cohort, but neither trial met its primary end point for superiority. Secondary end points and longer-term follow-up have been hypothesis-generating in their suggestion of secondary benefits.

INTRODUCTION AND RATIONALE

Complications of balloon angioplasty that threaten coronary blood flow, termed *acute and threatened occlusions,* usually require urgent surgical intervention and are the main causes of procedure-related morbidity and mortality. Before the advent of stents as a bail-out treatment for impending vessel closure, this complication occurred in about 6% of balloon angioplasty procedures. Patients who required emergent surgery in this setting had a 50% likelihood of suffering MI, and mortality rates were as high as 10%.[1] In these early studies, patient characteristics that included compromised ventricular function, LMCA disease, multivessel disease, and older age were identified as risk factors for balloon angioplasty–related mortality.[2,3] With the development of coronary stents and advanced pharmacotherapy to seal dissections and improve blood flow in thrombotic lesions, respectively, the need for urgent surgery was reduced with a concomitant reduction in PCI-related morbidity and mortality.[4]

In the current era, studies have demonstrated that the need for urgent surgery after PCI has been reduced to less than 1%, with a marked reduction in procedure-related mortality.[5] In one comparison of patients treated in 1997 and 1998 with those treated in 1985 and 1986, the rate of in-hospital deaths, MI, and coronary artery bypass grafting (CABG) fell from 7.9% to 4.9%, despite the treatment of more complex lesions and stent use in only 71% of patients.[6] Most of the differences between these periods were accounted for by the reduction in the need for emergent CABG from 3.7% to 0.4%.[6] Nonetheless, morbidity and mortality among patients who required emergent CABG remained high.[5] Moreover, the increased confidence afforded by stents and improved operator techniques and experience have prompted interventions on more complex lesions and in patients with more severe cardiac and noncardiac diseases. In particular, results of the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial now suggest reasonable outcomes in select patients with LMCA disease or multivessel coronary disease, and completed and ongoing trials of high-risk PCI with cardiac assist device placement indicate that extremely high-risk patient populations are, indeed, being increasingly considered for PCI.[7,8] ACCF/AHA clinical guidelines have kept pace and currently support percutaneous unprotected left main stenting in appropriate high-risk surgical patients as a class IIb indication.[9] Given the large amount of the myocardium in jeopardy in these subsets, as well as the baseline comorbidities frequently present (including reduced ventricular reserve), the potential for severe clinical decompensation in such patients is a real concern. It has therefore become essential to precisely identify the predictors of risk and to consider the use of hemodynamic support for patients at high risk for procedural complications and in-hospital mortality.

Although a number of investigators have used commonsense definitions to classify patients at high risk, two studies systematically developed risk models.[10-13] In the *Mayo Clinic model,* clinical and angiographic variables were used to predict in-hospital complications after PCI.[8] The variables were age, shock, renal insufficiency, urgent procedures, heart failure, thrombus, and LMCA or multivessel disease. A score based on these factors predicted the risk of complications and identified a "highest risk" group with an event rate that exceeded 25%.[13] In a similar study of 46,000 procedures in the mandatory New York State Hospital PCI reporting system, investigators included nine factors in a risk score: (1) ejection fraction, (2) previous MI, (3) gender,

TABLE 36-1 Predictors of Risk During Percutaneous Coronary Intervention

Factor	Reference
Clinical and Patient Related	
Older age	3, 12, 13, 54
Cardiogenic shock	6, 12, 13, 54
Recent myocardial infarction	6, 12, 13, 54
Congestive heart failure	12-14, 54
Prior coronary artery bypass grafting/ revascularization	87
Peripheral vascular disease	12, 54
Chronic renal insufficiency	12-13, 54
Angiographic	
Left main coronary artery/multivessel disease	12, 13, 54, 88, 91
Complex lesions (bifurcation, calcification, total occlusion)	16
Decreased Thrombolysis in Myocardial Infarction (TIMI) flow	89
Left ventricular dysfunction	6, 12, 14, 15, 54
Thrombus	13, 16

(4) age, (5) hemodynamic state, (6) peripheral arterial disease (PAD), (7) CHF, (8) renal failure, and (9) LMCA disease. Using this *New York State Hospital model*, a graded risk score for in-hospital mortality was derived and validated. About 2% of all patients had a greater than 5% risk for in-hospital death, and about 4% of patients had a greater than 3% risk.[12] Other studies have confirmed these risk factors for PCI-related complications,[3,14,15] but neither model may accurately represent the higher-risk patient populations undergoing intervention in the current era. In addition to these clinical risk factors, angiographic factors of lesion complexity—thrombus, calcification, and bifurcations—have been shown to be associated with more dissections, distal embolization, and side-branch occlusions, resulting in a threefold increase for in-hospital death.[16]

Several patient characteristics deserve separate discussion. Although female sex was initially associated with complications in early studies of balloon angioplasty, more recent studies have failed to demonstrate an important effect on outcome.[12,13,17,18] Similarly, patients with diabetes have more complex lesion characteristics and risk factors but no increase in in-hospital mortality after multivariable adjustment.[19] More recently, baseline LV dysfunction and the extent of the myocardium in jeopardy during the procedure have reemerged as perhaps the strongest clinical risk factors for intraprocedural decompensation and in-hospital mortality. Accordingly, recent studies on high-risk PCI have used the combination of severe ventricular dysfunction (represented by ejection fraction <30% to 35%) and either LMCA disease, last patent conduit, or multivessel disease as high-risk PCI inclusion criteria.[20] Thus it is clear that despite major advances in the technical and procedural performance of modern PCI, clinical and angiographic predictors of significant morbidity and mortality can be identified (Table 36-1). Moreover, it appears likely that increasing numbers of patients will be undergoing high-risk PCI, including the very old and those with LMCA disease, multivessel disease, and significant ventricular dysfunction. In many cases, bypass surgery is not a viable option, leaving PCI as the only remaining possible mechanism to improve ventricular function and reduce ischemic symptoms. Finally, patients undergoing PCI in the setting of acute myocardial infarction (AMI) with cardiogenic shock represent an especially high-risk group in whom hemodynamic support devices have been utilized, and national guidelines now support their use after initial attempts at medical stabilization.[9] Together, these data provide the rationale and impetus for the increased use of hemodynamic support during complex or high-risk PCI in various clinical settings in the current era. The remainder of this chapter will discuss the approach to such patients, the devices currently available to provide support, and the results that may be achieved by using them.

APPROACH TO THE PATIENT

Mechanical circulatory support at the time of PCI has historically been instituted in one of two settings: *electively* for presumed high-risk intervention and *emergently* for periprocedural hemodynamic instability. Specific indications, however, remain unclear because of limitations in performing large-scale randomized trials and evaluating specific devices in individual patient subsets. Nevertheless, a review of existing literature and ongoing clinical trials provides a framework for both patient and device selection when evaluating patients for elective or emergent support. Electively placed mechanical support is aimed at improving procedural success by minimizing myocardial ischemia and maintaining hemodynamic stability, thereby reducing clinical decompensation and resultant mortality in high-risk preselected patient subsets, as discussed in the previous section. In this setting, prophylactic insertion of the IABP or the Impella ventricular assist device (VAD) appears to have the most robust observational data for improving procedural success with a minimal increase in complications.[20-26] Despite encouraging registry data, however, a randomized controlled trial (RCT) failed to show clinical benefit to routine prophylactic IABP insertion in patients undergoing high-risk PCI.[27] The more powerful Impella device was subsequently studied in patients deemed to need hemodynamic support for high-risk PCI. Whereas the device was successful in providing superior hemodynamic support, in comparison to routine IABP use, no difference was reported in major adverse events at 30 days.[28] However, secondary end points in each of these trials were hypothesis-generating, in that procedural complications and long-term mortality were improved with routine IABP use in the BCIS-1 trial, and repeat revascularization, total length of stay, and 90-day major adverse events were improved with Impella, especially in patients who did not undergo rotational atherectomy.[28,29]

The use of mechanical circulatory support in the emergent setting for patients with documented hemodynamic instability or cardiogenic shock is more familiar to interventional cardiologists. Instability may be present before PCI (as in acute MI with compromised ventricular function) or may develop as a consequence of procedural complications such as coronary dissection, poor coronary reflow, or thromboembolism. A common underlying finding in most of these patients is ventricular dysfunction. Although a large RCT has not been performed, a pooled meta-analysis of IABP use in patients with acute ST-elevation myocardial infarction (STEMI) found no benefit to IABP use in conjunction with primary angioplasty, but some benefit was seen in those receiving thrombolytic therapy.[30] The more recent Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II)[31] trial similarly found no benefit to routine IABP use in patients presenting with cardiogenic shock. Available percutaneous VADs (pVADs) appear to improve hemodynamic parameters in patients with acute clinical decompensation, but only registry data are available to suggest improved outcome.[32] As a result, determining whether and which device to use in specific settings remains controversial and is primarily guided by experience and expert consensus, with the field as a whole shifting toward more powerful support earlier in the course of clinical deterioration.

Device selection is based on several factors; these include ease and rapidity of institution, level of invasiveness and complications, physician familiarity, requisite technical expertise, level of anticipated circulatory support, and available supportive clinical trial data. An IABP is the least invasive and most familiar device and may be instituted rapidly, but it also provides the least support, averaging 0.5 L/minute augmentation in cardiac output.[33] It may be left in place for several days and has a low vascular complication rate.[34] Conversely, full CPS is significantly more invasive, and it requires timely surgical and perfusionist collaboration for institution and removal, but it can produce greater improvement in cardiac output, approximating normal

physiology. CPS cannot be maintained indefinitely, however, because hematologic and pulmonary complications increase as bypass time approaches 6 hours, and in the absence of concomitant LV venting or unloading, its deleterious effect on myocardial oxygen consumption remains a concern.[34] Percutaneous ventricular assist devices (pVADs), such as the TandemHeart or the Impella 2.5 or CP, provide an intermediate level of support that approaches 2.5 to 4 L/minute; in addition, these devices can be placed emergently in the catheterization laboratory (cath lab) without surgical backup, which has prompted their increased use recently. Unlike the Impella, the TandemHeart requires transseptal puncture to deliver the inflow cannula into the left atrium, so it requires a somewhat larger arterial cannula. Thus only patients with a larger femoral arterial diameter are able to accommodate device placement, which can be performed only by those skilled in the transseptal technique. Consequently, compared with the Impella device, cath lab utilization rate of the TandemHeart appears to have stabilized in recent years. In both devices, the cannulae are larger than with an IABP and may result in significant vascular morbidity. However, unlike full CPS, the use of a pVAD has been successful for intermediate lengths of time (up to 14 days). Relatively smaller cannulae, as with the Impella, are likely to reduce femoral complications.

Historically, elective high-risk PCI has been performed safely with either provisional or prophylactic IABP support. As described above, however, RCT data have suggested that routine prophylactic IABP support may offer little meaningful benefit in these patients over the short term.[27] In those select patients who appear to require additional circulatory support, as defined by the inclusion criteria of completed and ongoing randomized trials, a pVAD may be considered, with the caveats that the inherent increase in delay and invasiveness (particularly access-site complications) may partially offset the benefit and that definitively supportive RCTs remain absent.[28] For patients who develop severe hemodynamic instability, cardiogenic shock, or frank arrest during PCI, bail-out use of the IABP appears beneficial and is certainly the most familiar and rapid strategy; however, the support provided may be insufficient.[31] Cath labs experienced in rapid pVAD placement may opt for these larger, more powerful devices as either an initial or rapidly escalating strategy. Developing data on hemodynamic parameters that might predict meaningful recovery, such as cardiac power output (CPO, measured in Watts), would at least theoretically support their use.[35] Although full CPS may be considered in cath labs equipped and staffed for timely initiation, its clinical use had been relegated to anecdotal experience over the past decade. However, newer and more compact CPS units have recently been developed, and consequently there has been a rise in their utilization in some cath labs. Nevertheless, in emergent settings, pVADs appear most promising and consequently have become increasingly prominent, but they require specialized technical expertise for optimal patient selection, device placement, and postprocedural management.

DESCRIPTION OF DEVICES

Intraaortic Balloon Pump

The IABP was first used clinically in cardiogenic shock by Kantrowitz in 1968.[36] As its application expanded to include refractory angina, severe hemodynamic compromise, and postcardiotomy pump failure and with the advent of percutaneous insertion, the IABP was one of the first hemodynamic devices used to support high-risk PCIs.[36-38]

The rapid filling of the balloon in early diastole augments diastolic pressure and thereby leads to increased coronary perfusion pressure, whereas deflation of the balloon at end diastole reduces effective aortic volume and decreases aortic systolic pressure, which leads to lower LV afterload. The net effect is a decrease in myocardial oxygen requirements from lower systolic wall tension and an increase in coronary perfusion pressure, which improves the myocardial supply/demand balance. Cardiac output increases because of the improved myocardial contractility as a result of the increased coronary blood flow and the reduced afterload.[39-41]

Insertion Technique

Evaluation of the iliac and femoral arteries is recommended to exclude significant arterial disease. Access in the common femoral artery is obtained via the Seldinger technique. The balloon can be inserted through an 8 or 9 F sheath or directly in a sheathless fashion. Before insertion, all the air in the balloon should be evacuated with a large syringe attached to the one-way valve to maintain the lowest possible profile during insertion. The balloon catheter is advanced under fluoroscopic guidance over a stiff 0.021-inch guidewire until the radiopaque tip marker reaches a level just distal to the left subclavian artery. After removal of the guidewire, the central lumen is flushed and connected to a pressure transducer. The balloon is then connected to the console, the system is purged with helium, and counterpulsation is started. Proper placement and inflation of the balloon should be done fluoroscopically, and the timing of inflation and deflation should be optimized by either the surface electrocardiogram (ECG) or the transduced pressure tracing to achieve optimal hemodynamic support.

Clinical Trials

Much of the observational data on the use of IABPs and other circulatory support devices during high-risk PCI comes from the present era of coronary interventions. Voudris and colleagues[23] showed that support with IABP use during elective high-risk angioplasty is both safe and feasible. During a 13-month period (in 1987 and 1988), 27 patients considered high risk because of decreased LV function or multivessel disease underwent angioplasty with IABP support. Primary success, according to contemporary American College of Cardiology (ACC) guidelines, was achieved in all 27 patients. No major cardiac events occurred during hospitalization, and only one IABP-related vascular complication was reported. After a mean follow-up period of 13 months, 2 deaths, 1 cardiac transplantation, and 6 cases of symptom-driven target-vessel revascularization (TVR, 22% rate of recurrent angina) were reported, and the TVR was also successfully performed with IABP support.[23]

Similar outcomes were reported by Kahn and associates[22] in a group of 28 high-risk patients during the same period. The most common high-risk feature in this cohort of patients was severe LV dysfunction, but some patients had critical stenoses in the LMCA or a single remaining coronary artery. Procedural success was 96% (90 of 94 lesions were successfully dilated). Eleven patients had intraprocedural hypotension, although the augmented diastolic pressure was maintained over 90 mm Hg in all cases, and angioplasty was completed in all patients. Vascular complications associated with the IABP occurred in 11% of the patients. In another series[24] of 21 patients with similar high-risk features, 90% of lesions attempted were successfully dilated without hemodynamic compromise; device-related complications (hematoma) occurred in 10% of the cases, and procedure-related complications occurred in 14%.

The beneficial effects of IABP support were also shown in high-risk coronary rotational atherectomy.[42] In a retrospective analysis, 28 patients scheduled to undergo rotational atherectomy were placed on IABP support before the coronary intervention. This group was compared with 131 patients with high-risk coronary lesions who did *not* have an IABP placed a priori. The group that received a planned IABP comprised patients who were older and had more LV dysfunction and a higher incidence of multivessel disease. Although systolic hypotension occurred in 11% of the patients in the study group, diastolic pressure augmentation provided by the IABP allowed successful completion of the procedure in all patients. Hypotension that necessitated IABP placement occurred in 7% of the patients in the comparison group. Slow flow occurred at a similar rate in both groups; however, 27% of the patients in the comparison group who experienced slow flow developed a non–Q wave MI, compared with none in the study group. No differences were reported in the rate of transfusion requirements or vascular complications.[42]

In a more recent study by Brodie and colleagues,[2] IABP was shown to reduce periprocedural events in a group that consisted of 213 patients who presented with acute MI and received an IABP. In

TABLE 36-2 Intraaortic Balloon Pump Observational Trials

First Author, Year	Year	Procedure	Number of Patients	Revasc. Success Rate (%)	Device-Related Complication Rate (%)	In-Hospital Mortality Rate
Anwar[21]	1990	PTCA	97	85.6	2	1
Kahn[22]	1990	PTCA	28	96	11	7.1
Voudris[23]	1990	PTCA	27	100	3.7	0
Kreidieh[24]	1992	PTCA	21	90	9.5	0
O'Murchu[42]	1995	Atherectomy/PTCA	28	100	7.1	0
Kaul[61]	1995	PTCA	20	95	0	5
Schreiber[62]	1998	PTCA	91	87	27	8.7
Brodie[2]	1999	PTCA/Stent*	108†	89.8	8‡	37§
Briguori[43]	2003	PTCA/Stent	61	94	0	8
Abdel-Wahab[44]	2010	Stent	48 (26 pre PCI, 22 post PCI)	100	NR	19% vs. 59%
Curtis[45]	2012	Stent	18,990	NR	4.8% to 5.1%	4.9%

NR, Not reported; *Revasc.,* revascularization.
*Stents were used in the last three years of the study.
†Includes patients with shock or congestive heart failure; the number of patients undergoing high-risk percutaneous coronary intervention (PCI) was not defined.
‡Includes patients who received an intraaortic balloon pump (IABP) after percutaneous transluminal coronary angioplasty (PTCA).
§Thirty-day mortality that includes patients with cardiogenic shock.

contrast to the earlier studies discussed, the majority of patients in this group were treated with stents, and about a third were treated with abciximab, reflecting the then-contemporary treatments. Whereas the indication for the IABP in most cases was cardiogenic shock, 80 patients were hemodynamically stable but were considered high risk because of LV dysfunction. In this group, the use of IABP support led to a decreased incidence of prolonged hypotension, cardiac arrest, and ventricular fibrillation; however, the difference was not statistically significant because of the low number of patients in this group. IABP use was associated with an increased risk of major bleeding and higher transfusion rates.

Although IABP use during high-risk coronary interventions had been shown, at least in registry and case series data, to be effective in supporting the circulation, the increased rates of vascular and hemorrhagic complications associated with its use demanded careful patient selection.[2,22,23,25,42] For this reason, a strategy of provisional IABP support was compared with prophylactic placement of IABP in high-risk interventions in a retrospective, nonrandomized study.[43] Sixty-one patients who received elective IABP were compared with 72 patients in whom support was initiated only when clinically necessary. The patients in the elective IABP group were slightly older, but other high-risk features were similar, including severity of LV dysfunction (ejection fraction <30%) and rates of multivessel disease and unstable angina. Rates of stent and glycoprotein inhibitor use were similar between the two groups. The rates of slow flow were similar in both groups, but hemodynamic deterioration occurred only in patients (15%) in the provisional IABP group, and all received urgent IABP support. Rates of vascular complications were low in this study, with only two patients in the provisional IABP group developing groin hematomas. No cases of major bleeding were reported. Although not statistically significant, three deaths occurred in the provisional IABP group in patients who required urgent placement of an IABP compared with one death in the elective group.[43] Similarly, in a study of 48 patients undergoing primary PCI for AMI complicated by cardiogenic shock, IABP placement prior to PCI resulted in reduced major adverse cardiac events (MACEs), including mortality, than postprocedure placement.[44]

More contemporary observational data has been less supportive. In particular, evaluation of collected data from the National Cardiovascular Data Registry (NCDR) found no difference in overall mortality with use of the IABP for high-risk PCI, and wide national variation was apparent in its use for this purpose.[45] Further, a meta-analysis of IABP use in AMI found no benefit to IABP use in this setting and found a higher incidence of stroke.[30] A summary of the published observational trials that used IABP during high-risk PCI is shown in Table 36-2.

Routine prophylactic use of IABP in high-risk PCI or cardiogenic shock has recently come into question, however, following the results of two large randomized trials.[27,31] Patients undergoing high-risk PCI, defined as severe LV systolic dysfunction (left ventricular ejection fraction [LVEF] <30%) and extensive coronary artery disease, were randomized in the BCIS-1 trial to either routine IABP or no planned IABP prior to PCI.[27] No difference was reported in the primary end point of major adverse cardiac and cerebrovascular events (MACCEs) at 28 days despite a marked reduction in procedural complications. In addition, bleeding and access-site complications trended higher with routine IABP use. Mortality was no different at 6 months but was significantly reduced at long-term follow-up of 51 months, a finding that can only be deemed hypothesis generating because the trial was not powered to reveal a mortality difference.[29]

In the setting of AMI complicated by cardiogenic shock, the IABP-SHOCK II trial randomized 600 patients to routine IABP versus no IABP.[31] All patients were expected to undergo early revascularization. By 30 days, no difference in mortality or any secondary end points was noted, and rates of bleeding, sepsis, and stroke were similar.[31] These findings highlight the importance of RCT data and appropriate selection and timing of clinical end points in order to fully elucidate the proper role of any cardiac assist device in high-risk PCI. A summary of the randomized trials in high-risk PCI, including the BCIS-1 and IABP-SHOCK II trials, is shown in Table 36-3.

Percutaneous Cardiopulmonary Support

The introduction in 1985 of the portable Bard CardioPulmonary Bypass Support system (CR Bard, Murray Hill, NJ) expanded the application of percutaneous CPS.[46] Although the most common application for temporary circulatory support is for patients who cannot be weaned from cardiopulmonary bypass after cardiac surgery, CPS has also been implemented in the cath lab either emergently as a bridge to cardiac surgery or prophylactically to support high-risk coronary interventions. Full CPS incorporates a heat exchanger, an adjustable blood reservoir, a pump, and an oxygenator and can temporarily substitute for the entire circulation, irrespective of cardiac rhythm. Because blood comes in contact with various biomaterials in the perfusion circuit, activation of blood proteins and cells leads to morbidity that limits the length of time it can be maintained. Other more simplified strategies use only a blood pump and extracorporeal membrane oxygenation (ECMO).

TABLE 36-3 Major Randomized Controlled Trials of Hemodynamic Support Devices

Study (Year)	Comparator Groups	Outcomes
BCIS-1[27,29] (2010)	IABP versus no IABP in high-risk PCI	• 28-day MACCEs (primary end point) 15.2% versus 16.0%, P = NS • NS difference 6-month mortality but significant by 1 year • Routine IABP reduced procedural complication rate
IABP-SHOCK II[31] (2012)	IABP versus no IABP in cardiogenic shock complicating acute myocardial infarction	• 30-day all-cause mortality (primary end point) 39.7% versus 41.3%, P = NS • NS difference in any secondary end points, including complications and length of stay
PROTECT II[28] (2012)	Impella 2.5 versus IABP in high-risk PCI	• 30-day MAEs (primary end point) 35.1% versus 40.1%, P = NS • 90-day per protocol definition MAE reduced with Impella • Impella provided statistically significant superiority in cardiac power output

IABP, Intraaortic balloon pumping; *MACCEs,* major adverse cardiovascular and cerebrovascular and events; *MAE,* major adverse event; *NS,* not significant; *PCI,* percutaneous coronary intervention.

CPS unloads the right ventricle but does not unload the left.[46] Pulmonary and systolic aortic pressures have been shown to decrease, whereas diastolic and mean systemic arterial pressures remain unchanged.[46,47] In normal functioning hearts, the reduction in preload and a small increase in afterload produced by the arterial inflow reduces wall stress and produces smaller end-diastolic LV volumes because the left ventricle is able to eject the blood it receives. However, in dilated and poorly contracting hearts, especially after cardiac arrest, the increase in afterload may impair LV emptying, and another means of assisting emptying of the ventricle (e.g., IABP or Impella) may be necessary to avoid further deterioration of heart function. Another very simple approach is to provide an external cardiac compression approximately every minute while the patient is on CPS. Studies have also shown that CPS does not increase coronary perfusion in the setting of an occlusion, so bypass surgery should be considered if circulation cannot be restored percutaneously. For these reasons, CPS may, at least in theory, be a poor choice for patients undergoing high-risk PCI, in whom unloading the left ventricle and maintaining antegrade coronary blood flow is a primary concern.

Insertion Technique

Before arterial cannulation, angiography of the iliofemoral arteries is performed to exclude significant arterial disease. Care should be taken to access the artery below the inguinal ligament in the common femoral artery. Invasive monitoring with a pulmonary artery catheter is recommended during support. Once venous access and arterial access are obtained with a flexible 0.038-inch guidewire and an 8-Fr dilator, anticoagulation is started with an antithrombin agent. The flexible wire is replaced with a stiff 0.038-inch guidewire, and both the vein and the artery are progressively dilated with 12-Fr and 14-Fr dilators. Finally, 18-Fr cannulae are placed, with the inflow at the level of the right atrium and the outflow at the level of the aortic bifurcation. The cannulae are then clamped before being connected to the primed perfusion circuit. Priming of the circuit should be performed by a perfusionist while access is being obtained. After carefully de-airing the system, the cannulae are connected to the perfusion circuit; support is started at 2 L/minute and then progressively advanced by 0.5-L/minute increments as needed.[47]

After successful coronary intervention, CPS is weaned quickly in those who can tolerate it, usually over 15 minutes, by gradually reducing the flow rate. Volume is infused to increase the LV filling pressure to at least 8 to 10 mm Hg or to prebypass levels, whichever is less. If necessary, inotropic agents may be used to facilitate the weaning of support. An intraaortic balloon or Impella device can also be used if weaning causes difficulties for the patient. The Bard percutaneous CPS system is a portable, battery-operated system that consists of a centrifugal pump (Bio-Medicus; Medtronic, Minneapolis, MN), a heat exchanger, and a membrane oxygenator. Venous inflow is achieved by active suction—not by gravity, as in the classic cardiopulmonary bypass system—which makes it essential that patients be well hydrated. To prevent air embolism, central venous access should be avoided while the pump is operating. Another portable CPS device, Cardiohelp (Maquet Cardiovascular, Rancho Dominguez, CA), is also available. Percutaneous cardiopulmonary support can only be performed for 6 hours. After that, platelet aggregation, hemolysis, and increased capillary permeability with plasma loss become major complications.

Clinical Trials

Early reports on small numbers of patients showed that using CPS for high-risk angioplasty was feasible, even though it had high rates of femoral access-site complications.[48-50] The national registry of elective supported angioplasty reported data on 801 patients who underwent elective angioplasty with CPS in 25 centers from 1988 to 1992. The suggested inclusion clinical criteria were (1) the presence of severe or unstable angina; (2) at least one likely dilatable coronary artery stenosis; and (3) LVEF less than 25% or a target vessel that supplies more than half of the viable myocardium or both.[51] Although the initial angioplasty success rate was high in this registry, the rates of device-related complications were also high. The strategy was thus changed to one of standby support for these high-risk interventions. Prophylactic support was implemented in 73% of the patients, and the last 27% registered had standby support. The overall primary success rate was 93%, and the success rate in the group that had standby support was 91%.[52] The rates of vascular complications (15% vs. 6.1%) and transfusions (31% vs. 14%) decreased with the change in strategy from prophylactic support to standby support. The mortality rate (6.3% vs. 6% in the prophylactic and standby groups, respectively) and the rate of emergent bypass surgery (2.5% vs. 3.2%) did not change, however, which reflects the high-risk profile of the patients in the registry. Only 16 of 217 patients (7.4%) in the standby strategy group required emergency initiation of bypass support. Of these 16 patients, 75% had successful angioplasty without any need for bypass surgery, which suggested that standby support reduced the need for emergency bypass surgery. The only group of patients who demonstrated a clear benefit to using prophylactic support was the group with an LVEF of 20% or less. In these patients, those treated with prophylactic placement of CPS before coronary intervention had a lower mortality compared with those who had CPS on standby (7% vs. 18%, $P < .05$). A separate analysis was done of the 42 patients in the registry with 60% or more LMCA stenosis who underwent balloon angioplasty, and the results were compared with those for high-risk patients who had another vessel dilated.[53] The hospital mortality was 14.3% in patients who had angioplasty of the LMCA (prior to the stent era), notably higher than the 4.6% hospital mortality in patients who did not have significant LMCA disease and had angioplasty of another vessel ($P < .001$).[53]

In the prestent era, additional support with CPS did not improve the outcome of percutaneous intervention in LMCA disease. As the insertion technique evolved from requiring surgical cutdown to a percutaneous approach, as described by Shawl and colleagues,[54] the experience with CPS continued to grow in the cath lab; this group reported

one of the largest series of supported angioplasty from 1988 to 1991.[54-56] Among the first 51 patients, 94% had three-vessel disease, 70% had an LVEF of 35% or less, and the majority had been turned down for bypass surgery.[54] All the patients tolerated the coronary intervention, and the mean coronary stenosis improved from 89% to 21%. The hospital mortality was 6%, which compared well with the 6.9% mortality in patients undergoing CABG with an LVEF of 35% or less at that time.[57] The most frequent complication was bleeding that required transfusion, which occurred in 40% of the patients. Other complications included pseudoaneurysm (8%), hematoma (2%), and femoral nerve weakness (8%). With improvement in the cannula removal technique, the requirement for transfusion decreased in later patients to 4% and eliminated the occurrence of femoral nerve injury.[55] CPS showed promising short- and long-term results in patients at particularly high risk (mean LVEF ≤ 19.5% ± 3.5%, 54% with dilation of the single remaining patent artery, 17% with dilation of an unprotected LMCA).[56] Angiographic success was achieved in 98.7% of the arteries attempted in 105 patients. Despite the occurrence of asystole in 5 patients (4.8%) and of electromechanical dissociation in 40 (38.1%) with balloon inflation, no procedural deaths were reported, and all patients were weaned off CPS after the angioplasty. The hospital mortality was 4.7%. After a mean follow-up of 24 (± 13) months, 97% of patients were in Canadian Cardiovascular Society (CCS) functional class I or II, compared with only 3% before the intervention ($P < .001$).[56]

Because of the high rate of complications, attention was turned to using CPS on a standby basis. Two retrospective analyses showed that the incidence of hemodynamic collapse that required support during angioplasty was less than 1%.[50,58] Subsequently, the National Registry of Elective Cardiopulmonary Support compared the usefulness of prophylactic percutaneous CPS with standby percutaneous CPS in patients undergoing high-risk angioplasty.[59] Mortality rates were similar: 6.4% in the prophylactic group and 6.1% in the standby group. The rates of procedural success were also similar in the two groups. However, morbidity was significantly higher in the prophylactic CPS group: 42% of patients had femoral access-site complications that necessitated blood transfusions compared with only 11.7% of patients in the standby group. Of 180 patients in the standby group, only 13 (7.2%) suffered irreversible hemodynamic collapse, and emergency CPS was initiated in less than 5 minutes in 12 of these 13 patients. The patients who did benefit from prophylactic CPS were those with an ejection fraction of 20% or less, and mortality was lower with support initiated before angioplasty (4.8% vs. 18.8%, $P < .05$).[59]

A more recent European study evaluated the usefulness of CPS during the stent era.[60] The report included two groups of patients: group I comprised 68 patients undergoing elective high-risk coronary intervention, and group II consisted of 24 patients who presented with acute MI and cardiogenic shock. In the elective group, primary success was achieved in 66 patients (97%), with complete revascularization obtained in 44% of the group. Four patients (5.9%) developed femoral artery complications, and one patient (1.5%) died before discharge. After 28 (± 19) months of follow-up, MACEs occurred in 30% of patients and included 7 deaths (10.3%). Compared with the previous literature on angioplasty supported by CPS, this study demonstrated that CPS could be used effectively during coronary stenting and also showed an improvement in the rate of complications.

Two studies compared CPS and IABP for high-risk coronary interventions. One prospective trial randomized patients to either CPS or IABP support during PCI that was considered high risk because of the presence of unstable angina with poor LV function in a target vessel supplying more than half of the remaining viable myocardium.[61] Between June 1991 and November 1993, 40 patients were randomized. All patients had a history of a prior MI, the majority had three-vessel disease, and the mean EF in both groups was lower than 25%. All patients were treated with angioplasty using balloon inflations lasting longer than 2 minutes. Patients in both groups tolerated balloon inflations lasting 2 to 3 minutes without hemodynamic decompensation. Primary success was achieved in 19 of 20 patients in both groups with similar angiographic results. No vascular or hemorrhagic complications were reported in the IABP group, whereas two patients assigned to CPS developed vascular complications that required surgical repair, and five other patients required blood transfusions.[61] One death occurred in each group, thought to be caused by acute vessel closure after discontinuation of support. The study authors concluded that both IABP and CPS were effective in supporting high-risk coronary interventions in the present era, but IABP had lower rates of complications.

Schreiber and colleagues[62] reported retrospective observational data to compare outcomes in a larger group of patients who had undergone high-risk PCI with hemodynamic support. Over a 4-year period, 149 patients who had high-risk PCI underwent prophylactic placement of either an IABP ($n = 91$) or CPS ($n = 58$). Patients who presented with acute MI, unstable angina, and stable angina were included if they were hemodynamically stable before the procedure. Patients were considered high risk if they had poor ventricular function, had a culprit vessel supplying the majority of the myocardium, or required multivessel PCI. Patients who received CPS were more likely to be male (91% vs. 73%, $P < .01$) and more likely to have a history of chronic angina (91% vs. 69%, $P = .003$), congestive heart failure (59% vs. 35%, $P = .008$), and a lower mean ejection fraction (26% ± 13% vs. 32% ± 14%, $P < .01$). Multivessel PCI was performed more often in the CPS group (40% vs. 20%, $P < .01$). Despite the higher severity of their disease, angioplasty was successful more often in the CPS group compared with the IABP group (99% vs. 87% of lesions, $P = .005$). MACEs—which included MI, stroke, need for CABG, and death—occurred at similar rates in both groups, although the rate of CABG trended higher in the IABP group without reaching statistical significance (1.7% vs. 6.5%, $P = .33$). Of note, the rate of death was high in both groups (12% in the CPS group, 8.7% in the IABP group, $P = .71$).[62] As in the study by Kaul and colleagues,[61] access-site complications and transfusions occurred more frequently in the CPS group. The higher angioplasty success rate in the CPS group is likely explained by the longer duration of balloon inflation tolerated by this group. This difference would likely not exist with the use of stents. More recent case series in the stent era have generally supported the feasibility of temporary cardiopulmonary support for high-risk PCI with high procedural success but at the continued cost of vascular complications.[63,64]

Accordingly, use of CPS for high-risk PCI has decreased recently with the advent of minimally invasive pVADs. The studies that describe CPS in high-risk PCI are summarized in Table 36-4. Complications of prolonged use of CPS and ECMO include bleeding, infection, thrombocytopenia, and compromised perfusion to the lower extremity. The complexity of therapy and the requirements for a surgeon and a bedside perfusionist are the drawbacks to this therapy. Nonetheless, the high level of support may be the only option for some patients who experience full cardiopulmonary collapse that requires intervention, especially when both respiratory and circulatory support are required.

Percutaneous Left Ventricular Assist Devices

Left Atrial–Femoral Artery Bypass

A recent innovation in circulatory support available to interventionalists is the percutaneous ventricular assist device (pVAD). The left atrial–femoral artery bypass strategy, first described in 1962 by Dennis,[65-67] was initially used in patients who could not be weaned from cardiopulmonary bypass after surgery. More recently, a dedicated system with a compact centrifugal pump, the TandemHeart pVAD, was developed to allow relatively rapid percutaneous institution of left atrial–femoral artery bypass (Fig. 36-1).[41] The pump cycles oxygenated blood from the left atrium to the femoral artery without the need for an external oxygenator or a heat exchanger.

The left atrial–femoral artery bypass system indirectly unloads the LV and decreases cardiac filling pressures, cardiac workload, and myocardial oxygen demand.[68,69] Similar to CPS, however, patients with cardiogenic shock as a result of severe LV dysfunction may paradoxically exhibit a rise in myocardial oxygen demand due to an increase in afterload. Such cases may require additional LV unloading maneuvers,

TABLE 36-4 Percutaneous Cardiopulmonary Support Observational Trials

First Author	Year	Procedure	*N*	Revasc. Success Rate (%)	Device-Related Complication Rate (%)	Transfusion Rate (%)	In-Hospital Mortality Rate (%)	Bypass Time (Min)
Vogel[92]	1988	PTCA	9	100	11	100	11.0	NR
Shawl[54]	1989	PTCA	511*	100	14	38	5.8	37
Shawl[55]	1990	PTCA	121†	NR	9.9	29.7	NR	37‡
Teirstein[59]	1993	PTCA	389§	88.7	12.6	39	6.4	NR
Sivananthan[49]	1994	PTCA	13	83	83	100	7.7	92.8 ± 46
Kaul[61]	1995	PTCA	20	95	10	25	5	NR
Vogel[52]	1995	PTCA	801‖	93	15¶	31¶	6.9	NR
Shawl[56]	1995	PTCA	107	98	4.7	1.9	4.7	46 ± 30
Schreiber[62]	1998	PTCA	58	99	50	60	12	60 ± 45
de Lezo[93]	2002	PTCA	68#	97	6	NR	1.5	NR
Vainer[63]	2007	Stent	15	93	13	53	27**	NR
Bagai[64]	2011	Stent	20	100	NR	NR	28.2%	NR

NR, Not reported; *PTCA,* percutaneous transluminal angioplasty.
*Includes 20 patients with left ventricular ejection fraction of 25% of less, which are included in the 1996 report.
†A total of 121 patients were reported, 101 of which underwent elective coronary interventions.
‡Time reported for the elective interventions.
§Number of patients with prophylactic percutaneous cardiopulmonary support (CPS) device placement.
‖27% of patients were treated with a standby strategy.
¶Complication and transfusion rates were reported for the group with percutaneous CPS devices placed prophylactically.
#A total of 92 patients were reported, 68 of whom had elective procedures.
**Death rate at 15 months and in-hospital mortality were not reported.

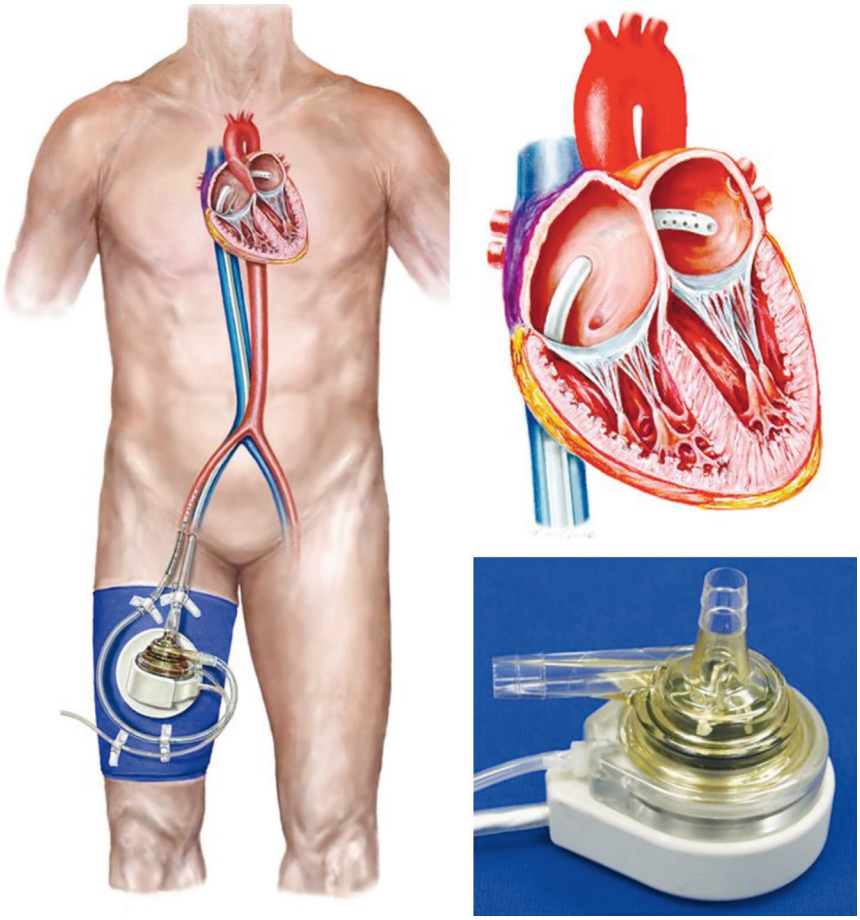

FIGURE 36-1 The TandemHeart percutaneous left ventricular assist device. The inflow cannula to the centrifugal pump is inserted transseptally to the left atrium, and the outflow is inserted in the femoral artery.

TABLE 36-5 Left Atrial–Femoral Artery Bypass Observational Trials

First Author	Year	N	Insertion Time (min)	Revasc. Success Rate (%)	Mean Support Duration	In-Hospital Mortality (n)	Other Complications
Glassman[74]*	1993	13	†	100	43 ± 17 min	0	• Transfusion in 1 of 13 patients • Small left-to-right shunts in 2 of 13 patients
Lemos[70]	2003	7‡	31 to 69	92.3	55 ± 96 hr	1	• Bleeding in 4 of 7 patients • Hypothermia in 2 of 7 patients
Aragon[68]	2005	8	†	100	§	1	• Acute renal failure requiring dialysis in 1 of 8 patients
Kar[73]	2006	5	†	100	107 min‖	1	• Blood transfusions in all patients • Groin hematomas in 2 of 5 patients
Al-Husami[94]	2008	6	36.5	100	†	1	• No vascular complications (all devices removed in the OR) • In 1 of 6, possible TIAs/seizure
Vranckx[75]	2008	23	35	91.3	31 ± 49.8 hr	5	• Bleeding in 27% • Hypothermia in 6 of 23 patients
Vranckx[95]	2009	9	27	100	93 min	0	• Vascular complications 44.4%
Thomas[76]	2010	37	†	100	†	11	• 82% transfusion rate
Alli[77]	2012	54	+	97	+	10¶	• 13% major vascular complication rate

OR, Operating room; *Revasc.,* revascularization; *TIA,* transient ischemic attack.
*The device used in this series was not the TandemHeart percutaneous ventricular assist device (pVAD).
†Not reported.
‡Five patients were hemodynamically stable prior to insertion of the pVAD.
§Not reported, but all patients had the pVAD removed in the catheterization laboratory at the end of the coronary intervention. The mean procedure time was 169 ± 21 minutes.
‖Excludes duration of support for one patient who required support for an additional 48 hours because of persistent poor left ventricular function.
¶30-day mortality.

such as IABP or Impella placement. Previous studies have shown a decrease in infarct size in the acutely ischemic myocardium with the use of a transseptal left ventricular assist device (LVAD). Predominant right ventricular failure and left atrial thrombus are contraindications to the use of a transseptal LVAD.

Insertion Technique

After angiography of the distal aorta and iliac vessels to exclude significant arterial occlusive disease, access in the femoral vein is obtained. After a transseptal puncture is performed, the interatrial septum is dilated in two stages with 14-Fr and 21-Fr dilators, and the 22-Fr inflow cannula is advanced to the left atrium under fluoroscopic and echocardiographic guidance.[69,70] The outflow 15-Fr to 17-Fr cannula (chosen based on the caliber of arterial vessels and desired flow rate) is then inserted by using the Seldinger technique over a stiff guidewire, and it is advanced to the common iliac artery. The cannulae are de-aired and connected to the pump.

The TandemHeart pVAD is a continuous-flow centrifugal pump that operates at 7500 rpm and provides up to 4.0 L/minute of blood flow. The pump contains a single moving part, an impeller suspended by a magnetic force on a thin lubricating film of fluid.[71] A continuous infusion of heparinized saline solution provides this hydrodynamic bearing for the pump, as well as local anticoagulation and cooling of the motor. Full systemic anticoagulation with heparin is required.

Clinical Trials

A small prospective feasibility study evaluated the hemodynamic effects of the TandemHeart pVAD in short-term stabilization of patients with cardiogenic shock.[69] The device was safely implanted in 18 patients, with a mean duration of support of 4 (± 3) days. Hemodynamic indices, including pulmonary capillary wedge pressure (PCWP), pulmonary arterial pressure (PAP), cardiac output, and systemic blood pressure showed a significant improvement on TandemHeart pVAD support. During support, hemolysis was negligible, bleeding that required transfusion occurred in five patients, and two with PAD required surgical placement of an antegrade perfusion cannula to relieve limb ischemia.

To date, mostly case reports and small series on the experience with the left atrial–femoral artery bypass system remain to support high-risk coronary interventions[68,70-74] (see Case Study 1); two small randomized trials have been undertaken, but no trials have been completed and no ongoing large randomized trials are underway. In early series, the device was shown to be easily implanted by interventionalists experienced in transseptal puncture and to provide circulatory support to allow high-risk coronary interventions to be done successfully in a controlled fashion (Table 36-5). Three case series were recently published.[75-77] In one, between 2000 and 2006, 23 patients with a mean age of 59 years underwent high-risk PCI using the TandemHeart device. Implantation was successful in all patients, and PCI was successful in 21 patients (91.3%). Hemodynamic parameters improved, including PCWP and systemic arterial pressure. Five patients died with the device in place, primarily from preexisting cardiogenic shock. Mild to moderate access-site bleeding was reported in 27% of patients. In the second series, 37 patients received the device for high-risk PCI or cardiogenic shock. The mean age was 73 years, and 97% were in New York Heart Association (NYHA) class III CHF or cardiogenic shock. Technical PCI success was reported in all patients, but 82% required blood transfusion after the procedure. Overall, however, 71% of patients in this extremely high-risk group survived to discharge. In the third study, from the Mayo Clinic, 54 patients were supported with the TandemHeart for high-risk PCI that included left main and multivessel stent placement in 64% of patients. Hemodynamics improved during support, including cardiac output and LV filling pressure; procedural success was high at 97%, and 6-month survival was 87%, but vascular complications occurred in 13%.[77]

Two small randomized trials have compared the TandemHeart to IABP in patients with cardiogenic shock.[78,79] Although benefit was seen in terms of hemodynamic parameters, a small meta-analysis that combined both studies did not suggest an effect on survival with use of the device.[80] Because of the transseptal puncture required, the TandemHeart pVAD may ultimately be best suited for elective initiation of hemodynamic support because insertion times tend to be longer compared with IABP and other pVAD devices (Impella). In addition, because it can provide up to 4.0 L/minute of flow, the TandemHeart

FIGURE 36-2 Baseline angiography showing distal left main coronary artery stenosis and subtotal occlusion of the proximal left anterior descending artery.

FIGURE 36-3 Percutaneous coronary intervention using two sirolimus-eluting stents in a "kissing" technique.

pVAD may be useful for high-risk PCI in the setting of cardiogenic shock, particularly when more potent Impella (CP or 5.0) or CPS devices are unavailable.

Case Study 1

An 80-year-old man with severe chronic obstructive pulmonary disease (COPD), chronic renal insufficiency, and carotid artery disease presented with unstable angina. Echocardiography revealed severe LV dysfunction (LVEF 10%), anterior wall akinesis, and moderate mitral regurgitation. Positron emission tomography (PET) showed lateral wall ischemia and high anterolateral viability. Cardiac catheterization revealed 95% distal LMCA disease involving the ostia of both the left anterior descending (LAD) and left circumflex (LCx) arteries (Fig. 36-2) and also revealed a 50% stenosis in the mid right coronary artery. The patient was thought to be at high risk for surgical revascularization; thus hemodynamically supported LMCA intervention with the TandemHeart pVAD was undertaken. After transseptal placement of a 21-Fr inflow cannula in the left atrium and placement of a 15-Fr outflow cannula in the right common iliac artery, left atrial–distal aorta bypass was achieved with a nonpulsatile flow rate of 3 L/minute. Bifurcation stenting of the LAD and LCx arteries was performed with two sirolimus-eluting stents deployed simultaneously using the "kissing" technique (Figs. 36-3 and 36-4). The decrease in aortic pulse pressure was significant because of diminished stroke volume, but the mean perfusion pressure was maintained, and the patient remained hemodynamically stable without angina or arrhythmia (Fig. 36-5). The patient was discharged 2 days after the procedure and remained angina-free at 1-month follow-up.[81]

FIGURE 36-4 Final angiography showing reconstruction of the distal left main coronary artery, proximal left anterior descending artery, and left circumflex coronary artery.

TRANSVALVULAR LEFT VENTRICULAR ASSIST DEVICES

In 1988, Wampler and colleagues[82] described a new catheter-mounted transvalvular LVAD, which was initially placed surgically via the femoral artery. Development of a smaller (13 Fr/14 Fr) system allowed percutaneous insertion of the device. Two investigational devices, the Impella and the Hemopump (Medtronic), have been tested clinically, although only the Impella is currently available for clinical use. The Impella Recover LP 2.5 is a microaxial rotary blood pump that unloads the LV by expelling blood from the LV to the aorta (Fig. 36-6). The device can deliver an output of up to 2.5 L/minute. The Impella device has been shown to directly unload the LV by decreasing the

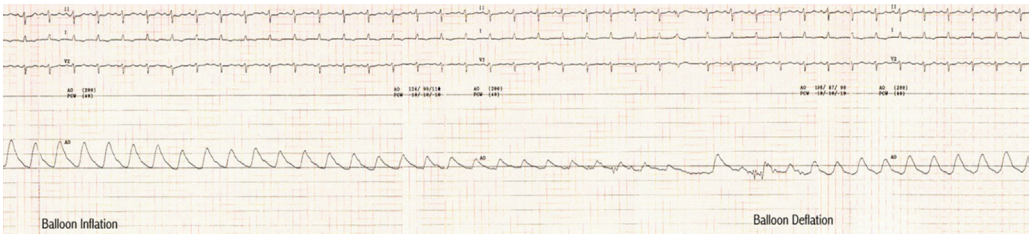

FIGURE 36-5 Aortic pressure tracing during balloon inflation shows a significant decrease in pulse pressure caused by diminished stroke volume with preserved mean perfusion pressure via the TandemHeart bypass circuit.

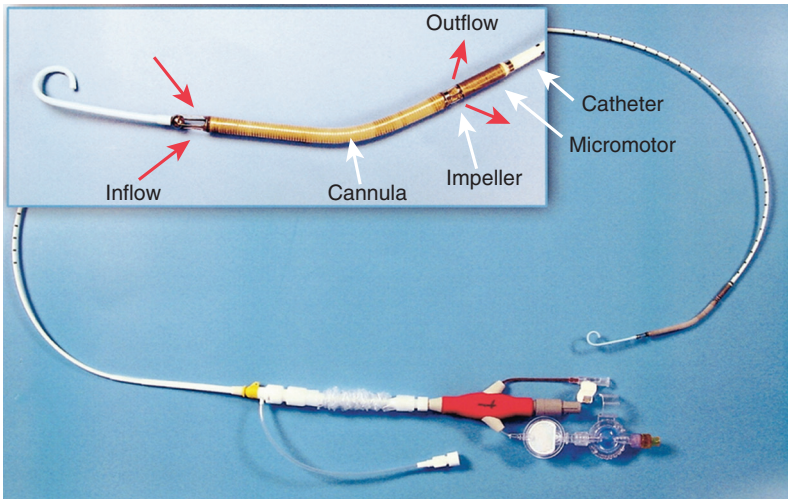

FIGURE 36-6 Impella Recover LP 2.5 device. (Adapted from Valgimigli M, Steendijk P, Sianos G, et al: Left ventricular unloading and concomitant total cardiac output increase by the use of percutaneous Impella Recover LP 2.5 assist device during high-risk coronary intervention. *Catheter Cardiovasc Interv* 65[2]:263-267, 2005.)

end-diastolic pressure, decreasing the end-diastolic and end-systolic volumes, and increasing the combined (device plus native heart) cardiac output, simultaneously improving coronary blood flow.[41,83,84] Notably, because the device withdraws blood from the LV during all phases of the cardiac cycle, including during isovolumic contraction and relaxation, theoretic benefits extend beyond comparable flow rates of other, indirect unloading devices (i.e., the TandemHeart and IABP). Larger Impella CP devices (delivering 3.5 to 4.0 L/min) and 5.0 devices with greater hemodynamic benefits are also available, but the 5.0 device typically requires surgical cutdown for placement.

Insertion Techniques

Before the procedure, an echocardiogram should be performed to exclude the presence of an LV thrombus or critical aortic stenosis. Angiography of the distal aorta and iliac vessels should also be performed before insertion of the femoral sheath. The Impella 2.5 percutaneous device has a maximal outer diameter of 12 F, whereas the Impella CP has a maximal outer diameter of 13 F. Often the vascular access site is "preclosed" with a suture-based closure device. After inserting an appropriately sized (usually 14 F) sheath in the femoral artery, an exchange length (300 cm) 0.014-inch guidewire is delivered to the LV with an end-hole angiographic catheter (Judkins Right 4 [JR4], Multipurpose A [MPA], etc.). The device is then advanced over the wire and is positioned across the aortic valve under fluoroscopic guidance. Recently, a wireless insertion technique has also been described.

Proper placement is critical to ensure unimpeded outflow of blood and catheter stability, and recent device modifications have improved on both of these aspects. The proximal part of the catheter connects to a portable mobile console that provides power and allows control of the pump.[84] The Impella Recover LP 2.5 device is mounted on a 9-Fr pigtail catheter (see Fig. 36-6), which sits in the LV cavity. The device provides flows of up to 2.5 L/minute at its maximal rotational speed of 50,000 rpm and can be safely left in place for up to 5 days.[83] The Impella CP can provide up to 4.0 L/minute of flow, whereas the 5.0 provides up to 5 L/minute of flow with similar implantation durations. A heparinized 20% dextrose solution continuously lubricates the pump. For prolonged support, heparin infusion to an activated clotting time (ACT) of 160 to 180 seconds is required.

Clinical Trials

Initial case studies evaluating the Impella 2.5 device in high-risk PCI suggested safety, feasibility, and minimal complications, with one report suggesting no significant benefit.[85] This was followed by A Prospective Feasibility Trial Investigating the Use of the Impella 2.5 System in Patients Undergoing High-Risk Percutaneous Coronary Intervention (PROTECT I),[20] the primary safety and feasibility study of 20 patients in the United States. Enrolling patients with LMCA or sole remaining conduit and severe LV dysfunction, the device was technically successful in all cases with a low complication rate. Several smaller registries have reported on use of the Impella 2.5 device in high-risk PCI, but the largest published series are the multicenter Europella Registry and the USpella Registry.[26,33,86,87] Case Study 2 represents an example of high-risk PCI utilizing Impella 2.5 support.

The baseline characteristics of the 144 patients in the EuroPella Registry suggested that these patients were indeed at high risk: 70% had an LVEF less than 30%, 36% had recent MI, 42% had prior surgical revascularization, 76% had previous MI, 20% had prior stroke, 26% had chronic lung disease, and 62% had diabetes. In addition, 55% had more than three target lesions, 52.8% had LMCA disease, 17.4% had intervention on a last remaining patent vessel, and 43.1% had refused CABG. The logistic EuroScore was 15 (± 12.2), which further indicated

TABLE 36-6 Transvalvular Left Ventricular Assist Device Observational Trials

First Author,	Year	*N*	Revasc. Success Rate	MACEs	Hemolysis	Support Duration (hr)
Dens*[86]	2006	23	100%	17%	22%	2.1 ± 1.6
Valgimigli[85]	2006	10	100%	30%†	60%	2.4 ± 1.5
Henriques[33]	2006	19	100%	5%	§	2.0‡
Burzotta[91]	2008	10	100%	0%	§	§
Dixon[20]	2009	20	100%	20%	10%	1.7 ± 0.6
Sjauw[26]	2009	144	100%	12.5%	<1%	1.45 ± 0.8
Maini[87]	2010	175	99%	8%	0%	1.0

*Revascularization (Revasc.) strategy included percutaneous coronary intervention (PCI) and off-pump coronary artery bypass (OPCAB).
†Four of ten patients also received a transfusion.
‡Maximum support time reported.
§Not reported.

the high-risk nature of this population. Despite this, overall mortality was 5.5% at 30 days. Another 5.5% required blood transfusion, and 0.7% required surgery for bleeding. No MI or need for emergent CABG was noted. Stroke occurred in 0.7% and vascular complications occurred in 4%.[26]

Recently, the results of the multicenter USPella Registry described outcomes in 251 patients using the Impella 2.5 device for a variety of real-world indications, including 178 for high-risk PCI.[87] Of these, 63% were in NYHA class III or IV heart failure, and 62% had an LVEF less than 30% before intervention. In addition, 56% of patients did not qualify for CABG because of excessive comorbidities. Results showed a 90% success rate and an 8% rate of 30-day MACEs. Survival was 96% at 30 days, 91% at 6 months, and 88% at 1 year. In addition, only 30% of patients remained in NYHA class III or IV heart failure, consistent with an absolute increase in mean ejection fraction from 31% to 37%. This latter improvement resulted in a 29% reduction in the anticipated need for implantable cardioverter defibrillators (ICDs) because the percentage of patients with an ejection fraction less than 30% was reduced from 62% to 44%.[32,87] Thus in real-world observational practice, Impella use appeared safe, feasible, and efficacious in improving signs and symptoms of heart failure and ventricular dysfunction. In the subset of patients who presented with AMI and cardiogenic shock, Impella also appeared to be safe and feasible; in addition, preprocedure placement of the Impella 2.5 appeared to improve survival compared with postprocedure placement, suggesting that early unloading may impact myocardial salvage and resultant long-term outcomes.[32]

The multicenter PROTECT II superiority trial randomized patients with similar inclusion criteria to PROTECT I to prophylactic IABP or Impella 2.5 support.[28] To date, PROTECT II is the largest RCT of high-risk PCI ever performed. Although the trial was terminated early for futility, 452 patients were ultimately randomized to IABP or Impella 2.5 for elective high-risk PCI. Enrolling, in general, a sicker patient population than the BCIS-1 trial, the primary end point, a composite of 11 end points at 30 days by intention-to-treat analysis, was no different between groups. However, the primary end point trended favoring Impella in the per-protocol population of patients who received the device per the inclusion and exclusion criteria (34.3% Impella vs. 42.2% IABP, $P = .092$). By 90 days, a prespecified secondary end point, the differences were magnified in the intention-to-treat population (40.6% Impella vs. 49.3% IABP, $P = .066$) and reached statistical significance in the per-protocol population (40.0% Impella vs. 51.0% IABP, $P = .023$).[28] Table 36-3 and Table 36-6 provide a summary of these trials.

The other transvalvular assist device, the Hemopump system, also expels blood from the LV to the aorta by using a rotating turbine that imparts both rotational and longitudinal velocities to the blood. This device has been shown to increase cardiac output and reduce mean PAP in clinical trials.[88-90] However, the Hemopump was not shown to significantly affect coronary blood flow velocities before or after angioplasty.[89] Small feasibility trials have shown the Hemopump to be safe in supporting high-risk interventions.[88-90] However, to date, the Hemopump is not available clinically.

Case Study 2

A 71-year-old man presented with accelerating angina over 1 month. A stress echo was performed but was terminated at 3 minutes because of chest pain and diffuse ST-segment depressions. Ejection fraction was 30%. The patient's metoprolol was increased and he was scheduled for cardiac catheterization. Patient history included hypertension, distant MI (treated medically), and significant vascular disease that included emergent repair of both an ascending aortic dissection and an abdominal aortic aneurysm, 10 and 3 years prior, respectively. The patient's coronary anatomy was not assessed at these times because of the emergent nature of his surgeries. At cardiac catheterization he was found to have distal left main bifurcation disease and moderate to severe systolic dysfunction, with an estimated ejection fraction of 25% (Video 36-1). Because of his prior operations, severe vascular disease, and COPD, he was felt to be a poor candidate for surgical revascularization. IABP placement was also relatively contraindicated because of the risk of repeated balloon-induced vascular trauma. Impella 2.5 supported high-risk PCI and was therefore considered. A right heart catheterization was performed to assess and maintain filling pressures, and the Impella device was inserted and placed across the aortic valve (Video 36-2). The LAD and LCx arteries wire wired, and simultaneous kissing stents were placed in the left main and daughter vessels (Video 36-3). During inflation, the patient remained hemodynamically stable with minimal decrease in systolic pressure (and pulse pressure) but with maintenance of diastolic pressure. After postdilation, the final angiographic result is seen in Video 36-4. Hemodynamics were reassessed, and the patient was weaned off the device over 15 minutes. The device was then removed. Preclose technique sutures were subsequently tied down with achievement of hemostasis. At 6 months, the ejection fraction improved to 35%, and the patient did not require implantable defibrillator placement. His angina was relieved after the procedure, and he was maintained on ischemic cardiomyopathy medications.

Guidelines on Use of Hemodynamic Support Devices in High-Risk Percutaneous Coronary Intervention

With the increasing dataset in recent years regarding percutaneous support devices, both observational and randomized, national guidelines have modified their recommendations in both high-risk PCI and cardiogenic shock subsets.[9] Accordingly, use of an appropriate percutaneous hemodynamic support device is now categorized as "may be reasonable" as an adjunct to high-risk PCI in carefully selected patients (class IIb recommendation). Ideal patients include predominantly those with the inclusion criteria specified within the BCIS-1 and PROTECT II trials, including left main and last patent conduit or

TABLE 36-7 Comparison of Circulatory Support Modalities

	Insertion Technique	Major Complications	Effect on Circulation	Length of Support	Advantages	Limitations	Contraindications
IABP	Percutaneous or surgical	• Limb ischemia • Stroke	Augments CO by up to 0.5 L/min	Days to weeks	• More prolonged support duration • Indirectly unloads the LV	• Requires stable rhythm • Lowest level of hemodynamic support	• Moderate to severe AI • Aortic disease • Uncontrolled sepsis • Coagulopathy • PAD
CPS	Percutaneous or surgical	• Bleeding, hemolysis • Stroke • Embolus	Provides complete circulatory support	Up to 6 hours	• Independent of rhythm • Allows controlled transfer to the OR • Full support	• Limited duration of support • Requires perfusionist • Does not unload the LV	• Moderate to severe AI • PAD • Coagulopathy
LA-FA pVAD	Percutaneous or surgical	• Pericardial tamponade • Aortic puncture • Limb ischemia	Augments CO by up to 3.5 L/min	Up to 14 days	• Prolonged support duration • Partial LV support • Indirectly unloads the LV	• Large arterial cannulae • Requires transseptal puncture • LV unloading may be limited in marked LV dysfunction	• PAD • RV failure • LA thrombus
LV-AO pVAD	Percutaneous or surgical	Limb ischemia	Augments CO by up to 2.5 L/min (2.5 device), 3.5 to 4.0 L/min (CP device) or 5.0 L/min (5.0 device)	Up to 14 days	• Prolonged support duration • Partial LV support • Markedly unloads the LV • Ease of use	Relatively large arterial cannula	• LV thrombus • VSD • Aortic stenosis • RV failure

AI, Aortic insufficiency; *CO,* cardiac output; *CPS,* cardiopulmonary support; *IABP,* intraaortic balloon pump; *LA,* left atrium; *LA-FA,* left atrium to femoral artery; *LV,* left ventricle; *LV-AO,* left ventricle–aorta; *OR,* operating room; *PAD,* peripheral arterial disease; *pVAD,* percutaneous ventricular assist device; *RV,* right ventricle; *VSD,* ventricular septal defect.

multivessel disease in the setting of markedly reduced ejection fraction. Therefore the IABP and Impella appear particularly suited for this indication. A class I recommendation is given to the use of cardiac support devices for patients with STEMI and persistent cardiogenic shock despite successful revascularization. Potent devices that include the TandemHeart, Impella CP or 5.0, or a CPS seem particularly suited for this indication; choice varies based on local experience, extent of support required, and device-specific complication rates. Currently, guidelines continue to support device placement after successful revascularization for patients who present with cardiogenic shock in the setting of AMI; whether earlier unloading prior to PCI will prove beneficial in this setting remains to be seen and is the subject of ongoing investigation.

CONCLUSION

With the development of stents and technical improvements in coronary wires, guiding catheters, and balloons, the rates of abrupt closure and hemodynamic collapse during percutaneous interventions have decreased. The improved technology has also allowed for higher-risk procedures, which would have been referred for bypass surgery in the early days of coronary angioplasty. Moreover, recent clinical trials have suggested that PCI may be a reasonable option in some patients with LMCA or multivessel coronary disease, many of whom are very old or have concomitant ventricular dysfunction, and recent PCI guidelines now allow LMCA stenting in appropriate candidates.[9] Furthermore, patients with AMI and cardiogenic shock remain an extremely high-risk PCI population. As a result, the field of high-risk PCI has evolved to include the use of cardiac assist devices to minimize periprocedural risk and improve short-term and long-term ventricular function and survival.

Although formal guidelines on the use of circulatory support devices during high-risk PCI are just now becoming available, much decision making continues to be left to the clinician. The decision to implement these devices, for example, is often at the discretion of the individual interventionalist and is based on the cumulative experience of completed and ongoing clinical trials. A thorough understanding of the high-risk clinical characteristics discussed in this chapter and the procedural and angiographic factors that portend a high risk of decompensation and mortality is the first step in the proper use of support devices. The choice of these devices should be based on the level of support provided by each device compared with the level of support necessary for the given clinical situation, the level of complexity of device insertion and maintenance of support, specific device-related risks, benefits and contraindications, local experience, and a working knowledge of the increasing evidence that supports their clinical use (Table 36-7). A multisociety consensus statement on the use of these devices in cardiovascular practice is currently in development and will provide more granular guidance on device choice in different settings and in future directions in this evolving field.

REFERENCES

1. Herrmann H, Hirshfeld J: Emergent stenting for failed percutaneous transluminal coronary angioplasty. In Herman HC, editor: *Clinical use of the Palmaz-Schatz intracoronary stent*, Mount Kisco, NY, 1993, Futura.
2. Brodie BR, Stuckey TD, Hansen D, et al: Intra-aortic balloon counterpulsation before primary percutaneous transluminal coronary angioplasty reduces catheterization laboratory events in high-risk patients with acute myocardial infarction. *Am J Cardiol* 84(1):18–23, 1999.
3. Cohen HA, Williams DO, Holmes DR, Jr, et al: Impact of age on procedural and 1-year outcome in percutaneous transluminal coronary angioplasty: a report from the NHLBI Dynamic Registry. *Am Heart J* 146(3):513–519, 2003.
4. Herrmann HC, Buchbinder M, Clemen MW, et al: Emergent use of balloon-expandable coronary artery stenting for failed percutaneous transluminal coronary angioplasty. *Circulation* 86(3): 812–819, 1992.
5. Seshadri N, Whitlow PL, Acharya N, et al: Emergency coronary artery bypass surgery in the contemporary percutaneous coronary intervention era. *Circulation* 106(18):2346–2350, 2002.
6. Williams DO, Holubkov R, Yeh W, et al: Percutaneous coronary intervention in the current era compared with 1985-1986: The National Heart, Lung, and Blood Institute Registries. *Circulation* 102(24):2945–2951, 2000.
7. Serruys PW, Morice MC, Kappetein AP, et al: Percutaneous coronary intervention versus coronary artery bypass grafting for severe coronary artery disease. *N Engl J Med* 360(10):961–972, 2009.
8. Syed AI, Karkar A, Torguson R, et al: Prophylactic intra-aortic balloon pump for high-risk percutaneous coronary intervention: will the Impella LP 2.5 device show superiority in a clinical randomized study? *Cardiovasc Revasc Med* 11(2):91–97, 2010.

9. Levine GN, Bates ER, Blankenship JC, et al: 2011 ACCF/AHA/SCAI Guidelines for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 58(24):e44–e122, 2011.
10. Hartzler GO, Rutherford BD, McConahay DR, et al: "High-risk" percutaneous transluminal coronary angioplasty. *Am J Cardiol* 61(14):33G–37G, 1988.
11. Block PC, Peterson ED, Krone R, et al: Identification of variables needed to risk adjust outcomes of coronary interventions: evidence-based guidelines for efficient data collection. *J Am Coll Cardiol* 32(1):275–282, 1998.
12. Wu C, Hannan EL, Walford G, et al: A risk score to predict in-hospital mortality for percutaneous coronary interventions. *J Am Coll Cardiol* 47(3):654–660, 2006.
13. Singh M, Rihal CS, Selzer F, et al: Validation of Mayo Clinic risk adjustment model for in-hospital complications after percutaneous coronary interventions, using the National Heart, Lung, and Blood Institute Dynamic Registry. *J Am Coll Cardiol* 42(10):1722–1728, 2003.
14. Holper EM, Blair J, Selzer F, et al: The impact of ejection fraction on outcomes after percutaneous coronary intervention in patients with congestive heart failure: an analysis of the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry and Dynamic Registry. *Am Heart J* 151(1):69–75, 2006.
15. Keelan PC, Johnston JM, Koru-Sengul T, et al: Comparison of in-hospital and one-year outcomes in patients with left ventricular ejection fractions < or = 40%, 41% to 49%, and > or = 50% having percutaneous coronary revascularization. *Am J Cardiol* 91(10):1168–1172, 2003.
16. Wilensky RL, Selzer F, Johnston J, et al: Relation of percutaneous coronary intervention of complex lesions to clinical outcomes (from the NHLBI Dynamic Registry). *Am J Cardiol* 90(3):216–221, 2002.
17. Bergelson BA, Jacobs AK, Cupples LA, et al: Prediction of risk for hemodynamic compromise during percutaneous transluminal coronary angioplasty. *Am J Cardiol* 70(20):1540–1545, 1992.
18. Myler RK, Shaw RE, Stertzer SH, et al: Lesion morphology and coronary angioplasty: current experience and analysis. *J Am Coll Cardiol* 19(7):1641–1652, 1992.
19. Laskey WK, Selzer F, Vlachos HA, et al: Comparison of in-hospital and one-year outcomes in patients with and without diabetes mellitus undergoing percutaneous catheter intervention (from the National Heart, Lung, and Blood Institute Dynamic Registry). *Am J Cardiol* 90(10):1062–1067, 2002.
20. Dixon SR, Henriques JP, Mauri L, et al: A prospective feasibility trial investigating the use of the Impella 2.5 system in patients undergoing high-risk percutaneous coronary intervention (The PROTECT I Trial): initial U.S. experience. *JACC Cardiovasc Interv* 2(2):91–96, 2009.
21. Anwar A, Mooney MR, Stertzer SH, et al: Intra-aortic balloon counterpulsation support for elective coronary angioplasty in the setting of poor left ventricular function: a two center experience. *J Invasive Cardiol* 2(4):175–180, 1990.
22. Kahn JK, Rutherford BD, McConahay DR, et al: Supported "high risk" coronary angioplasty using intraaortic balloon pump counterpulsation. *J Am Coll Cardiol* 15(5):1151–1155, 1990.
23. Voudris V, Marco J, Morice MC, et al: "High-risk" percutaneous transluminal coronary angioplasty with preventive intra-aortic balloon counterpulsation. *Cathet Cardiovasc Diagn* 19(3):160–164, 1990.
24. Kreidieh I, Davies DW, Lim R, et al: High-risk coronary angioplasty with elective intra-aortic balloon pump support. *Int J Cardiol* 35(2):147–152, 1992.
25. Osterne EC, Alexim GA, da Motta VP, et al: Intraaortic balloon pump support during coronary angioplasty. Initial experience. *Arq Bras Cardiol* 73(2):191–200, 1999.
26. Sjauw KD, Konorza T, Erbel R, et al: Supported high-risk percutaneous coronary intervention with the Impella 2.5 device: the Europella registry. *J Am Coll Cardiol* 54(25):2430–2434, 2009.
27. Perera D, Stables R, Thomas M, et al: Elective intra-aortic balloon counterpulsation during high risk percutaneous coronary intervention: a randomized controlled trial. *JAMA* 304(8):867–874, 2010.
28. O'Neill WW, Kleiman NS, Moses J, et al: A prospective randomized clinical trial of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention. *Circulation* 126(4):1717–1727, 2012.
29. Perera D, Stables R, Clayton T, et al: Long-term mortality data from the balloon pump-assisted coronary intervention study (BCIS-1): a randomized, controlled trial of elective balloon counterpulsation during high-risk percutaneous coronary intervention. *Circulation* 127(2):207–212, 2013.
30. Sjauw KD, Engstrom AE, Vis MM, et al: A systematic review and meta-analysis of intra-aortic balloon pump therapy in ST elevation myocardial infarction: Should we change the guidelines? *Eur Heart J* 30(4):389–390, 2009.
31. Thiele H, Zeymer U, Neumann FJ, et al: Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 367(14):1287–1296, 2012.
32. O'Neill WW, Schreiber T, Wohns DH, et al: The current use of Impella 2.5 in acute myocardial infarction complicated by cardiogenic shock: results from the USPella Registry. *J Interv Cardiol* 27(1):1–11, 2014.
33. Henriques JP, Remmelink M, Baan J, Jr, et al: Safety and feasibility of elective high-risk percutaneous coronary intervention procedures with left ventricular support of the Impella Recover LP 2.5. *Am J Cardiol* 97(7):990–992, 2006.
34. Mulukutla SR, Pacella JJ, Cohen A: Percutaneous mechanical assist devices for severe left ventricular dysfunction. In Hasdai E, et al, editors: *Contemporary cardiology: Cardiogenic shock: diagnosis and treatment*, Totowa, NJ, 2002, Humana Press.
35. Mendoza DD, Cooper HA, Panza JA: Cardiac power output predicts mortality across a broad spectrum of patients with acute cardiac disease. *Am Heart J* 153(3):366–370, 2007.
36. Kantrowitz A, Tjonneland S, Freed PS, et al: Initial clinical experience with intraaortic balloon pumping in cardiogenic shock. *JAMA* 203(2):113–118, 1968.
37. Bolooki H: Current status of circulatory support with an intra-aortic balloon pump. *Cardiol Clin* 3(1):123–133, 1985.
38. Bregman D, Casarella WJ: Percutaneous intraaortic balloon pumping: initial clinical experience. *Ann Thorac Surg* 29(2):153–155, 1980.
39. Weber KT, Janicki JS: Intraaortic balloon counterpulsation. A review of physiological principles, clinical results, and device safety. *Ann Thorac Surg* 17(6):602–636, 1974.
40. Buckley MJ, Leinbach RC, Kastor JA, et al: Hemodynamic evaluation of intra-aortic balloon pumping in man. *Circulation* 41(5 Suppl):II130–II136, 1970.
41. Naidu SS: Novel percutaneous cardiac assist devices—the science of and indications for hemodynamic support. *Circulation* 123(5):533–543, 2011.
42. O'Murchu B, Foreman RD, Shaw RE, et al: Role of intraaortic balloon pump counterpulsation in high risk coronary rotational atherectomy. *J Am Coll Cardiol* 26(5):1270–1275, 1995.
43. Briguori C, Sarais C, Pagnotta P, et al: Elective versus provisional intra-aortic balloon pumping in high-risk percutaneous transluminal coronary angioplasty. *Am Heart J* 145(4):700–707, 2003.
44. Abdel-Wahab M, Saad M, Kynast J, et al: Comparison of hospital mortality with intra-aortic balloon counterpulsation insertion before versus after primary percutaneous coronary intervention for cardiogenic shock complicating acute myocardial infarction. *Am J Cardiol* 105(7):967–971, 2010.
45. Curtis JP, Rathore SS, Wang Y, et al: Use and effectiveness of intra-aortic balloon pumps among patients undergoing high risk percutaneous coronary intervention: insights from the National Cardiovascular Data Registry. *Circ Cardiovasc Qual Outcomes* 5(1):21–30, 2012.
46. Litzie A: Extracorporeal cardiopulmonary bypass support: a historical and current perspective. In Shawl F, editor: *Supported complex and high risk coronary angioplasty*, Boston, MA, 1991, Kluwer Academic Publishers.
47. Shawl F: Percutaneous cardiopulmonary bypass support: technique, indications and complications. In Shawl F, editor: *Supported complex and high risk coronary angioplasty*, Boston, MA, 1991, Kluwer Academic Publishers.
48. Vogel RA: The Maryland experience: Angioplasty and valvuloplasty using percutaneous cardiopulmonary support. *Am J Cardiol* 62(18):11K–14K, 1988.
49. Sivananthan MU, Rees MR, Browne TF, et al: Coronary angioplasty in high risk patients with percutaneous cardiopulmonary support. *Eur Heart J* 15(8):1057–1062, 1994.
50. Ferrari M, Scholz KH, Figulla HR: PTCA with the use of cardiac assist devices: risk stratification, short- and long-term results. *Cathet Cardiovasc Diagn* 38(3):242–248, 1996.
51. Vogel RA, Shawl F, Tommaso C, et al: Initial report of the National Registry of Elective Cardiopulmonary Bypass Supported Coronary Angioplasty. *J Am Coll Cardiol* 15(1):23–29, 1990.
52. Vogel RA: Cardiopulmonary bypass support of high risk coronary angioplasty patients: registry results. *J Interv Cardiol* 8(2):193–197, 1995.
53. Tommaso CL, Vogel JH, Vogel RA: Coronary angioplasty in high-risk patients with left main coronary stenosis: results from the National Registry of Elective Supported Angioplasty. *Cathet Cardiovasc Diagn* 25(3):169–173, 1992.
54. Shawl FA, Domanski MJ, Punja S, et al: Percutaneous cardiopulmonary bypass support in high-risk patients undergoing percutaneous transluminal coronary angioplasty. *Am J Cardiol* 64(19):1258–1263, 1989.
55. Shawl FA, Domanski MJ, Wish MH, et al: Percutaneous cardiopulmonary bypass support in the catheterization laboratory: technique and complications. *Am Heart J* 120(1):195–203, 1990.
56. Shawl FA, Quyyumi AA, Bajaj S, et al: Percutaneous cardiopulmonary bypass-supported coronary angioplasty in patients with unstable angina pectoris or myocardial infarction and a left ventricular ejection fraction < or = 25%. *Am J Cardiol* 77(1):14–19, 1996.
57. Alderman EL, Fisher LD, Litwin P, et al: Results of coronary artery surgery in patients with poor left ventricular function (CASS). *Circulation* 68(4):785–795, 1983.
58. Guarneri EM, Califano JR, Schatz RA, et al: Utility of standby cardiopulmonary support for elective coronary interventions. *Catheter Cardiovasc Interv* 46(1):32–35, 1999.
59. Teirstein PS, Vogel RA, Dorros G, et al: Prophylactic versus standby cardiopulmonary support for high risk percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 21(3):590–596, 1993.
60. Suarez de Lezo J, Pan M, Medina A, et al: Percutaneous cardiopulmonary support in critical patients needing coronary interventions with stents. *Catheter Cardiovasc Interv* 57(4):467–475, 2002.
61. Kaul U, Sahay S, Bahl VK, et al: Coronary angioplasty in high risk patients: comparison of elective intraaortic balloon pump and percutaneous cardiopulmonary bypass support—a randomized study. *J Interv Cardiol* 8(2):199–205, 1995.
62. Schreiber TL, Kodali UR, O'Neill WW, et al: Comparison of acute results of prophylactic intraaortic balloon pumping with cardiopulmonary support for percutaneous transluminal coronary angioplasty (PCTA). *Cathet Cardiovasc Diagn* 45(2):115–119, 1998.
63. Vainer J, van Ommen V, Maessen J, et al: Elective high risk percutaneous coronary interventions supported by extracorporeal life support. *Am J Cardiol* 99(6):771–773, 2007.
64. Bagai J, Webb D, Kasasbeh H, et al: Efficacy and safety of percutaneous life support during high-risk percutaneous coronary intervention, refractory shock, and in-laboratory cardiopulmonary arrest. *J Invasive Cardiol* 23(4):141–147, 2011.
65. Killen DA, Piehler JM, Borkon AM, et al: Bio-medicus ventricular assist device for salvage of cardiac surgical patients. *Ann Thorac Surg* 52(2):230–235, 1991.
66. Pavie A, Leger P, Nzomvuama A, et al: Left centrifugal pump cardiac assist with transseptal percutaneous left atrial cannula. *Artif Organs* 22(6):502–507, 1998.
67. Edmunds LH, Jr, Herrmann HC, DiSesa VJ, et al: Left ventricular assist without thoracotomy: clinical experience with the Dennis method. *Ann Thorac Surg* 57(4):880–885, 1994.
68. Aragon J, Lee MS, Kar S, et al: Percutaneous left ventricular assist device: "TandemHeart" for high-risk coronary intervention. *Catheter Cardiovasc Interv* 65(3):346–352, 2005.
69. Thiele H, Lauer B, Hambrecht R, et al: Reversal of cardiogenic shock by percutaneous left atrial-to-femoral arterial bypass assistance. *Circulation* 104(24):2917–2922, 2001.
70. Lemos PA, Cummins P, Lee CH, et al: Usefulness of percutaneous left ventricular assistance to support high-risk percutaneous coronary interventions. *Am J Cardiol* 91(4):479–481, 2003.
71. Vranckx P, Foley DP, de Feijter PJ, et al: Clinical introduction of the TandemHeart, a percutaneous left ventricular assist device, for circulatory support during high-risk percutaneous coronary intervention. *Int J Cardiovasc Interv* 5(1):35–39, 2003.
72. Kar B, Butkevich A, Civitello AB, et al: Hemodynamic support with a percutaneous left ventricular assist device during stenting of an unprotected left main coronary artery. *Tex Heart Inst J* 31(1):84–86, 2004.
73. Kar B, Forrester M, Gemmato C, et al: Use of the TandemHeart percutaneous ventricular assist device to support patients undergoing high-risk percutaneous coronary intervention. *J Invasive Cardiol* 18(3):93–96, 2006.
74. Glassman E, Chinitz LA, Levite HA, et al: Percutaneous left atrial to femoral arterial bypass pumping for circulatory support in high-risk coronary angioplasty. *Cathet Cardiovasc Diagn* 29(3):210–216, 1993.
75. Vranckx P, Meliga E, De Jaegere PP, et al: The TandemHeart, percutaneous transseptal left ventricular assist device: a safeguard in high-risk percutaneous coronary interventions. The six-year Rotterdam experience. *EuroIntervention* 4(3):331–337, 2008.
76. Thomas JL, Al-Ameri H, Economides C, et al: Use of a percutaneous left ventricular assist device for high-risk cardiac interventions and cardiogenic shock. *J Invasive Cardiol* 22(8):360–364, 2010.
77. Alli OO, Singh IM, Holmes DR, et al: Percutaneous left ventricular assist device with TandemHeart for high-risk percutaneous coronary intervention: the Mayo Clinic experience. *Catheter Cardiovasc Interv* 80(5):728–734, 2012.
78. Burkhoff D, Cohen H, Brunckhorst C, et al: A randomized multicenter clinical study to evaluate the safety and efficacy of the TandemHeart percutaneous ventricular assist device versus conventional therapy with intraaortic balloon pumping for treatment of cardiogenic shock. *Am Heart J* 152(3):469–478, 2006.
79. Thiele H, Sick P, Boudriot E, et al: Randomized comparison of intra-aortic balloon support with a percutaneous left ventricular assist device in patients with revascularized acute myocardial infarction complicated by cardiogenic shock. *Eur Heart J* 26(13):1276–1283, 2005.
80. Sjauw KD, Engstrom AE, Henriques JP: Percutaneous mechanical cardiac assist in myocardial infarction. Where are we now, where are we going? *Acute Card Care* 9(4):222–230, 2007.
81. Naidu SS, Rohatgi S, Herrmann HC, Glaser R: Unprotected left main "kissing" stent implantation with a percutaneous ventricular assist device. *J Invasive Cardiol* 16(11):683–684, 2004.
82. Wampler RK, Moise JC, Frazier OH, et al: In vivo evaluation of a peripheral vascular access axial flow blood pump. *ASAIO Trans* 34(3):450–454, 1988.
83. Valgimigli M, Steendijk P, Sianos G, et al: Left ventricular unloading and concomitant total cardiac output increase by the use of percutaneous Impella Recover LP 2.5 assist device during high-risk coronary intervention. *Catheter Cardiovasc Interv* 65(2):263–267, 2005.
84. Reesink KD, Dekker AL, Van Ommen V, et al: Miniature intracardiac assist device provides more effective cardiac unloading and circulatory support during severe left heart failure than intraaortic balloon pumping. *Chest* 126(3):896–902, 2004.
85. Valgimigli M, Steendijk P, Serruys PW, et al: Use of Impella Recover LP 2.5 left ventricular assist device during high-risk percutaneous coronary interventions: clinical, haemodynamic and biochemical findings. *EuroIntervention* 2:91–100, 2006.
86. Dens J, Meyns B, Hilgers RD, et al: First experience with the Impella Recover LP 2.5 micro axial pump in patients with cardiogenic shock or undergoing high-risk revascularization. *EuroIntervention* 2:84–90, 2006.

87. Maini B, Naidu SS, Mulukutla S, et al: Real-world use of the Impella 2.5 circulatory support system in complex high-risk percutaneous coronary intervention: the USPella Registry. *Catheter Cardiovasc Interv* 80(5):717–725, 2012.
88. Scholz KH, Dubois-Rande JL, Urban P, et al: Clinical experience with the percutaneous hemopump during high-risk coronary angioplasty. *Am J Cardiol* 82(9):1107–1110, A6, 1998.
89. Dubois-Rande JL, Teiger E, Garot J, et al: Effects of the 14F hemopump on coronary hemodynamics in patients undergoing high-risk coronary angioplasty. *Am Heart J* 135(5 Pt 1):844–849, 1998.
90. Smalling RW, Sweeney M, Lachterman B, et al: Transvalvular left ventricular assistance in cardiogenic shock secondary to acute myocardial infarction. Evidence for recovery from near fatal myocardial stunning. *J Am Coll Cardiol* 23(3):637–644, 1994.
91. Burzotta F, Paloscia L, Trani C, et al: Feasibility and long-term safety of elective Impella-assisted high-risk percutaneous coronary intervention: a pilot two-centre study. *J Cardiovasc Med* 9(10):1004–1010, 2008.
92. Vogel RA, Tommaso CL, Gundry SR: Initial experience with coronary angioplasty and aortic valvuloplasty using elective semipercutaneous cardiopulmonary support. *Am J Cardiol* 62(10 Pt 1): 811–813, 1988.
93. de Lezo JS, Medina A, Romero M, et al: Effectiveness of percutaneous device occlusion for atrial septal defect in adult patients with pulmonary hypertension. *Am Heart J* 144(5):877–880, 2002.
94. Al-Husami W, Yturralde F, Mohanty G, et al: Single-center experience with the TandemHeart percutaneous ventricular assist device to support patients undergoing high-risk percutaneous coronary intervention. *J Invasive Cardiol* 20(6):319–322, 2008.
95. Vranckx P, Schultz CJ, Valgimigli M, et al: Assisted circulation using the TandemHeart during very high-risk PCI of the unprotected left main coronary artery in patients declined for CABG. *Catheter Cardiovasc Interv* 74(2):302–310, 2009.

37 Regional Centers of Excellence for the Care of Patients With Acute Ischemic Heart Disease

DEAN J. KEREIAKES | TIMOTHY D. HENRY

KEY POINTS

- Current clinical practice guidelines for the care of patients who present with ST-segment elevation myocardial infarction (STEMI) provide a class I recommendation that "all communities should create and maintain a regional system of STEMI care that includes assessment and continuous quality improvement of EMS [emergency medical services] and hospital-based activities" (class I, level of evidence B).
- "Regional" care for patients with acute coronary syndromes implies "meaningful networking associations" between community and rural hospitals that do not provide tertiary cardiovascular services and a tertiary cardiovascular service provider. The definition of *networking* ranges from being a merged affiliate (same hospital system) to sharing common patient care protocols, as well as tracking, reporting, and auditing clinical practice guideline compliance, core measures, and clinical outcomes.
- For both physician operators and hospitals/facilities, a direct relationship exists between annual volume of cardiovascular procedures—coronary bypass surgery, coronary angioplasty, and stenting—and optimal clinical outcomes, including survival. Those doctors and hospitals performing the highest annual volumes of procedures have the best outcomes.
- The prehospital phase of acute STEMI is critically important. The performance and transmission of a 12-lead electrocardiogram by emergency medical services (EMS) providers in the field at the point of first medical contact has been demonstrated to significantly reduce time delays to initiation of STEMI treatment and to reduce mortality. Strategies are currently being evaluated to further reduce time delay to treatment, and these include prehospital catheterization laboratory (cath lab) activation by EMS and emergency department bypass with direct transport of STEMI patients to the cath lab.
- A system for STEMI care should comprise multiple integral components that include a patient care focus, enhanced operational efficiency, appropriate system incentives (pay for performance, pay for value), specific outcome and process measures, and mechanisms for quality review with continuous quality improvement.
- Because of marked regional variation in EMS and hospital resources, geography, population density, and transport distances, no single "system model" for STEMI care is likely to be either practical or achievable in the United States. With specific goals to (1) accelerate the implementation of STEMI care systems in selected U.S. metropolitan areas, (2) facilitate more effective delivery of STEMI care, and (3) improve clinical outcomes, the regional systems of care demonstration project—Mission: Lifeline STEMI Accelerator—was created as a national outcomes research study. Data should soon be available in regard to individual hospitals and regional performance, with inclusion of prehospital, emergency department, cath lab, and in-hospital management and clinical outcomes.

The rapid restoration of normal coronary blood flow via pharmacologic and/or mechanical recanalization of an occluded coronary artery limits the extent of myocardial necrosis and reduces mortality of patients who present with STEMI.[1] Furthermore, primary percutaneous coronary intervention (PPCI) has demonstrated more frequent, complete, and durable coronary reperfusion in both randomized controlled trials (RCTs) and observational studies and is the preferred revascularization modality by current guidelines if PPCI can be provided in a prompt, expert manner.[1,2] Indeed, current American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines recommend EMS transport directly to a PCI-capable hospital for PPCI as the recommended strategy for STEMI patients, with an ideal first medical contact to PCI device-time system goal of 90 minutes or less (class I, level of evidence B).[1] However, particularly in the United States, a concerted, integrated approach to STEMI therapy has been complicated by the diversity and extent of resources required for comprehensive treatment and by the various settings (urban, suburban, rural) in which care is delivered. Data from national registries have demonstrated a failure to achieve recommended system goals, particularly among STEMI patients who presented to hospitals without PCI capability and required interhospital transfer for PPCI.[3] The creation of specialized care centers for other medical emergencies, such as trauma and acute stroke, has been shown to improve clinical outcomes;[4,5] therefore the concept of developing regional centers of excellence for STEMI care[6] has become the focus of a collaborative initiative of the AHA and the ACCF as well as individual states.[3]

The term *regional* implies meaningful networking associations between all prehospital and hospital-based constituents that enable rapid recognition and timely reperfusion of STEMI patients in an integrated fashion.[3,7] These initiatives have been in part prompted by studies that demonstrate shortfalls in the achievement of quality-ensured, guideline-compliant care in addition to disparities in treatment on the basis of age, sex, race, geographic location, or time of STEMI presentation.[3] System-related delays to STEMI reperfusion have been correlated with higher rates of morbidity and mortality. Through focus on system process components, multiple national initiatives such as Get With The Guidelines, the Guidelines Applied to Practice (GAP) project, the National Registry of Myocardial Infarction (NRMI), the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines? (CRUSADE) registry, and the D2B (door-to-balloon) Alliance have demonstrated a positive impact as reflected by increased clinical practice guideline (CPG) adherence for early (≤24 hr) and predischarge medical therapies and a reduction in D2B and door-to-needle (D2N) times, as well as door-in–door-out (DIDO) times, for patients who require interhospital transfer.[8] Nevertheless, broader and more region-specific system-based initiatives such as Mission: Lifeline are required to reduce total ischemic time—that is, time from chest pain symptom onset to coronary recanalization—which is the principal determinant of outcome.[7] *Total ischemic time* comprises the aggregate of time intervals from STEMI symptom onset and system activation (911 call) to EMS contact at the scene (first medical contact), transport times, and in-hospital D2B times.[9] Any delay in reperfusion (i.e., prolongation of total ischemic time) is associated with higher short-term (in-hospital, 30-day) and late (1-year) mortality in a continuous, nonlinear fashion.[10-12] Because only a minority of U.S. hospitals are capable of performing PCI, the provision of prompt, expert PCI as the preferred reperfusion modality for the majority of STEMI patients is a formidable challenge that will ultimately require regional integration of resources.[3]

THE CASE FOR REGIONALIZED CARE

Based in part on experience with trauma and stroke care in the United States and on the experience of regionalized systems for acute coronary syndrome (ACS) care in several European countries, proponents of regionalized centers of excellence for the care of ACS in the United States assert that such a strategy will provide better care and will also improve access to specialist physicians with consequent better clinical outcomes. Several basic tenets form the foundation of this premise and include observations that (1) annual PCI procedural volumes are related to clinical outcomes, (2) medical resources are limited, and (3) regionalization facilitates CPG adherence, quality and outcomes monitoring, and access to advanced technology and expertise.

A direct relationship has been demonstrated between both hospital facility and physician operator annual procedural volumes and optimal clinical outcomes following either elective or primary PCI and coronary artery bypass grafting (CABG).[13-20] Physicians and hospitals with the highest procedure volumes have lower risk-adjusted in-hospital mortality even in the current era of coronary stenting. Indeed, the relative benefit of PPCI versus fibrinolysis for the treatment of STEMI may be lost when PPCI is performed in a low-volume institution.[13] Although no differences in outcomes were observed in the American College of Cardiology National Cardiovascular Data Registry (NCDR) among PPCI centers stratified on the basis of cardiac surgery capability (with vs. without),[21] risk-adjusted hospital mortality was increased (hazard ratio [HR] 1.20; 95% confidence interval [CI], 1.08 to 1.33; $P = .001$) among centers that perform in the lowest tertile of annual PPCI volumes (<36 procedures/yr) when compared with those in the highest tertile (>60 procedures/yr).[18] Institutional annual PPCI volume significantly influences the process of care as reflected by compliance with guideline-recommended D2B times under 90 minutes (Fig. 37-1). Similarly, data from the New York statewide database demonstrate that hospital annual PPCI volume influences in-hospital mortality by about 50% after the procedure (Fig. 37-2, *A*).[17] In the Cardiovascular Patient Outcomes Research Team (C-PORT) PPCI trial,[22] a significant reduction in risk-adjusted mortality was observed among those hospitals without cardiac surgical capability who were in the highest tertile of annual PPCI procedural volume (mean 83 procedures/yr). A pooled analysis of multiple studies that included over one million PCI procedures confirmed the relationship between lower annual hospital PCI volumes (≤200 cases) with an increase in in-hospital mortality and the requirement for emergency CABG following PCI.[23] Notably, a meta-regression analysis[24] demonstrated that this PCI volume–in-hospital mortality effect size grows stronger as the proportion of PCIs performed using stents (vs. balloon angioplasty alone) increases. These specific data on annual institutional volume and outcome have been acknowledged by both the recent ACCF/AHA/SCAI (Society for Cardiovascular Angiography and Interventions) 2013 Update of the Clinical Competence Statement on Coronary Artery Interventional Procedures[25] and the SCAI/ACC/AHA 2014 Expert Consensus Document regarding PCI without on-site surgical backup as follows[26]: "It is important to note that a signal exists suggesting that an institutional volume threshold [below] 200 PCI/year appears to be consistently associated with worse outcomes across various studies." The Clinical Competence Statement then continues, "Accordingly, the writing committee recommends that an institution without on-site surgery with a volume fewer than 200 PCI annually, unless in a region underserved because of geography, should strongly consider whether or not it should continue to offer this service."[25]

A similar PCI volume–outcome (in-hospital mortality) relationship has been demonstrated for physician operators by the New York statewide database for PPCI[17] (see Fig. 37-2, *B*) and by the ACC/NCDR for both elective and nonelective PCI.[19] In-hospital mortality was increased for elective (no STEMI/shock) PCI (HR 1.27; 95% CI, 1.11 to 1.45; $P < .001$) and nonelective (STEMI/shock) PCI (HR 1.10; 95% CI, 1.00 to 1.21; $P = .06$) among physician operators who performed fewer than 75 PCIs per year (vs. ≥75 PCIs/yr).[19] Despite these data in support of higher annual volume credentialing numbers for physician operators, both the 2013 Clinical Competency Statement and the 2014 Expert Consensus Document allow for lower annual PCI volumes (≥50 total PCI and ≥11 PPCI/yr) for credentialing.[25,26] Considering the declining number of PCI procedures performed annually in the United States, the reduction in disease prevalence for both coronary artery disease (CAD) and STEMI, and the need for medical cost reduction while maintaining or increasing quality, a more reasonable approach might be to promote regionalization, with fewer institutions providing PCI, and to encourage operators to maintain higher annual volume thresholds rather than to arbitrarily lower the previously established annual PCI volume threshold (≥75 PCI/yr). This is important because 26% of all centers that report to the ACC/NCDR performed fewer than 200 PCIs per year, and 38% performed fewer than 36 PCIs per year.[18,27] In addition, recent data suggest that the performance of inappropriate

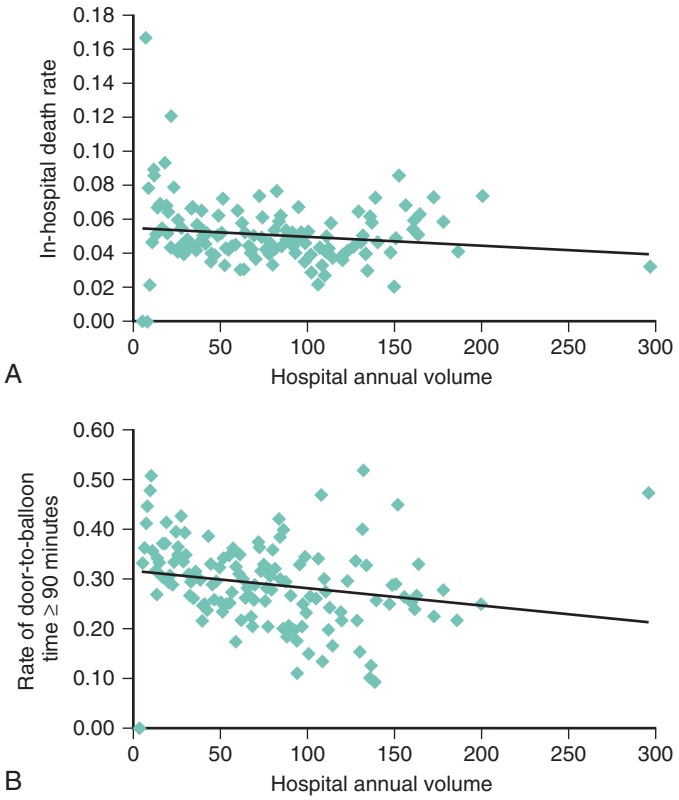

FIGURE 37-1 **A,** Primary percutaneous intervention (PPCI) annual volume was shown to be inversely related to in-hospital mortality among 86,044 ST-segment elevation myocardial infarction patients reported by 738 participating American College of Cardiology (ACC)/National Cardiovascular Data Registry (NCDR) hospitals from 2006 through 2009 following multivariate adjustment. Hazard for in-hospital death was increased (1.20; 95% confidence interval [CI], 1.08 to 1.33; $P = .001$) in low-volume (≤36 PPCI/yr) versus high-volume (>60 PPCI/yr) centers. **B,** The portion of patients who achieved guideline-compliant door-to-balloon (D2B) times (<90 min) as reported to ACC/NCDR is directly proportional to institutional annual PPCI volume. D2B times were significantly shorter in high-volume hospitals compared with low-volume hospitals (median 72 min, interquartile range [IR] 53 to 91 vs. median 77 min, IR 57 to 100; $P < .0001$). (From Kontos Wang Y, Chaudhry SI, et al: Lower hospital volume is associated with higher in-hospital mortality in patients undergoing primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction: a report from the NCDR. *Circ Cardiovasc Qual Outcomes* 6:659-667, 2013.)

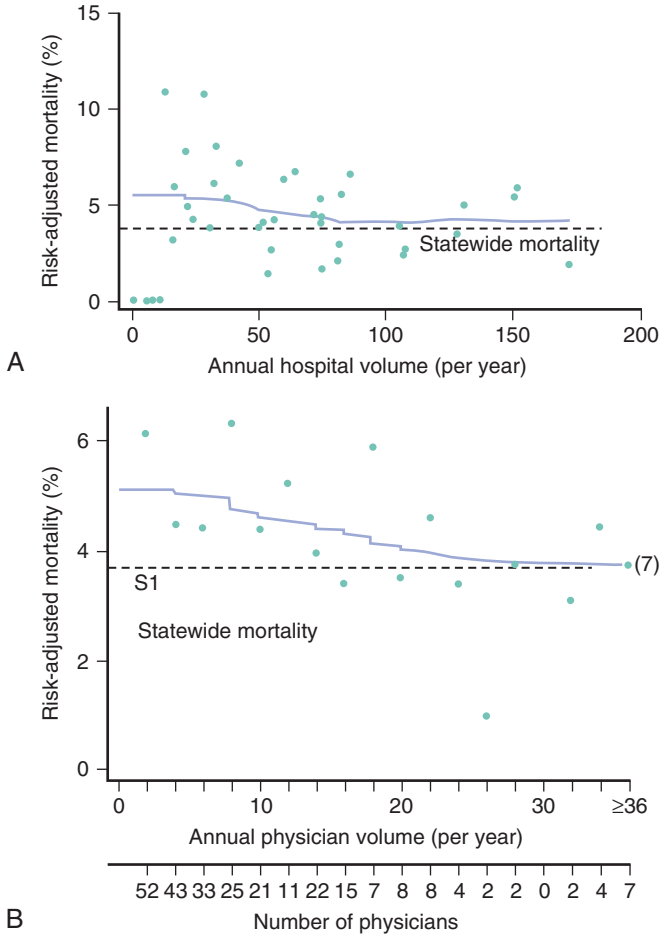

FIGURE 37-2 **A,** Annual institutional primary percutaneous coronary intervention (PPCI) volume is inversely proportional to risk-adjusted in-hospital mortality among 7321 patients reported to the New York statewide database (NYSD) from 2000 through 2002. Hospitals that reported performing 50 or fewer PPCIs per year had higher mortality compared with those that reported performing more than 50 PPCIs per year—5.40% versus 3.40%, respectively (odds ratio [OR] 0.58; 95% confidence interval [CI], 0.38 to 0.88). **B,** Annual physician operator PPCI volume was inversely proportional to risk-adjusted in-hospital mortality in the NYSD. Physicians who performed more than 10 PPCIs per year (vs. ≤10 PPCI/yr) or more than 20 PPCIs per year (vs. ≤20 PPCI/yr) had lower in-hospital mortality (OR 0.66 [95% CI, 0.48 to 0.92] and OR 0.63 [95% CI, 0.44 to 0.91], respectively). (From Srinivas VS, Hailpern SM, Koss E, et al: Effect of physician volume on the relationship between hospital volume and mortality during primary angioplasty. *J Am Coll Cardiol* 53:574-579, 2009.)

PCI using current appropriate use criteria (AUC) may be increased in lower-volume centers.[28] Finally, hospitals that choose to perform PCI must commit to providing this service nonstop (i.e., 24 hours a day, 7 days a week, 365 days a year) in order to achieve optimal outcome and performance metrics. Indeed, among 39,911 reperfused patients treated at 444 PCI-capable, NRMI-reporting hospitals, PPCI was less frequently utilized (vs. fibrinolysis) in patients who were nonwhite, over 85 years of age, or who presented with STEMI during off hours (evenings and weekends).[29] In addition, the degree of hospital PPCI specialization—that is, that portion of total STEMI cases treated with PPCI versus fibrinolysis—appears to significantly impact both clinical outcomes (in-hospital mortality) following PPCI as well as hospital system performance metrics (D2B times).[30] The best results were achieved by hospitals in the highest quartile of PPCI specialization, those with more than 88.5% of all STEMI cases treated with PPCI; this suggests that the axiom "practice makes perfect" is applicable to PPCI. Thus the commitment to PPCI on the part of both hospitals and physician operators must be unwavering and not a function of convenience.

ADHERENCE TO PRACTICE GUIDELINES

The process of care as measured by ACC/AHA guideline adherence has been linked to both in-hospital and late (6- to 12-month) survival following presentation of ACS.[31,32] An analysis of hospital composite guideline adherence quartiles demonstrated an inverse relationship between the adherence to guideline-compliant care and the risk-adjusted in-hospital mortality rate.[33] For every 10% increase in guideline adherence, a 10% relative reduction in in-hospital mortality was observed.[33] This observation supports the central hypothesis of hospital quality improvement, that better adherence with evidence-based care practices will result in better outcomes for patients.[34]

Both compliance with CPG and the ability to monitor or audit adherence to guidelines may be enhanced in higher-volume regional programs.[32] Adherence to guidelines was improved following establishment of an integrated regional program for ACS care and was highest among the cohort of patients who received PCI.[35] Lower-volume small community hospitals may be less likely to allocate the capital resources and personnel required to adequately track, collate, and report clinical outcomes or process measures (i.e., guideline compliance). Certainly, from the perspectives of national and regional payers and the Centers for Medicare and Medicaid Services (CMS), monitoring and auditing data derived from multiple small hospitals versus those from fewer, larger, networked systems have different levels of complexity. Indeed, in a survey commissioned by the AHA, only slightly more than half of the hospitals queried were systematically tracking times to STEMI treatment (D2N or D2B times), infection rates, readmission or stroke rates (to 30 days post procedure), recurrent MI, or mortality following either PCI or coronary bypass surgery.[3] This observation is made more meaningful by the fact that multiple national initiatives—such as Get With The Guidelines (GWTG), the Cardiac Hospitalization Atherosclerosis Management Program (CHAMP), the GAP project, the NRMI, and the CRUSADE Acute Coronary Treatment and Intervention Outcomes Network (ACTION) registry—have recently placed emphasis on system quality through systematic measurement of both care processes and clinical outcomes.[8] Despite such efforts, recent data from the NCDR Pinnacle Registry suggests that at least a third of patients with symptomatic CAD receive suboptimal secondary prescription for antiplatelet, beta-blocker, statin, and angiotensin converter enzyme inhibitor (ACEI)–angiotensin receptor blocker (ARB) therapies.[36] Furthermore, those patients with either diabetes or MI within 12 months (high-risk cohorts) were least likely to have optimal secondary prevention therapies prescribed. Finally, even when prescriptions are written, the medication's "optimal" dose regimen (consistent with evidence-based randomized trials) is infrequently prescribed.[37] In follow-up of patients after MI, 30% to 40% had no prescriptions for beta-blockers, statins, or ACEI-ARB therapies, and fewer than 30% of patients were at a goal or "optimal" dose regimen for any therapy.[37]

The D2B Alliance was initiated in November of 2006 and has resulted in increased use of recommended strategies for process improvement and a greater number of patients being treated within guideline recommendations.[38] Despite documented process improvement as reflected by progressive reduction in D2B times, mortality following PPCI appears to have plateaued, and focus has now turned toward total ischemic time as the principal determinant of outcomes.[39] Because the relationship between total ischemic time and the extent of myocardial necrosis is nonlinear, even optimally short D2B times may have little impact on the degree of myocardial salvage or survival in patients who present to the hospital late following infarct symptom

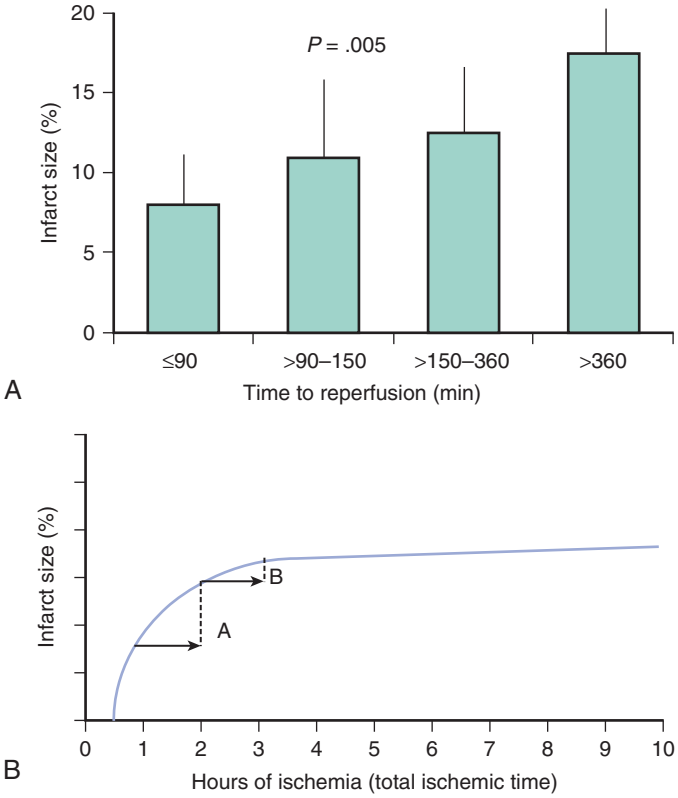

FIGURE 37-3 **A,** Relationship between chest pain symptom onset to balloon inflation (time to perfusion/total ischemic time) and infarct size as determined by gadolinium-enhanced cardiovascular magnetic resonance imaging. **B,** Relationship between a 1-hour door-to-balloon (D2B) time percutaneous coronary intervention (PCI) delay and infarct size as a function of total ischemic time. Infarct size may be variably influenced by a similar D2B time (1 hr) depending on the length of the time delay to PCI-hospital presentation (A vs. B). (**A,** From Francone M, Bucciarelli-Ducci C, Carbone I, et al: Impact of primary coronary angioplasty delay on myocardial salvage, infarct size, and microvascular damage in patients with ST-segment elevation myocardial infarction: insight from cardiovascular magnetic resonance. *J Am Coll Cardiol* 54:2145-2153, 2009; **B,** From Garcia-Dorado D, Garcia del Blanco B: Door-to-balloon time and mortality, *N Engl J Med* 370:179, 2014.)

onset (Fig. 37-3).[11,12,39] Furthermore, because of a lack of integrated systems for STEMI care, patients who require transfer from non–PCI-capable facilities for PPCI continue to experience long door-to-door-to-balloon (D2D2B) times, as well as total ischemic times, with consequent poor clinical outcomes.

PERCUTANEOUS CORONARY INTERVENTION CENTERS WITHOUT ON-SITE CARDIAC SURGERY

The current trend toward proliferation of "PCI centers" that lack on-site cardiac surgical facilities for the performance of PPCI in STEMI may be associated with suboptimal clinical outcomes. In an analysis of 625,854 Medicare patients undergoing PCI, in-hospital and 30-day mortality was increased in those centers without on-site cardiac surgery[40] with the greatest hazard observed in hospitals that performed a low number of PCI procedures (≤50) in Medicare patients. Even in the context of a completely integrated community hospital–tertiary hospital system, the performance of PPCI without on-site cardiac surgery (even following exclusion of the sickest patients) was associated with a trend toward increased hospital mortality when compared with PPCI performed at the tertiary center.[41] Although single-center studies have reported excellent outcomes in patients undergoing PPCI at hospitals without on-site cardiac surgery,[42] the one randomized trial that compared fibrinolysis to primary PCI at hospitals without surgery on site (C-PORT PPCI) was flawed by an inadequate sample size, relatively high rates of stroke and recurrent MI observed in the fibrinolytic treatment arm, and a large portion of subjects (31%) enrolled at a single center.[43] More recently, large registry data have suggested a similar risk for mortality following both PPCI and elective PCI performed at hospitals with, versus those without, cardiac surgical facilities.[21]

Elective PCI at hospitals without surgery on site (no-SOS sites) has been evaluated in two large-scale randomized trials.[44,45] The Cardiovascular Patient Outcomes Research Team Elective Angioplasty Study (C-PORT E)[44] screened 99,479 patients, consented 75,674 subjects for trial participation, and randomized 18,867 subjects on a 3:1 basis to have PCI either at a no-SOS or an SOS facility, respectively. Approximately 75% of consented subjects were excluded from randomization in large part because of clinical and/or angiographic risk. The hypothesis of C-PORT E was that PCI performed at no-SOS facilities would be noninferior with respect to the primary end points (death at 6 weeks and major adverse cardiovascular events [MACEs] to 9 months) when compared with PCI at SOS facilities, and it is curious in that PCI has never been demonstrated to reduce mortality in stable ischemic heart disease patients when compared with medical therapy alone. As such, the absence of a difference in mortality between randomly assigned treatment groups (both PCI) was predictable. Nevertheless, despite the inherent low-risk characteristics of the randomized cohort, PCI failure was increased on both a per-patient ($P = .007$) and per-lesion ($P = .04$) basis when performed at the no-SOS facilities (Fig. 37-4, *A*). In addition, a significant ($P = .0098$) increase in target-vessel revascularization (TVR, the need for additional procedures performed on the intervened-upon artery) and a trend ($P = .0977$) toward an increased frequency of MACEs was observed by intention-to-treat (ITT) analysis through 9 months follow-up (see Fig. 37-4, *B*). Furthermore, a per-protocol analysis of subjects who actually received the randomly assigned treatment demonstrated highly statistically significant increases in both TVR and MACE rates among those subjects who had PCI at no-SOS facilities.

Of interest, although the C-PORT E no-SOS sites more frequently used bare-metal, rather than drug-eluting, stents when compared with SOS sites, a similar (~33%) increase in TVR was observed for both stent types when the index PCI was performed at a no-SOS center. Finally, PCI was more costly when performed at no-SOS centers, driven largely by the relative cost increment observed in lower volume (<200 PCI/yr) participation.

The PCI Outcomes in Community Versus Tertiary Settings (MASS-COMM) trial[45] randomly assigned 3691 patients on a 3:1 basis to PCI at no-SOS ($n = 2774$) or SOS centers ($n = 917$), respectively. Clinical follow-up to 1 year was complete in only 87.9% and 85.8% of subjects treated at no-SOS and SOS sites, respectively. No differences in MACE or the requirement for repeat revascularization was observed by type of PCI site at either 30 days or 12 months. Wide variability was apparent in outcomes among participating hospitals as reflected by absolute differences between sites of 14% and 17% in MACE rates at 30 days and 12 months, respectively. This interhospital variation in treatment effect was most marked among no-SOS centers and raises concern with regard to the credibility of pooling such widely discrepant outcomes data. In addition, although an annual operator PCI volume requirement of 75 or more procedures per year is stated in the MASS-COMM study methods section,[45] minimum annual operator volumes of fewer than 30 PCIs per year were recorded during 4 of the 6 years of the study. Finally, the PCI success rates achieved in MASS-COMM are concerning on both a per-patient and a per-lesion basis. In an adjudicated angiographic review cohort, the per-patient PCI success rates were 81.3% and 74.7% in non-SOS and SOS centers, respectively, whereas the per-lesion PCI success rates were 95.6% and 97%,

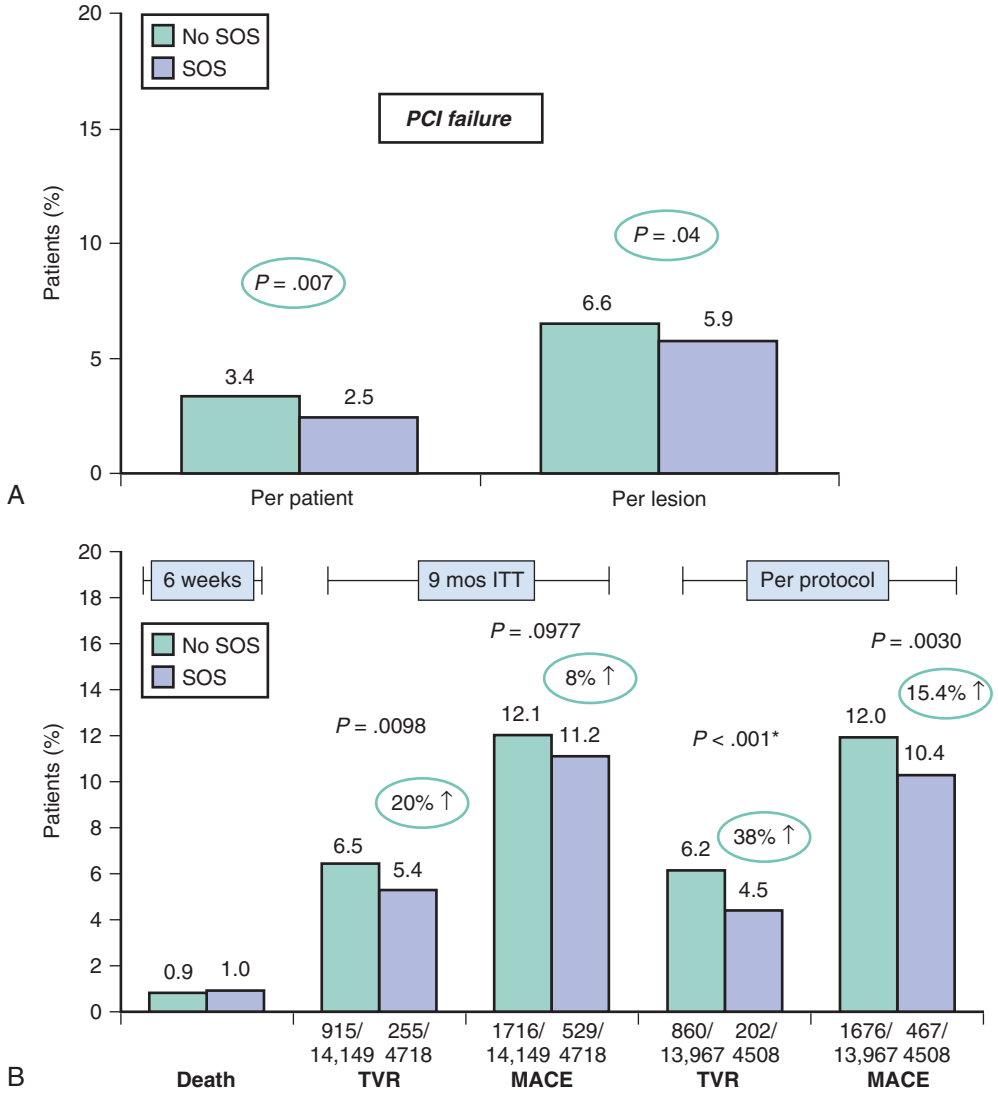

FIGURE 37-4 Analysis in the C-PORT E trial. **A,** Per-patient and per-lesion percutaneous coronary intervention (PCI) failure rates by randomly assigned site for PCI. **B,** Outcomes by PCI site, intention to treat (ITT), and actual treatment received (per protocol). *MACE,* Major adverse cardiovascular event; *SOS,* surgery on site; *TVR,* target-vessel revascularization. *Chi-squared analysis. (Adapted from Aversano T, Lemmon CC, Liu L, et al: Outcomes of PCI at hospitals with or without on-site cardiac surgery. *N Engl J Med* 366:1792-1802, 2012.)

respectively.[45] The MASS-COMM authors did not report a cost economic analysis for this trial as was performed in C-PORT E.

The impact of C-PORT E and MASS-COMM has been the proliferation of low-volume PCI programs, particularly those with no SOS. Indeed, 49% of centers that currently report to the ACC/NCDR perform 400 or fewer PCIs per year, and 25% perform 200 or fewer PCIs per year. Of note, about 90% of no-SOS centers perform 400 or fewer PCIs per year, and 83% of the centers that perform 200 or fewer PCIs per year are no-SOS centers.[27] Furthermore, the impact of no-SOS centers in geographic proximity to SOS centers on SOS-center PCI volume has been a point of concern. Indeed, during the 6-year duration of the MASS-COMM study, a 40% reduction in SOS-center operator annual PCI volume was observed (vs. a 9% reduction in participating no-SOS centers).[45] Clearly, the growth in the number of PCI centers has exceeded by almost threefold the growth in the U.S. population and has occurred despite a concomitant significant decline in disease (CAD, MI) prevalence.[46] In fact, despite a 44% increase in PCI capacity (521 new PCI programs) in the United States between 2000 and 2006, only a 1% increase in PCI access was achieved when a ground transport time to PCI of 60 minutes or less is used to define *access*.[47] This systematic reduplication of PCI services at an estimated cost of several billion dollars appears to be driven by market share competition and not the desire to strategically improve access to PPCI.[48] Indeed, it has been estimated that about 80% of new PCI programs have opened within a 12-mile radius of an existing SOS PCI center.[48] With these concerns in mind, the writing group of the 2014 SCAI/ACCF/AHA Expert Consensus Document Update on PCI without on-site surgical backup states "the development of PCI facilities within a 30-minute emergency transfer time to an established facility is strongly discouraged."[26]

Based on these and other data, the current ACCF/AHA guidelines for the performance of PCI designate a class IIb (procedure/treatment may be considered, usefulness/efficacy is less well established) level of evidence B indication for elective PCI and a class IIa (it is reasonable to perform the procedure) level of evidence B for primary PCI in no-SOS hospitals; they also note the need for appropriate planning for program development to be accomplished at all no-SOS facilities and the importance of using rigorous clinical/angiographic criteria for proper patient selection for elective PCI.[1,2]

LIMITED MEDICAL RESOURCES

The current trend for proliferation of small "heart centers" under the premise of patient convenience is counter to the well-established link between higher procedural volumes and better clinical outcomes, and it taxes critically limited resource pools, including those of specialized nurses and subspecialty-trained physician providers.[49] Patients with more complex cardiovascular illness (congestive heart failure, acute MI) fare better with subspecialty (cardiologist) compared with generalist care.[6,8,50]

One strategy for dealing with the mismatch between the consensus evidence in favor of an interventional (catheter-based) approach to the treatment of ACS and the ability to deliver such care is to construct regionalized systems for ACS care[6,8,51] and to have medical centers extend care coordination beyond the traditional boundaries of a hospital. A *system* is defined as an integrated group of entities within a region that coordinate the provision of diagnostic and treatment services. A *STEMI care system* includes EMS providers, referral (non–PCI-capable) hospitals, PCI-capable hospitals, and others.[3,7] Participants share protocols and have predefined action plans based on regional consensus of how best to provide optimal patient care that complies with contemporary professional society guidelines.

The proliferation of small "heart" programs focused on PCI with duplication of services further taxes limited resource pools and appears unnecessary in the context that the majority (>80%) of the adult U.S. population lives within a 60-minute ground transport commute to an existing PCI center.[47] In fact, the proliferation/expansion of PCI-capable hospitals in the United States has been largely confined to urban and suburban regions and has had very limited impact on an increase in access to PCI for STEMI patients.[52] Indeed, it appears that most metropolitan regions in the United States would be better served from a cost-effectiveness perspective to adopt the strategy of EMS integration with existing PCI-capable facilities rather than to build additional PCI centers in geographic proximity.[53]

BENEFIT OF CATHETER-BASED THERAPY FOR ACUTE CORONARY SYNDROMES

ST-Elevation Myocardial Infarction

The relative advantage of PCI versus fibrinolytic therapy depends on several factors. First, because primary PCI entails an obligate time delay for implementation compared with fibrinolysis, the relative advantage of PCI depends on the relative time delay to definitive treatment (balloon inflation). Pooled analyses of multiple RCTs suggest that the survival advantage in favor of PCI is inversely proportional to the relative time delay for PCI implementation and may be lost if the PCI-related time delay (D2B time minus DTN time) exceeds 60 to 110 minutes.[54-56] Differences between these analyses may be explained by differences in patient risk profiles. Indeed, a survival advantage in favor of PCI is evident only when the risk of death to 30 days following fibrinolytic therapy exceeds about 4%.[57] Longer relative time delays may still be associated with a PCI survival advantage in those patients at highest risk for death following fibrinolysis.[58] The PCI-related time delay associated with mortality equipoise compared with fibrinolysis is influenced significantly by patient-related variables that include age and infarct location regardless of patient-related time delays (less than vs. more than 120 min) to presentation.[55] Thus accurate risk assessment should be part of any STEMI treatment triage algorithm.

As noted previously, the relative survival advantage of PCI versus fibrinolysis is also dependent on the case volume experience of both the interventional cardiologist and the facility. In general, optimal outcomes have been correlated with higher procedural volumes on the part of both the facility and operator. Transport of the STEMI patient to a center capable of performing PCI yields superior clinical outcomes compared with on-site (community hospital) fibrinolytic therapy when the D2D2B time is less than 120 minutes.[59] Notably, no adverse outcomes related to patient transport have been observed in these analyses.

Despite significant improvement in D2B treatment times for patients who present to PCI-capable facilities, STEMI patients who present first to a non-PCI facility and are subsequently transported to a PCI facility often incur prolonged time delays to definitive treatment.[60,61] Indeed, initial presentation to a non-PCI center has been identified as a major determinant of prolonged time delay to PCI treatment due to the lack of a well-defined integrated system with protocol-driven algorithms for care and dedicated transport facilities.[62] Data from NMRI demonstrated that D2D2B times for patients who required transport for PCI were a median of 180 minutes, and only 15% received PCI within 120 minutes from initial hospital presentation.[60] Not surprisingly, although both the diagnosis of STEMI[63] and in-hospital mortality rates associated with STEMI have declined over the past 8 to 15 years,[64] mortality rates remain consistently higher for those STEMI patients who require transfer for PCI, compared with those who do not, and likely reflect the incremental, protracted delay to treatment.[61] This outcome and performance gap exists despite the availability of technology that allows EMS personnel to transmit a prehospital 12-lead electrocardiogram (ECG) and makes the diagnosis of STEMI evident at the point of first medical contact. The integration of EMS and incorporation of the prehospital phase for ACS evaluation and diagnosis are integral components of any regionalized system for STEMI care. Earlier STEMI diagnosis via a transmitted prehospital 12-lead ECG facilitates in-hospital STEMI treatment.[65-67] Hospitals that demonstrate the shortest D2B times incorporate prehospital STEMI diagnosis (transmitted ECG) with a multidisciplinary team approach in which either the emergency physician or specially trained EMS providers activate the cardiac cath lab prior to cardiology consultation.[68] Indeed, the facilitation of in-hospital PCI treatment for STEMI patients with a transmitted prehospital ECG has resulted in significant reductions in D2B times and has also shown improvement in in-hospital and 30-day survival.[69-72] The consistent, significant relationships that have been demonstrated between earlier STEMI diagnosis, more rapid treatment, and improved outcomes has prompted a consensus recommendation for the implementation of prehospital 12-lead ECG systems by all EMS providers.[73] Multiple reports from established STEMI systems of care that use EMS integration with prehospital 12-lead ECG diagnosis of STEMI and prehospital ambulance triage to the nearest PCI-capable facility (bypassing non–PCI-capable facilities) have demonstrated reduced time delays to treatment, reduced infarct size, and improved survival among triaged patients compared with those who require subsequent interhospital transfer for PCI.[74-78] Indeed, prehospital ECG capability, specialized EMS training, and integration have spawned a new paradigm for prehospital diagnosis and triage of STEMI patients (Fig. 37-5).[79]

Nevertheless, the rapid transport of patients with STEMI to the nearest PCI-capable facility for care may be limited by several factors. First, only a minority (≤5%) of EMS-transported patients with chest pain actually have STEMI.[80] Second, only a minority (<50%) of EMS systems have 12-lead ECG capabilities.[80] Third, a precedent mandate exists for transport of patients with suspected STEMI to the nearest facility, even when fibrinolysis may be contraindicated and that facility does not provide primary PCI. Fourth, evolution toward a more integrated process of prehospital care is complicated by the fact that 329 different EMS regions exist in the United States with more than 993 hospital-based EMS systems.[3,80] Remarkably, hospital-based EMS systems represent only 6.5% of all EMS providers with the remainder comprised of private, third-party systems (48.6%) and fire station–based systems (44.9%).[3] Although the transport time to a specialized PCI center may appear long, it can be more than counterbalanced by an integrated EMS system that incorporates prenotification. A doubling of the recommended transport time has been proposed for suspected STEMI patients who are transported to a "center of excellence," where the target D2B time is 60 minutes or less.[26,51] Such efficiency of process can be achieved only through an integrated system for STEMI care that incorporates the prehospital ECG for earlier diagnosis; expedited

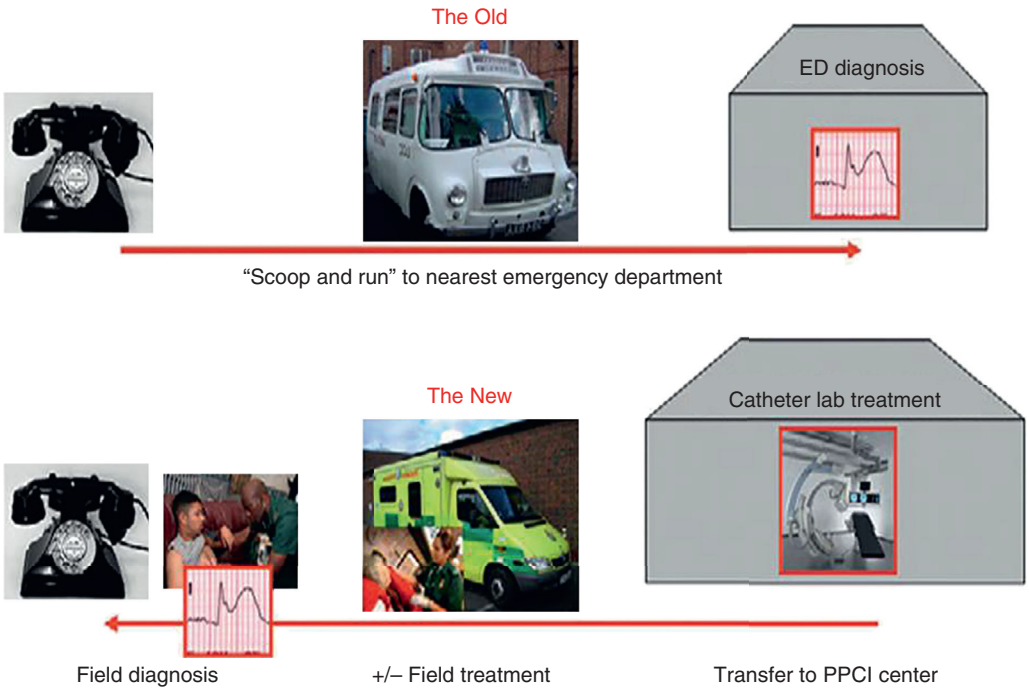

FIGURE 37-5 Evolving paradigms in prehospital diagnosis, triage, and treatment of ST-elevation myocardial infarction (STEMI). Prehospital diagnosis (with or without field treatment) and triage to a primary percutaneous coronary intervention (PPCI) center ("the new") has reduced total time delays to STEMI treatment. *ED,* Emergency department. (From Dalby M, Whitbread M: The role of the emergency services in the optimization of primary angioplasty: experience from London and the Heart Attack Team. *EuroIntervention* 9:517-523, 2013.)

triage; and readily available, rehearsed transport systems. A "network" approach with earlier activation of transport systems between the referral and PCI centers has achieved sustainable first D2B times of 90 minutes or less for STEMI patients who required interhospital transfer for PCI.[81,82] Finally, a more uniform evolution toward integration in the process of STEMI care has been impeded by diverging incentives, the lack of coordinated objectives, and ostensibly competing strategies. For example, in many regions, particularly those without state-regulated certificate of need requirements, a proliferation of new cath labs for the provision of primary PCI in no-SOS centers has occurred.[46,48] Conversely, other regions—including Minneapolis, Los Angeles, Boston, and the state of North Carolina—have developed integrated EMS systems with a focus on prehospital diagnosis and triage to an established center of excellence proficient in both primary and elective PCI. These competing strategies—one focused on building more small PCI centers, the other on more efficient and effective utilization of existing PCI centers through prehospital-EMS integration—have drawn support from the divergent financial incentives present among various stakeholders in the process of care. Only recently have sophisticated modeling techniques been utilized to compare the relative efficacy and/or cost of these "build more" versus "use more effectively" strategies for PCI facilities as they specifically pertain to the care of STEMI patients.[53] Of note, the strategy focused on EMS integration, prehospital diagnosis, and triage with more effective utilization of existing PCI facilities was found to be more effective and less costly than the strategy of creating new PCI facilities (Fig. 37-6).[53] The coordination of strategies and the integration of essential prehospital and hospital resources for ACS care on the state level has been the focus of the national Mission: Lifeline initiative of the AHA in conjunction with the ACC.

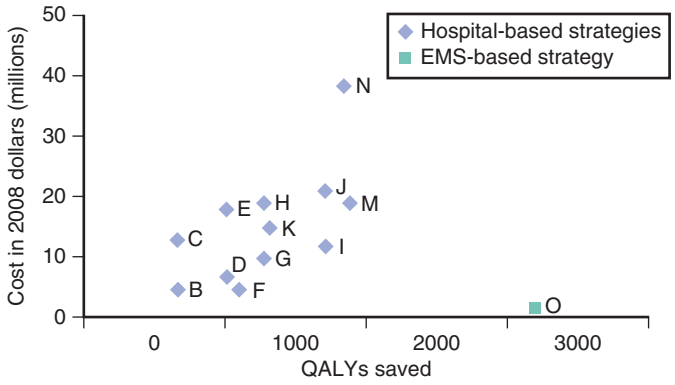

FIGURE 37-6 Comparative effectiveness of ST-segment elevation myocardial infarction regionalization strategies. Hospital-based (expansion of percutaneous coronary intervention [PCI]-capable facilities) versus emergency medical services (EMS)-based (regionalization with EMS integration for existing PCI facilities) demonstrates that the EMS-based strategy is less costly and more effective. *QALYs,* Quality adjust life-years. (From Concannon TW, Kent DM, Normand SL, et al: Comparative effectiveness of ST-segment-elevation myocardial infarction regionalization strategies. *Circ Cardiovasc Qual Outcomes* 3:506-513, 2010).

Non–ST-Segment Elevation Acute Coronary Syndromes

In the context of therapeutic innovation in catheter-based technology and adjunctive pharmacotherapy, the cumulative weight of data from RCTs supports the use of an early invasive (angiography followed by revascularization if feasible) versus conservative (medical therapy with angiography for spontaneous or provoked ischemia) strategy in the treatment of non–ST-segment elevation acute coronary syndrome (NSTEACS). Furthermore, the ACC/AHA CPG clearly recommends risk assessment before triage for invasive treatment.[1] The relative benefit of invasive versus conservative treatment is directly proportional to patient risk profile as reflected by the Thrombolysis in Myocardial Infarction (TIMI) study, the Platelet Glycoprotein IIb/IIIa

in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, and the Global Registry of Acute Coronary Events (GRACE) risk-stratification schemes.[83]

In addition, the magnitude of benefit attributable to the invasive treatment strategy appears to be inversely correlated with the duration of time delay from presentation to revascularization[84-86] and directly correlated with both the relative extent of revascularization in the active treatment versus the control/conservative groups and the duration of clinical follow-up.[87-89] Recent data suggest that earlier revascularization (≤24 hr after presentation) provides greater benefit as reflected by a reduction in the occurrence of cardiovascular death, MI, or stroke than later (≥36 hr) revascularization, particularly in those NSTEACS patients at highest risk.[85]

Similarly, pooled patient-level data from the Fast Revascularization During Instability in Coronary Disease (FRISC II), Invasive Versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS), and Randomized Intervention Treatment of Angina 3 (RITA-3) randomized trials show durable long-term (5-year) relative clinical benefit for the invasive treatment strategy.[89] The major source of controversy no longer surrounds the choice of treatment strategy (invasive vs. conservative) but rather the fact that although the benefit of an early invasive strategy is proportional to patient risk, the propensity to receive such treatment is greatest in patients at lower risk.[90-93] This treatment-risk paradox may be due to physician misconceptions regarding benefit-harm tradeoffs, concerns about treatment complications, or public reporting and has been observed in relationship to the performance of angiography and/or PCI and in the use of platelet inhibitor therapies.[94]

Finally, the transport of patients from a non-PCI facility to one capable of performing PCI for NSTEACS was also inversely proportional to patient risk strata.[95] The importance of the treatment-risk paradox is further magnified by the observation that compliance with the current ACC/AHA CPG recommendations, including early angiography, is inversely correlated with in-hospital mortality for ACS.[33] Furthermore, evidence-based therapies—which includes antiplatelet agents, beta-blockers, lipid-lowering agents, and ACEIs—initiated before hospital discharge are associated with an incremental survival advantage in follow-up. The fact that performance measures such as CPG compliance relate process of care to mortality presents an opportunity to define strategies that enhance current CPG compliance and utilization.

REGIONAL CENTERS OF CARE FOR ST-ELEVATION MYOCARDIAL INFARCTION PATIENTS

The technology currently available to many EMS providers allows transmission of a prehospital 12-lead ECG to make the diagnosis of STEMI evident at first medical contact. The integration of EMS and incorporation of the prehospital phase for ACS evaluation and diagnosis are integral components of a regionalized system for STEMI care. In addition, STEMI is the logical initial objective for a regionalized ACS treatment strategy in that five of Medicare's ten quality indicators focus on STEMI care.[3] Thus several system process/quality measures are already in place to provide a performance incentive to define regional networks for STEMI care. The development of regional networks for STEMI care should facilitate CPG adherence as well as the ability to monitor, audit, and adjudicate data. Indeed, important features of a regional care system include common data collection, data sharing, ongoing feedback, and quality improvement.[7] Greater adherence to CPGs has been observed in hospitals with higher STEMI volumes, those with cardiovascular surgical facilities on-site,[96] and following the implementation of national process-of-care and quality initiatives (D2B Alliance).[38]

Model Systems of Care

A regionalized approach to the provision of primary PCI therapy for STEMI has been successfully implemented in major U.S. metropolitan areas such as Minneapolis, Minnesota and Charlotte, North Carolina.[81,97,98] Through partnership with community hospitals in standardized protocol-driven algorithms for care and designated transport systems—along with enhanced multidisciplinary communication among EMS personnel, emergency department physicians, and interventional cardiologists—the Minneapolis Heart Institute at Abbott Northwestern Hospital and the Sanger Heart and Vascular Institute at Carolinas Medical Center have both demonstrated the ability to promptly access and treat STEMI patients who originate from up to 200 miles from the PCI center.[81,98] By focusing on collaboration and integration of resources, community hospitals initiate adjunctive pharmacotherapies in patients who present with STEMI and emergently transport them to the interventional team waiting at the central PCI center. These data demonstrate that regional systems in the United States can achieve results at least similar to those of smaller European centers with organized transfer systems. Indeed, D2D2B times for transfer-in patients with STEMI were 90 minutes or less in 56% and 120 minutes or less in greater than 90% of patients, respectively, using an integrated regional system approach. Similar results have been duplicated in other regional STEMI systems.[71,99-102]

A statewide approach is also being used in North Carolina, known as *Reperfusion of Acute Myocardial Infarction in North Carolina Emergency Departments* (RACE).[103,104] This initiative uses standardized protocols and integrated systems for the treatment and timely transfer of patients with STEMI in five regions in North Carolina. The RACE program demonstrated a significant improvement in time to treatment at both PCI and non-PCI hospitals and resulted in increased timely access to PCI on a statewide level.[103,104] The success of these regional programs resulted in a new class I recommendation in the most recent ACC/AHA STEMI guidelines that "each community should develop a STEMI system of care."[1,105] Additional class I system and performance goals are listed in Table 37-1.

The limitations of the prior nonintegrated, nonregionalized process for STEMI care in the United States was reflected by the absence of improvement in prolonged times to treatment despite widespread dissemination of benchmark goals for therapy (door-to–fibrinolytic infusion times of 30 min or less or a D2B time of 90 min or less) in the form of CPGs.[106] With marked regional variation in both EMS and hospital resources along with geography, population density, and transport facility distances, no single "system model" for STEMI care is likely to be either practical or achievable in the United States.[107,108] In addition to larger regional and statewide initiatives for STEMI care process integration, a number of smaller local and community STEMI systems have been developed. In a survey of 381 separate systems across 47 states, 202 involved a single PCI hospital, 150 included two to five PCI hospitals, and 29 included more than five PCI-capable hospitals.[107] Marked intersystem variability in the processes of STEMI care was observed. With specific goals to accelerate the implementation of STEMI care systems in selected U.S. metropolitan areas, to facilitate more effective delivery of STEMI care, and to improve clinical outcomes following STEMI, the regional systems of care demonstration project Mission: Lifeline STEMI Accelerator was created as a national outcomes research study initiated by the Duke Clinical Research Institute (DCRI) in collaboration with the AHA.[7] Participating regions were selected through a competitive application process. A total of 17 regions were selected to participate, and variability was wide in the number of PCI hospitals (3 to 33), non-PCI hospitals (3 to 30), and EMS agencies (1 to 500) in each region. Regional meetings of stakeholders were held that included cardiologists and emergency medicine physicians from both PCI-capable and non-PCI hospitals, EMS directors, senior hospital administrators, and regional AHA and Department of Health representatives. Region-specific data were examined, and specific STEMI case examples focused on prehospital ECG early STEMI identification and transmission and overread; "single call" cath lab activation and interhospital transfer protocols and resources were reviewed. All participating centers entered patient-level data in the ACTION–GWTG registry. ACTION–GWTG is a comprehensive acute MI database jointly owned and managed by the ACC

TABLE 37-1 Regional Systems of ST-Elevation Myocardial Infarction Care, Reperfusion Therapy, and Time-to-Treatment Goals: Class I Recommendations

1. All communities should create and maintain a regional system of STEMI care that includes assessment and continuous quality improvement of EMS and hospital-based activities. Performance can be facilitated by participating in programs such as Mission: Lifeline and the D2B Alliance. *(Level of evidence: B)*
2. Performance of a 12-lead ECG by EMS personnel at FMC is recommended in patients with symptoms consistent with STEMI. *(Level of evidence: B)*
3. Reperfusion therapy should be administered to all eligible patients with STEMI with symptom onset within the previous 12 hours. *(Level of evidence: A)*
4. Primary PCI is the recommended method of reperfusion when it can be performed in a timely fashion by experienced operators. *(Level of evidence: A)*
5. EMS transport directly to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI, with an ideal FMC-to-device time system goal of 90 minutes or less. *(Level of evidence: B)*
6. Immediate transfer to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI who initially arrive at or are transported to a non–PCI-capable hospital, with an FMC-to-device time system goal of 120 minutes or less. *(Level of evidence: B)*
7. In the absence of contraindications, fibrinolytic therapy should be administered to patients with STEMI at non–PCI-capable hospitals when the anticipated FMC-to-device time at a PCI-capable hospital exceeds 120 minutes because of unavoidable delays. *(Level of evidence: B)*
8. When fibrinolytic therapy is indicated or chosen as the primary reperfusion strategy, it should be administered within 30 minutes of hospital arrival. *(Level of evidence: B)*

From O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 127:e362-e425, 2013.
D2B, Door-to-balloon; *ECG,* electrocardiography; *EMS,* emergency medical services; *FMC,* first medical contact; *PCI,* percutaneous coronary intervention; *STEMI,* ST-elevation myocardial infarction.

and AHA that permits assessment of both individual hospital and regional performance with inclusion of prehospital, emergency department, cath lab, and in-hospital management and outcome data.[109] Multiple system performance and outcome measures are analyzed by region and among regions with a focus on first medical contact to device activation (reperfusion) times in addition to in-hospital mortality, bleeding, stroke, congestive heart failure, and cardiogenic shock. The central goal of the Mission Lifeline Accelerator project is to facilitate and expedite implementation of STEMI care systems in 17 selected metropolitan regions with the aim to improve utilization and timeliness of reperfusion therapy to improve clinical outcomes in STEMI. Data from this important project was anticipated before the end of 2014.[7]

Care Following ST-Elevation Myocardial Infarction

An additional important objective of regional systems for STEMI care should be to ensure that CPG-compliant care is uniformly administered and that cardiac rehabilitation and healthy lifestyle-modification programs are readily available to STEMI patients following hospital discharge. The most recent ACCF/AHA STEMI guidelines give a class I recommendation for (1) the development of posthospital systems of care designed to prevent hospital readmission (level of evidence [LOE] B); (2) exercise-based cardiac rehabilitation and secondary prevention programs (LOE B); (3) a clear, detailed, and evidence-based plan of care to promote medication adherence, timely follow-up, and appropriate dietary and physical activities (LOE C); and (4) encouragement and advice to stop smoking and to avoid secondhand smoke (LOE A).[1] STEMI care systems coordinate the effective transition of patients during and after hospital discharge.

The realization that all hospitals are not equal in regard to the care of STEMI[110] and the demonstration of improved patient outcomes in specialized centers for care of both trauma and stroke have shattered the antiquated concept that patients with suspected MI should be transported to the nearest hospital.

In addition to concentrating high-volume expertise and technology, regionalized "centers of excellence" are also integrated with EMS so that the diagnosis of MI can be made more rapidly and the system for providing PCI is more responsive. The prehospital care for ACS, especially STEMI, is critically important. Recent multicenter data indicate that utilizing prehospital ECG in STEMI receiving centers results in 86% of patients being treated with D2B times under 90 minutes in diverse regions across the United States.[111]

Future Care of ST-Elevation Myocardial Infarction Patients

At present, the lack of a coordinated system of care denies many patients the benefit of timely PPCI. A coordinated system for the provision of PCI could prevent an estimated six to eight major adverse cardiovascular and cerebrovascular events (MACCEs) per 100 STEMI patients treated and might thus affect 35,000 patients yearly.[3,80] However, the current scheme for cardiovascular reimbursement could penalize community hospitals without cardiac cath labs when patients are transferred or admitted directly to a regional center.[3] An adjustment to the reimbursement strategy, possibly to include regional networks of partnering community and tertiary care centers, must be addressed. Non–PCI-capable hospitals could be incentivized to risk stratify and transfer STEMI patients based on risk as well as transport time and distance. Such contractually defined networks could provide similar quality-ensured and monitored, protocol-driven algorithms for care with predefined systems for prompt patient transport. Confounding issues such as case mix index could be defined by the system rather than by the individual hospital.

Credentialing and criteria for development of a center of excellence for STEMI care should include the established ability to provide prehospital diagnosis of STEMI with a transmitted 12-lead ECG via integration with local and regional EMS providers.[3,80] To be successful, a system for care of STEMI patients should comprise multiple integral components that include a patient care focus, enhanced operational efficiency, appropriate system incentives (pay for performance, pay for value), specific outcome and process measures, and mechanisms for quality review with continuous quality improvement. Professional societies and organizations are in the process of developing the credentialing criteria for these centers. State and/or local government agencies could be charged with the oversight of legitimacy for regional STEMI networks, and CPG adherence and monitoring could be performed by established systems rather than by individual hospitals and centers. Treatment, outcome, and performance data acquisition and analysis will be standardized with appropriate and timely feedback to participating systems and centers. Individual states have been charged with development of regional coordinators to provide oversight, monitoring, and support for participating systems and centers. We support the development and credentialing for the designation in a manner similar to established stroke and trauma center designations. Suggested criteria are listed in Table 37-2.

The process for development of systems of care for STEMI patients has already been initiated by the AHA and is the subject of ongoing stakeholder meetings. The AHA has issued a call to action to improve the implementation and timeliness of infarct reperfusion with PPCI that carefully considers the ideal system from the perspective of each constituent, which includes the patient, physician, EMS provider, non-PCI capable hospital, PCI-capable center, and payer. Given the importance of time to treatment for STEMI patients, the ideal system of care will likely be different for various geographic locales (urban/suburban vs. rural) and will consider the risk of MI in the individual patient. Recommendations should be forthcoming for additional research and requisite changes in policy to support the construct and implementation of systems that will improve quality care and outcomes for STEMI patients.

TABLE 37-2 Criteria for Acute Cardiovascular Care Centers

Criteria for a Level 1 Acute Cardiovascular Emergency Center

1. 24-hour cardiac catheterization laboratory available
2. 24-hour cardiovascular surgery availability
3. Comprehensive interventional cardiology and cardiovascular surgery services
4. More than 200 PCI patients/year (>36 STEMI) per hospital
5. More than 75 PCI patients/year per interventional cardiologist
6. EMS integration with prehospital 12-lead ECG transmission
7. Standardized protocols at referral and receiving hospitals
8. Transfer agreements in place/transportation system available
9. Education and training programs for transport, referral, and receiving hospital personnel
10. Quality assurance program
11. Comprehensive care for cardiogenic shock including advanced hemodynamic support (i.e., ECMO, LVAD, Impella, and/or TandemHeart)
12. Comprehensive care for out-of-hospital cardiac arrest (i.e., hypothermia, Lucas device, etc.)
13. Comprehensive care for acute aortic dissection and abdominal aortic aneurysm

Criteria for a Level 2 Acute Cardiovascular Emergency Center

Same as in 1 through 10 above with transfer agreements/protocols in place with a level 1 center for cardiogenic shock, out-of-hospital cardiac arrest, and aortic disease

Criteria for a Level 3 Acute Cardiovascular Emergency Center

Same as for level 2 but without 24-hour surgical availability and with transfer agreements/protocols in place with level 1 and/or 2 centers

Criteria for a Level 4 Acute Cardiovascular Emergency Center

No PCI or surgical availability but with transfer agreements/protocols in place with level 1, 2, and 3 centers

Modified from Henry TD, Atkins JM, Cunningham MS, et al: ST-segment elevation myocardial infarction: recommendations on triage of patients to heart attack centers—is it time for a national policy for the treatment of ST-segment elevation myocardial infarction? *J Am Coll Cardiol* 47:1339-1345, 2006.
ECG, Electrocardiography; *ECMO,* extracorporeal membrane oxygenation; *EMS,* emergency medical services; *LVAD,* left ventricular assist device; *PCI,* percutaneous coronary intervention; *STEMI,* ST-elevation myocardial infarction.

REFERENCES

1. O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 127:e362–e425, 2013.
2. Levine GN, Bates ER, Blankenship JC, et al: 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: Executive Summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 124:2574–2609, 2011.
3. Jacobs AK, Antman EM, Ellrodt G, et al: Recommendation to develop strategies to increase the number of ST-segment elevation myocardial infarction patients with timely access to primary percutaneous coronary intervention—The American Heart Association's acute myocardial infarction (AMI) Advisory Working Group. *Circulation* 113:2152–2163, 2006.
4. MacKenzie EJ, Rivara FP, Jurkovich GJ, et al: A national evaluation of the effect of trauma-center care on mortality. *N Engl J Med* 354:366–378, 2006.
5. Schwamm LH, Pancioli A, Acker JE, 3rd, et al: American Stroke Association's task force on the development of stroke systems. Recommendations for the establishment of stroke systems of care: recommendations from the American Stroke Association's tasks force on the development of stroke systems. *Circulation* 111:1078–1091, 2005.
6. Topol EJ, Kereiakes DJ: Regionalization of care for acute ischemic heart disease—a call for specialized centers. *Circulation* 107:1463–1466, 2003.
7. Bagai A, Al-Khalidi HR, Sherwood MW, et al: Regional systems of care demonstration project: Mission: Lifeline STEMI Systems Accelerator: Design and methodology. *Am Heart J* 167:15–21, e3, 2014.
8. Califf RM, Faxon DP: Need for centers to care for patients with acute coronary syndromes. *Circulation* 107:1467–1470, 2003.
9. Parikh SV, Jacobi JA, Chu E, et al: Treatment delay in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: a key process analysis of patient and program factors. *Am Heart J* 155:290–297, 2008.
10. De Luca G, Suryapranata H, Otteryanger JP, Antman EM: Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation* 109:1223–1225, 2004.
11. Francone M, Bucciarelli-Ducci C, Carbone I, et al: Impact of primary coronary angioplasty delay on myocardial salvage, infarct size, and microvascular damage in patients with ST-segment elevation myocardial infarction: insight from cardiovascular magnetic resonance. *J Am Coll Cardiol* 54:2145–2153, 2009.
12. Garcia-Dorado D, Garcia del Blanco B: Door-to-balloon time and mortality. *N Engl J Med* 370:179, 2014.
13. Magid DJ, Calonge GN, Rumsfeld JS, et al: Relation between hospital primary angioplasty volume and mortality for patients with acute MI treated with primary angioplasty vs. thrombolytic therapy. *JAMA* 284:3131–3138, 2000.
14. Moscucci M, Share D, Smith D, et al: Relationship between operator volume and adverse outcome in contemporary percutaneous coronary intervention practice: an analysis of a quality-controlled multicenter percutaneous coronary intervention clinical database. *J Am Coll Cardiol* 456:625–632, 2005.
15. Hannan EL, Wu C, Walford G, et al: Volume-outcome relationships for percutaneous coronary interventions in the stent era. *Circulation* 112:1171–1179, 2005.
16. Vakili BA, Brown DL: 1995 Coronary angioplasty reporting system of the New York State Department of Health. Relation between hospital primary angioplasty volume and mortality for patients with acute MI treated with primary angioplasty vs. thrombolytic therapy. *Am J Cardiol* 91:726–728, 2003.
17. Srinivas VS, Hailpern SM, Koss E, et al: Effect of physician volume on the relationship between hospital volume and mortality during primary angioplasty. *J Am Coll Cardiol* 53:574–579, 2009.
18. Kontos MC, Wang Y, Chaudhry SI, et al: Lower hospital volume is associated with higher in-hospital mortality in patients undergoing primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction: a report from the NCDR. *Circ Cardiovasc Qual Outcomes* 6:659–667, 2013.
19. Minges KE, Wang Y, Dodson JA, et al: Physician annual volume and in-hospital mortality following percutaneous coronary intervention. *Circulation* 124:A16550 [abstract], 2011.
20. Strom J, Wimmer N, Wasfy J, Yeh R: Re-examining the operator volume-outcomes relationship in percutaneous coronary intervention: A systematic review. *J Am Coll Cardiol* 63:A420 [abstract ACC2014 2904-4], 2014.
21. Kutcher MA, Klein LW, Ou FS, et al: National Cardiovascular Data Registry. Percutaneous coronary interventions in facilities without cardiac surgery on site: a report from the National Cardiovascular Data Registry (NCDR). *J Am Coll Cardiol* 54:16–24, 2009.
22. Aversano T: Relationship between institutional primary percutaneous coronary intervention volume and mortality in hospitals without on-site cardiac surgery: the C-PORT experience [abstract]. *Circulation* 118:S_1076, 2008.
23. Keeley EC, Grines CL: Should patients with acute myocardial infarction be transferred to a tertiary center for primary angioplasty or receive it at qualified hospitals in the community? The case for emergency transfer for primary percutaneous coronary intervention. *Circulation* 112:3520–3532, 2005.
24. Post PN, Kujipers M, Ebels T, Zijlstra F: The relation between volume and outcome of coronary interventions: a systematic review and meta-analysis. *Eur Heart J* 31:1985–1992, 2010.
25. Harold JG, Bass TA, Bashore TM, et al: ACCF/AHA/SCAI 2013 Update of the Clinical Competence Statement on Coronary Artery Interventional Procedures. *Catheter Cardiovasc Interv* 82:E69–E111, 2013.
26. Dehmer GJ, Blankenship JC, Cilingiroglu M, et al: SCAI/ACC/AHA Expert Consensus Document: 2014 Update on Percutaneous Coronary Intervention Without On-Site Surgical Backup. *Catheter Cardiovasc Interv* 84(2):169–187, 2014.
27. Dehmer GJ, Weaver D, Roe MT, et al: A contemporary view of diagnostic cardiac catheterization and percutaneous coronary intervention in the United States: a report from the CathPCI Registry of the National Cardiovascular Data Registry 2010 through June 2011. *J Am Coll Cardiol* 60:2017–2031, 2012.
28. Chan PS, Rao SV, Bhatt DL, et al: Patient and hospital characteristics associated with inappropriate percutaneous coronary interventions. *J Am Coll Cardiol* 62:2274–2281, 2013.
29. Fazel R, Krumholz HM, Bates ER, et al: Choice of reperfusion strategy at hospitals with primary percutaneous coronary intervention: a National Registry of Myocardial Infarction analysis. *Circulation* 120:2455–2461, 2009.
30. Nallamothu BK, Wang Y, Magid DJ, et al: Relation between hospital specialization with primary percutaneous coronary intervention and clinical outcomes in ST-segment elevation myocardial infarction: National Registry of Myocardial Infarction-4 analysis. *Circulation* 113:222–229, 2006.
31. Mukherjee D, Fang J, Chetcuti S, et al: Impact of combination evidence-based medical therapy on mortality in patients with acute coronary syndromes. *Circulation* 109:745–749, 2004.
32. Tay E, Chan MY, Tan WD, et al: Impact of combination evidence-based medical therapy on mortality following myocardial infarction in patients with and without renal dysfunction [abstract]. *J Am Coll Cardiol* 47:161A, 2006.
33. Peterson ED, Roe MT, Mulgund J, et al: Association between hospital process performance and outcomes among patients with acute coronary syndromes. *JAMA* 295:1912–1920, 2006.
34. Califf RM, Peterson ED, Gibbons RM, et al: Integrating quality into the cycle of therapeutic development. *J Am Coll Cardiol* 40:1895–1901, 2002.
35. Corbelli JC, Janicke DM, Cziraky MJ, et al: Acute coronary syndrome emergency treatment strategies: improved treatment and reduced mortality in patients with acute coronary syndrome using guideline-based critical care pathways. *Am Heart J* 157:61–68, 2009.
36. Maddox TM, Chan PS, Spertus JA, et al: Variations in coronary artery disease secondary prevention prescriptions among outpatient cardiology practices: insights from the NCDR (National Cardiovascular Data Registry). *J Am Coll Cardiol* 63:539–546, 2014.
37. Arnold SV, Spertus JA, Masoudi FA, et al: Beyond medication prescription as performance measures: optimal secondary prevention medication dosing after acute myocardial infarction. *J Am Coll Cardiol* 62:1791–1801, 2013.
38. Bradley EH, Nallamothu BK, Herrin J, et al: National efforts to improve door-to-balloon time results from the Door-to-Balloon Alliance. *J Am Coll Cardiol* 54:2423–2429, 2009.

39. Menees DS, Peterson ED, Wang Y, et al: Door-to-balloon time and mortality among patients undergoing primary PCI. *N Engl J Med* 369:901–909, 2013.
40. Wennberg DE, Lucas FL, Siewers AD, et al: Outcomes of percutaneous coronary interventions performed at centers without and with onsite coronary artery bypass graft surgery. *JAMA* 292:1961–1968, 2004.
41. Ting HH, Raveendran G, Lennon RJ, et al: A total of 1,007 percutaneous coronary interventions without onsite cardiac surgery: acute and long-term outcomes. *J Am Coll Cardiol* 47:1713–1721, 2006.
42. Wharton TP, Jr: Should patients with acute myocardial infarction be transferred to a tertiary center for primary angioplasty or receive it at qualified hospitals in community? The case for community hospital angioplasty. *Circulation* 12:3509–3520, 2005.
43. Aversano T, Aversano LT, Passamani E, et al: Thrombolytic therapy vs. primary percutaneous coronary intervention for myocardial infarction in patients presenting to hospitals without on-site cardiac surgery: a randomized controlled trial. *JAMA* 287:1943–1951, 2002.
44. Aversano T, Lemmon CC, Liu L, et al: Outcomes of PCI at hospitals with or without on-site cardiac surgery. *N Engl J Med* 366:1792–1802, 2012.
45. Jacobs AK, Normand SL, Mauri L: PCI at hospitals with or without on-site cardiac surgery. *N Engl J Med* 369:392–393, 2013.
46. Langabeer JR, Henry TD, Kereiakes DJ, et al: Growth in percutaneous coronary intervention capacity relative to population and disease prevalence. *J Am Heart Assoc* 2:e000370, 2013.
47. Nallamothu BK, Bates ER, Wang Y, et al: Driving times and distances to hospitals with percutaneous coronary intervention in the United States—implications for pre-hospital triage of patients with ST-elevation myocardial infarction. *Circulation* 113:1189–1195, 2006.
48. Concannon TW, Nelson J, Kent DM, et al: Evidence of systematic duplication by new percutaneous coronary intervention programs. *Circ Cardiovasc Qual Outcomes* 6:e58, 2013.
49. Kereiakes DJ, Willerson JT: The United States cardiovascular care deficit. *Circulation* 109:821–823, 2004.
50. Greenfield S, Kaplan SH, Kahn R, et al: Profiling care provided by different groups of physicians: effects of patient case-mix (bias) and physician-level clustering on quality assessment results. *Ann Intern Med* 136:111–121, 2002.
51. Jacobs AK: Primary angioplasty for acute myocardial infarction: is it worth the wait? *N Engl J Med* 349:798–800, 2003.
52. Buckley JW, Bates ER, Nallamothu BK: Primary percutaneous coronary intervention expansion to hospitals without on-site cardiac surgery in Michigan: a geographic information systems analysis. *Am Heart J* 155:668–672, 2008.
53. Concannon TW, Kent DM, Normand SL, et al: Comparative effectiveness of ST-segment-elevation myocardial infarction regionalization strategies. *Circ Cardiovasc Qual Outcomes* 3: 506–513, 2010.
54. Nallamothu BK, Bates RK: Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: is timing (almost) everything? *Am J Cardiol* 92:824–826, 2003.
55. Betriu A, Masotti M: Comparison of mortality rates in acute myocardial infarction treated by percutaneous coronary intervention versus fibrinolysis. *Am J Cardiol* 95:100–101, 2005.
56. Pinto DS, Kirtane AJ, Nallamothu BK, et al: Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. *Circulation* 114:2019–2025, 2006.
57. Tarantini G, Razzolini R, Ramondo A, et al: Explanation for the survival benefit of primary angioplasty over thrombolytic therapy in patients with ST-elevation acute myocardial infarction. *Am J Cardiol* 1:1503–1505, 2005.
58. Tarantini G, Razzolini R, Napodano M, et al: Editor's Choice: Acceptable reperfusion delay to prefer primary angioplasty over fibrin-specific thrombolytic therapy is affected (mainly) by the patient's mortality risk: 1 h does not fit all. *Eur Heart J* 31:676–683, 2010.
59. Dalby M, Bouzamondo A, Lechat P, Montalescot G: Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. *Circulation* 108:1809–1814, 2003.
60. Nallamothu BK, Bates ER, Herrin J, et al: Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NRMI)-3/4 analysis. *Circulation* 111:761–767, 2005.
61. Gibson CM, Pride YB, Frederick PD, et al: Trends in reperfusion strategies, door-to-needle and door-to-balloon times, and in-hospital mortality among patients with ST-segment elevation myocardial infarction enrolled in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J* 156:1035–1044, 2008.
62. Blankenship JC, Scott TD, Skelding KA, et al: Abstract 4505: Presentation to non-PCI center is major modifiable factor associated with delayed door-to-balloon time in HORIZONS-AMI. *Circulation* 118:S_903, 2008.
63. Chen J, Normand SL, Wang Y, et al: Recent declines in hospitalizations for acute myocardial infarction for Medicare fee-for-service beneficiaries: progress and continuing challenges. *Circulation* 121:1322–1328, 2010.
64. Roe MT, Messenger JC, Weintraub WS, et al: Treatments, trends, and outcomes of acute myocardial infarction and percutaneous coronary intervention. *J Am Coll Cardiol* 56:254–263, 2010.
65. Kereiakes DJ, Gibler WB, Martin LH, et al: Relative importance of emergency medical system transport and the pre-hospital electrocardiogram on reducing hospital time delay to therapy for acute myocardial infarction: a preliminary report from the Cincinnati Heart Project. *Am Heart J* 123:835–840, 1992.
66. Diercks DB, Kontos MC, Chen AY, et al: Utilization and impact of pre-hospital electrocardiograms for patients with acute ST-segment elevation myocardial infarction: data from the NCDR (National Cardiovascular Data Registry) ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry. *J Am Coll Cardiol* 53:161–166, 2009.
67. Curtis JP, Portnay EL, Wang Y, et al: National Registry of Myocardial Infarction-4: the pre-hospital electrocardiogram and time to reperfusion in patients with acute myocardial infarction, 2000-2002: findings from the National Registry of Myocardial Infarction-4. *J Am Coll Cardiol* 47:1544–1552, 2006.
68. Bradley EH, Roumanis SA, Radford MJ, et al: Achieving door-to-balloon times that meet quality guidelines: how do successful hospitals do it? *J Am Coll Cardiol* 46:1236–1241, 2005.
69. Bjorklund E, Stenestrand U, Landback J, et al: A pre-hospital diagnostic strategy reduced time to treatment and mortality in real life patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention [abstract]. *J Am Coll Cardiol* 47:192A, 2006.
70. Pederson SH, Galatius S, Hansen PR, et al: Field triage reduces treatment delay and improves long-term clinical outcome in patients with acute ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *J Am Coll Cardiol* 54:2296–2302, 2009.
71. Le May MR, So DY, Dionne R, et al: A citywide protocol for primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 358:231–240, 2008.
72. Quinn T, Johnsen S, Gale CP, et al: Effects of prehospital 12-lead ECG on processes of care and mortality in acute coronary syndrome: a linked cohort study from the Myocardial Ischaemia National Audit Project. *Heart* 100:944–950, 2014.
73. Garvey JL, MacLead BA, Dopko G, et al: Pre-hospital 12-lead electrocardiography programs: a call for implementation by emergency medical services systems providing advanced life support—National Heart Attach Alert Program (NHAAP) Coordinating Committee; National Heart, Lung, and Blood Institute (NHLBI); National Institutes of Health. *J Am Coll Cardiol* 47:485–491, 2006.
74. Dieker HJ, Liem SSB, Aidi HE, et al: Pre-hospital triage for primary angioplasty. *JACC Cardiovasc Interv* 3:705–711, 2010.
75. Postma S, Dambrink JH, de Boer MJ, et al: Prehospital triage in the ambulance reduces infarct size and improves clinical outcome. *Am Heart J* 161:276–282, 2001.
76. Chan AW, Kornder J, Elliott H, et al: Improved survival associated with pre-hospital triage strategy in a large regional ST-segment elevation myocardial infarction program. *JACC Cardiovasc Interv* 5:1239–1246, 2012.
77. Le May MR, Wells GA, So DY, et al: Reduction in mortality as a result of direct transport from the field to a receiving center for primary percutaneous coronary intervention. *J Am Coll Cardiol* 60:1223–1230, 2012.
78. Nestler DM, White RD, Rihal CS, et al: Impact of prehospital electrocardiogram protocol and immediate catheterization team activation for patients with ST-elevation myocardial infarction. *Circ Cardiovasc Qual Outcomes* 4:640–646, 2011.
79. Dalby M, Whitbread M: The role of the emergency services in the optimization of primary angioplasty: experience from London and the Heart Attack Team. *EuroIntervention* 9:517–523, 2013.
80. Jacobs AK, Antman EM, Faxon DP, et al: Development of systems of care for ST-elevation myocardial infarction patients: executive summary. *Circulation* 116:217–230, 2007.
81. Wilson BH, Humphrey AD, Cedarholm JC, et al: Achieving sustainable first door-to-balloon times of 90 minutes for regional transfer ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv* 6:1064–1071, 2013.
82. Blankenship JC, Scott TD, Skelding KA, et al: Door-to-balloon times under 90 minutes can be routinely achieved for patients transferred to ST-segment-elevation myocardial infarction percutaneous coronary intervention in a rural setting. *J Am Coll Cardiol* 57:272–279, 2011.
83. Kereiakes DJ, Antman EM: Clinical guidelines and practice: In search of the truth. *J Am Coll Cardiol* 48:1129–1135, 2006.
84. Tricoci P, Lokhnygina Y, Berdan LG, et al: Time to coronary angiography and outcomes among patients with high-risk non ST-segment elevation acute coronary syndromes: results from the SYNERGY trial. *Circulation* 116:2669–2677, 2007.
85. Mehta SR, Granger CB, Boden WE, et al: Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 360:2165–2175, 2009.
86. Sorajja P, Gersh BJ, Cox DA, et al: Impact of delay to angioplasty in patients with acute coronary syndromes undergoing invasive management: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) trial. *J Am Coll Cardiol* 55:1416–1424, 2010.
87. Bavry AA, Kumbhani DJ, Rassi AN, et al: Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol* 48:1319–1325, 2006.
88. Fast Revascularization during InStability in Coronary artery disease (FRISC-II) Investigators: 5-year outcomes in the FRISC-II randomized trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. *Lancet* 368:998–1004, 2006.
89. Fox KA, Clayton TC, Damman P, et al: Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome: a meta-analysis of individual patient data. *J Am Coll Cardiol* 55:2435–2445, 2010.
90. Roe MT, Peterson ED, Newby LK, et al: The influence of risk status on guideline adherence for patients with non-ST-segment elevation acute coronary syndromes. *Am Heart J* 151:1205–1213, 2006.
91. Roe MT, Peterson ED, Yui L, et al: Relationship between risk stratification by cardiac troponin level and adherence to guidelines for non-ST-segment elevation acute coronary syndrome. *Arch Intern Med* 165:1870–1876, 2005.
92. Fox KA, Anderson FA, Jr, Dabbous OH, et al: Intervention in acute coronary syndromes: Do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). *Heart* 93:177–182, 2007.
93. Tarantini G, Razzolini R, Ramondo A, et al: Patient risk profile and benefit from an invasive approach in the initial management of non-ST-segment elevation acute coronary syndrome. *J Cardiovasc Med (Hagerstown)* 8:799–802, 2007.
94. McCabe JM, Joynt KE, Welt FG, Resnic FS: Impact of public reporting and outlier status identification on percutaneous coronary intervention case selection in Massachusetts. *JACC Cardiovasc Interv* 6:625–630, 2013.
95. Roe MT, Chen AY, Delong ER, et al: Patterns of transfer for patients with non-ST-segment elevation acute coronary syndrome from community to tertiary care hospitals. *Am Heart J* 156:185–192, 2008.
96. Investigators NRMI: Outcomes among patients with non-ST-segment elevation myocardial infarction presenting to interventional hospitals with and without on-site cardiac surgery. *JACC Cardiovasc Interv* 2:944–952, 2009.
97. Henry TD, Atkins JM, Cunningham MS, et al: ST-segment elevation myocardial infarction: recommendations on triage of patients to heart attack centers—is it time for a national policy for the treatment of ST-segment elevation myocardial infarction? *J Am Coll Cardiol* 47:1339–1345, 2006.
98. Henry TD, Sharkey SE, Burke MN, et al: A regional system to provide timely access to percutaneous coronary intervention for ST-elevation myocardial infarction. *Circulation* 116:721–728, 2007.
99. Aguirre FV, Varghese JJ, Kelley MP, et al: Rural interhospital transfer of ST-elevation myocardial infarction patients for percutaneous coronary revascularization: The Stat Heart Program. *Circulation* 117:1145–1152, 2008.
100. Ting HH, Rihal CS, Gersh BJ, et al: Regional systems of care to optimize timeliness of reperfusion therapy for ST-elevation myocardial infarction: the Mayo Clinic STEMI Protocol. *Circulation* 116:729–736, 2007.
101. Glickman SW, Granger CB, Ou FS, et al: Impact of a statewide ST-segment-elevation myocardial infarction regionalization program on treatment times for women, minorities, and the elderly. *Circ Cardiovasc Qual Outcomes* 3:514–521, 2010.
102. Parikh SV, Treichler DB, DePaola S, et al: Systems-based improvement in door-to-balloon times at a large urban teaching hospital: a follow-up study from Parkland Health and Hospital System. *Circ Cardiovasc Qual Outcomes* 2:116–122, 2009.
103. Jollis JG, Roettig ML, Aluko AO, et al: Implementation of a statewide system for coronary reperfusion for ST-segment elevation myocardial infarction. *JAMA* 298:2371–2380, 2007.
104. Jollis AG, Al-Khalidi HR, Monk L, et al: Expansion of a regional ST-segment-elevation myocardial infarction system to an entire state. *Circulation* 126:189–195, 2012.
105. Henry TD, Gibson CM, Pinto DS: Moving toward improved care for the patient with ST-elevation myocardial infarction: a mandate for systems of care. *Circ Cardiovasc Qual Outcomes* 3:441–443, 2010.
106. Investigators NRMI: Hospital improvement in time to reperfusion in patients with acute myocardial infarction, 1999 to 2002. *J Am Coll Cardiol* 47:45–51, 2006.
107. Jollis JG, Granger CB, Henry TD, et al: Systems of care for ST-segment-elevation myocardial infarction: a report from the American Heart Association's Mission:Lifeline. *Circ Cardiovasc Qual Outcomes* 5:423–428, 2012.
108. Nallamothu BK, Krumholz HM, Ko DT, et al: Development of systems of care for ST-elevation myocardial infarction patients: gaps, barriers, and implications. *Circulation* 116:e68–e72, 2007.
109. Peterson ED, Roe MT, Rumsfeld JS, et al: A call to ACTION (Acute Coronary Treatment and Intervention Outcomes Network): a national effort to promote timely clinical feedback and support continuous quality improvement for acute myocardial infarction. *Circ Cardiovasc Qual Outcomes* 2:491–499, 2009.
110. Weaver WD: All hospitals are not equal for treatment of patients with acute myocardial infarction. *Circulation* 108:1768–1771, 2003.
111. Rokos IC, French WJ, Koenig WJ, et al: Integration of pre-hospital electrocardiograms and ST-elevation myocardial infarction receiving center (SRC) networks: impact on door-to-balloon times across 10 independent regions. *JACC Cardiovasc Interv* 2:339–346, 2009.

Post–Percutaneous Coronary Intervention Hospitalization, Length of Stay, and Discharge Planning

38

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KEY POINTS

- Comprehensive post–percutaneous coronary intervention (PCI) discharge management is an integral aspect of postprocedure care and includes direct patient communication, monitoring for procedural or vascular complications, and clear discharge instructions with a specific follow-up plan.
- Medication reconciliation, especially regarding dual-antiplatelet therapy after PCI, is critical for aggressive secondary prevention and to prevent late complications.
- Evaluation of cardiac biomarkers after PCI is controversial. Although it is reasonable to check biomarkers in all patients after PCI, it is necessary and recommended to check them in patients with procedural angiographic complications or in those who have signs or symptoms suggestive of postprocedure ischemia.
- There is no role for routine measurement of platelet function after PCI.
- Overall length of stay following PCI has become shorter over time, a change attributable not only to technological, pharmacologic, and procedural innovations but also to payer expectations. This has led to increasing interest in same-day discharge (SDD) programs.
- SDD may be a reasonable option for elective PCI patients with no procedural complications and an uneventful postdischarge course.
- SDD is associated with improved patient satisfaction and considerable cost savings, primarily attributed to the shorter duration of monitoring after the procedure.

Percutaneous coronary intervention (PCI) is one of the most common procedures in the United States; performed half a million times annually,[1] it remains a cornerstone in the management of coronary artery disease (CAD). Historically, a large proportion of PCI procedures were performed during inpatient hospitalization, which allowed for a significant amount of time for monitoring after the procedure to ensure procedural success, identify bleeding or vascular complications, and initiate secondary prevention. However, technological, pharmacologic, and procedural innovations, as well as payer expectations and cost considerations, have led to a shorter length of stay after the procedure and have obviated hospital admission. In this environment, many institutions have developed programs that allow for same-day discharge (SDD) of patients undergoing elective, uncomplicated PCI. Because PCI performance measures track not only the proportion of patients discharged on guideline-recommended medical therapies but also the post-PCI readmission rates, discharge planning has taken on an increasingly important role not only to ensure safe, event-free discharge on appropriate guideline-recommended therapies but also to minimize hospital readmission. This chapter will focus on postprocedural management of PCI patients with an emphasis on appropriate discharge planning and instructions, the role of cardiac biomarker testing, and the evolution of successful SDD programs.

POST–PERCUTANEOUS CORONARY INTERVENTION DISCHARGE PLANNING

Discharge planning following PCI should begin prior to the procedure, with an emphasis on gathering information regarding preprocedure activity levels, medication adherence, and patient social support at home. Postprocedure management focuses on (1) access-site management and monitoring for new ischemia and bleeding or vascular complications and (2) appropriate communication, both oral and written, between the provider team and the patient regarding procedural outcome, medication changes, and safety plan in the setting of an adverse event. The Society for Cardiovascular Angiography and Interventions (SCAI) has offered a consensus statement regarding the best practices following PCI.[2]

Physician-Patient Communication

The results of the procedure, including any complications and/or unexpected findings, should be explained clearly to the patient and his or her family. The type of intervention, if any, and the duration of dual-antiplatelet therapy (DAPT) should also be discussed and reinforced repeatedly by the team of care providers throughout the duration of the patient stay.

Access-Site Management

Typically, manual compression, a compression device, and/or a vascular closure device (VCD) are used in patients following transfemoral access, whereas a wristband compression device is used most frequently among patients undergoing transradial access. For patients undergoing transfemoral access who are anticoagulated with heparin, the access sheaths can generally be removed once the activated clotting time (ACT) falls below 175 seconds if a VCD is not used. The use of bivalirudin typically does not necessitate checking an ACT unless significant renal impairment is evident (i.e., creatinine clearance <30 mL/min or hemodialysis); in that situation, sheaths may be removed once the ACT falls below 180 seconds. In patients without significant renal dysfunction, the femoral arterial sheath can be removed 2 hours after the discontinuation of the bivalirudin infusion if a VCD is not used.

Postprocedure Ambulation

The access site, method of hemostasis, intensity of procedure sedation, and anticoagulation strategy drive recommendations for activity immediately after PCI. Patients who undergo transradial catheterization may ambulate as soon as sedation wanes. For those who undergo transfemoral catheterization and PCI, strict bed rest is typically recommended for 4 to 8 hours if manual compression is used or 1 to 4 hours if a VCD is used; prior to ambulation, a care provider must ensure that hemostasis is achieved and no diminution of downstream peripheral pulses is evident.

Postprocedure Monitoring

After the procedure, patients are generally monitored in a telemetry setting, with monitoring of vital signs every 15 minutes for the first 2 hours by trained nursing personnel. Although most patients go home on the same day within 2 to 6 hours after diagnostic cardiac catheterization, lengths of monitoring times vary following PCI; these will be discussed in greater detail elsewhere, along with the role of laboratory testing after PCI.

Discharge Physical Examination

Although a full physical examination is generally performed prior to discharge, additional focus should be directed to the access site to ensure adequate hemostasis and perfusion. The access site should be auscultated to ensure no bruit, which may be concerning for a pseudoaneurysm or arteriovenous (AV) fistula, each of which requires additional testing to confirm, typically via ultrasound. Distal pulses should be palpated to ensure no decrease in downstream perfusion. Patients should also be able to demonstrate their baseline level of ambulation without difficulty and should ensure pain is well controlled prior to consideration of discharge after the procedure.

Discharge Instructions

Patients should be provided with clear instructions regarding physical activity after the procedure, the need for additional laboratory testing afterward, and follow-up. Discharge instructions also should have clear contact information for the recovery unit or the physician in case of complications after discharge. Additionally, discharge instructions should address the concerns outlined below.

Site Management

Patients should be advised that minor bruising and/or pain at the access site is normal, and it should resolve within 1 month. Patients undergoing transfemoral access should not strain or lift anything greater than 5 pounds for 48 hours after the procedure and should apply pressure to the access site when sneezing or coughing. Clear instructions should be provided for an action plan for access-site complications that include active arterial bleeding, hematoma, local erythema or purulence, or downstream neurologic symptoms such as numbness, tingling, or paresthesia.

Activity Levels

Although it is important to maintain preprocedure activity levels, most patients are advised to refrain from physical exercise for at least 48 hours after the procedure. Patients who undergo PCI should be enrolled in a postprocedure cardiac rehabilitation program to develop a plan of graded exercise.

Driving and Return to Work

Most patients are advised to refrain from driving for at least 48 hours afterward. The decision to return to work is individualized and often is related to job satisfaction, finances, and/or employer policies.[3] Recommendations regarding return to work also depend on the type of work the patient performs, including physical demands, mental stress, and safety considerations.

Sexual Activity

Most patients are advised to refrain from sexual activity for 1 week after cardiac catheterization to allow for access-site healing. Other recommendations are based on the patient's level of fitness. According to an American Heart Association (AHA) consensus statement,[4] sexual activity is reasonable for patients at low risk for cardiovascular complications and for those who can exercise for 3 to 5 metabolic equivalents (METs) without symptoms or electrocardiographic (ECG) changes. In previous studies of sudden cardiac death related to sexual activity, most patients who died during intercourse were men (82% to 93%) who participated in extramarital sexual activity (75%), typically with a younger partner after excessive food and alcohol consumption.[5,6]

Medication Reconciliation

Medication reconciliation is a critical aspect of postprocedure discharge planning, and major changes are typically reinforced at multiple instances during the patient stay by trained personnel, which may include physicians, nurses, trainees, or pharmacists. Barring specific contraindications, many patients who undergo PCI will be on DAPT with aspirin and an additional platelet inhibitor (currently available agents are $P2Y_{12}$ antagonists), a beta-blocker, an angiotensin-converting enzyme (ACE) inhibitor, and a high-intensity statin.[7-9] Patients should be provided with clear instructions regarding which medications should be stopped, which have changed in dosage, and which should be taken after the procedure. Recommendations for postprocedure DAPT should be clearly stated on the discharge paperwork, and given the critical nature of uninterrupted therapy, a clear plan should be outlined for the patient to obtain the antiplatelet as an outpatient. SCAI has recommended that diabetic patients should hold their metformin for 48 hours afterward. Patients previously on warfarin who have stopped it for the procedure should be restarted on their regimen and should have an international normalized ratio (INR) value checked within 1 week after the procedure to ensure a therapeutic range. No consensus guidelines have been provided for the novel oral anticoagulants (NOACs), but they are generally started after the procedure as hemostasis is achieved and do not require close monitoring.

Communication to the Referring Physician

An appropriate transition of care from the invasive cardiologist to the primary cardiologist or referring physician is also an integral component of postprocedure care. This communication is typically performed verbally and in the form of a procedure note that clearly identifies the indications for the procedure, diagnostic findings, interventions performed, and a plan for postprocedure management.

Follow-up

SCAI has recommended that the patient follow up with his or her primary care physician, cardiologist, or midlevel physician extender within 2 to 4 weeks after the procedure or sooner for patients with procedural complications or comorbidities such as anemia or renal dysfunction, which requires more frequent laboratory test monitoring. The purpose of this follow-up visit is to (1) ensure compliance with the medication regimen, especially with regard to DAPT; (2) reconcile medications to ensure that the changes made upon discharge have been followed; (3) reinforce aggressive secondary prevention measures, including dietary and exercise habits and smoking cessation; and 4) confirm that the patient has enrolled in a cardiac rehabilitation program. A sample discharge checklist is provided in Table 38-1.

THE ROLE OF POST–PERCUTANEOUS CORONARY INTERVENTION MONITORING OF CARDIAC BIOMARKERS, PLATELET INHIBITION, AND RENAL FUNCTION

The purpose of checking cardiac biomarkers after a PCI procedure is to assess for evidence of periprocedural myocardial damage. Historically, cardiac biomarkers had been checked serially every 8 to 12 hours after PCI; however, the routine measurement of cardiac biomarkers is controversial because the clinical implications and prognostic significance of an elevated biomarker level in the absence of angiographic complications or signs and symptoms of a new acute myocardial infarction (MI) are unclear. In this setting, ascribing significant importance to biomarker elevation in the absence of clear evidence of adverse

clinical outcomes may lead to a longer hospital length of stay and may subject the patient to unnecessary evaluation and testing, increasing the potential for iatrogenic complications. As hospital length of stay is decreasing, there is increasing tension with regard to the role of routine biomarker testing after PCI.

Traditionally, creatine kinase MB (CK-MB) levels were checked routinely after PCI; now some institutions have transitioned to cardiac troponin (cTn), a much more sensitive and specific biomarker able to detect even small amounts of myocardial damage; unsurprisingly, rates of detection of myocardial injury have risen using the more sensitive assay. In one series of 4930 patients undergoing elective PCI, Novack and colleagues[10] reported that only 7.2% of patients had CK-MB levels greater than three times the upper limit of normal (ULN), but 24.3% had cTn levels three or more times the ULN. Previous studies have noted an association between elevated postprocedure biomarkers and mortality, but it is unclear whether this is an epiphenomenon due primarily to the extent of complex coronary disease and not necessarily to the procedure.[11] The importance of relatively small biomarker increases is uncertain. In a series of 5850 patients, Jeremias and colleagues[12] reported an association between periprocedural MI and 1-year mortality, but only in patients with a CK-MB level eight times normal or with a Q-wave MI. Additionally, that study questioned the importance of postprocedure biomarker elevations in the absence of an angiographically evident complication.

In 2007, the first proposed universal definition for myocardial infarction[13] suggested that a *peri-PCI MI* (type 4a) be determined by a biomarker elevation of three or more times the 99th percentile of the upper reference limit (URL) in patients with normal preprocedure biomarker levels. However, the authors clearly note that this designation was by arbitrary convention in the absence of clear data. In the third universal definition for MI,[14] this was further refined to more than five times the URL of the cardiac troponin (cTn) and evidence of (1) prolonged ischemia (chest pain >20 min), (2) ischemic ECG changes or pathologic Q-waves, or (3) angiographic evidence of a flow-limiting complication (i.e., loss of side branch, no-reflow phenomenon, embolization), or (4) imaging evidence of loss of viable myocardium.

In this setting, a consensus statement from SCAI[15] suggests that a *clinically relevant* MI after coronary revascularization be defined as an MI resulting in a CK-MB elevation of 10 or more times the ULN with a lower threshold of five or more times the ULN in patients with new pathologic Q-waves after MI; if a CK-MB assay is unavailable, the ratio of cTn to CK-MB should be 7:1 (i.e., a clinically relevant MI would be 70 or more times the ULN using a cTn assay). For patients with elevated baseline CK-MB or cTn levels that are stable or falling, the elevation should rise by an absolute increment to those described above. For patients with elevated CK-MB or cTn levels that are rising, the elevation should rise by an absolute increment, but additionally there should be new ECG or clinical signs concerning for a clinically relevant MI (new heart failure or hypotension). Table 38-2 describes the evolution of the definition of a peri-PCI MI, incorporating the proposed definition of a clinically relevant MI.

The current PCI guidelines recommend measurement of a CK-MB or cTn value for patients with signs or symptoms of MI or in asymptomatic patients with significant persistent angiographic complications such as large side occlusion no-reflow phenomenon or thrombosis (class I, level of evidence C) but offer only a weak recommendation for routine measurement of cardiac biomarkers in all patients after PCI (class IIb, level of evidence C).[8] In the absence of routine biomarker

TABLE 38-1 Checklist for Discharge

Physician to Patient Communication

- Operator has spoken to the patient or patient representative and has described the procedure, its complications, and any unexpected findings.

Postprocedure Monitoring

- No signs or symptoms of new ischemia are apparent.
- No new abnormalities on telemetry or electrocardiogram are apparent.
- Patient is able to ambulate without difficulty.
- Patient is able to tolerate food.

Access-Site Management

- Hemostasis has been achieved.
- No significant pain/tenderness is present at the access site.
- No bruit or thrill is evident.
- Distal pulses are intact.

Medication Reconciliation

- A plan for dual-antiplatelet therapy has been reviewed.
- Other medications have been reviewed and reconciled.

Follow-up

- Follow-up has been scheduled.
- A plan for follow-up laboratory testing (if any) has been reviewed.

TABLE 38-2 Changes in the Definition of a Periprocedural Percutaneous Coronary Intervention Myocardial Infarction and the Proposed Definition of a Clinically Relevant Myocardial Infarction

Biomarker Elevation Pattern	First Definition[13]	Third Definition[14]	Clinically Relevant MI[15]
Normal biomarkers at baseline	Elevation of biomarkers >3× 99th percentile URL	Elevation of cTn >5× 99th percentile URL *and* either: a) evidence of prolonged ischemia; b) ischemic ST-changes or new Q-waves; c) angiographic evidence of a flow-limiting lesion; or d) imaging evidence of loss of viable myocardium	Peak CK-MB (cTn) rises to ≥10× ULN (≥70× ULN for cTn) or ≥5× ULN (≥35× ULN for cTn) with new pathologic Q-waves in two or more contiguous leads *or* new LBBB
Elevated at baseline but stable	No guidance; continue to measure biomarkers and use features of ECG and imaging	A greater than 20% rise of cTn from the most recent preprocedure value	CK-MB (or cTn) rises by an absolute increment the same as those described above from the most recent preprocedure level
Elevated at baseline and not stable or falling	No guidance	No guidance	CK-MB (or cTn) rises by an absolute increment as those described above from the most recent preprocedure level plus ST-elevation or depression along with signs of clinically relevant MI (new/worsening heart failure, hypotension, etc.)

CK-MB, Creatine kinase MB; *cTn,* cardiac troponin; *ECG,* electrocardiogram; *LBBB,* left bundle branch block; *MI,* myocardial infarction; *ULN,* upper limit of normal; *URL,* upper reference limit.

testing, the SCAI consensus document[15] recommends performing an ECG 1 to 4 hours after an uncomplicated PCI; if normal, biomarkers do not need to be checked. In the presence of clinical symptoms, angiographic complications, or ECG changes, CK-MB—or cTn if CK-MB is unavailable—should be measured 8 to 12 hours after the procedure; if elevated, they should be measured every 8 to 12 hours thereafter until they peak.

Platelet Function

Platelet function testing has been used to assess the degree of platelet reactivity; although high levels of platelet reactivity have been associated with adverse outcomes,[16-18] antiplatelet strategies tailored to platelet reactivity have failed to show a benefit. In the Gauging Responsiveness With a VerifyNow P2Y12 Assay–Impact on Thrombosis and Safety (GRAVITAS) trial,[19] 2214 patients with high platelet reactivity were randomized to high- or low-dose clopidogrel; at 6 months, no difference was reported in the primary composite end point (2.3% vs. 2.3%, hazard ratio [HR] 1.01; 95% confidence interval [CI], 0.58 to 1.76; $P = .97$). Similarly, in the Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting (ARCTIC) trial,[20] 2440 patients scheduled for PCI were randomized to a strategy of platelet function testing and dose adjustment in those with elevated platelet reactivity, but no reduction was shown in the primary composite end point in the monitored group (HR 1.13; 95% CI, 0.98 to 1.29; $P = .10$). Given the lack of clinical benefit, routine platelet function testing is not currently recommended.[7,8]

Renal Function

Postprocedure renal injury is common, especially in patients with preexisting renal insufficiency, and it can be due to aortic atheroemboli, contrast-induced injury, or a combination of the two. Currently, the only strategies proven to minimize risk include volume expansion and minimization of contrast use. Because creatinine increase is observed 48 to 72 hours after PCI in affected patients, measuring renal function within the first 24 hours after PCI has limited utility. SCAI recommends that patients at increased risk for contrast-induced nephropathy (CIN) should have a serum creatinine value checked about 5 to 7 days after the procedure.[2]

TRENDS IN POSTPROCEDURE LENGTH OF STAY

Over the last decade, a significant push has been observed toward a shorter length of stay for all hospitalizations and most procedures, and PCI has not escaped this general trend. With respect to PCI, the drivers for a shorter hospital stay have focused on procedure-specific technological advances and payer considerations.

Technological, Pharmacologic, and Procedural Advances

Over the past three decades, significant technological, pharmacologic, and procedural advances have fundamentally improved both the safety and the efficacy of PCI. The initial development of stent technology to supplement balloon angioplasty has markedly reduced rates of acute vessel closure. Iterative improvements in stent technology in materials, polymer coating, and antimitogenic drug delivery have made stents more durable, easier to deliver, and less likely to incite neointimal hyperplasia, further decreasing the need for repeat intervention. Advances in miniaturization and guidewire technology have virtually eliminated femoral and brachial cutdown techniques as catheters have decreased in size from 9 to 5 Fr. Even more "slender" 4- and 3-Fr guide catheters are available in some countries.[21]

These changes have been paralleled by improvements in preprocedural and periprocedural pharmacologic management. The development of more potent oral antiplatelet agents, such as prasugrel[22] and ticagrelor,[23] as well as strategies for appropriate upstream utilization, have led to a more tailored approach to periprocedural antithrombotic strategy, including the use of heparin as monotherapy during PCI.[24] More tailored provisional use of glycoprotein (GP) IIb/IIIa inhibitors, rather than routine use, has led to decreased bleeding with similar efficacy.[25] The introduction and widespread adoption of the direct thrombin inhibitor bivalirudin have led to further increases in safety with similar efficacy.[26-28]

Additionally, these advances have been coupled with procedural innovations, namely, transradial (TR) PCI, to further improve efficacy and safety. Although first described in 1989 by Campeau[29] and by Otaki[30] in 1992 and later popularized by Kiemeneij and Laarman[31,32] in 1994, the TR technique has not been widely adopted by operators in the United States, although that has been changing recently. Feldman and colleagues[33] performed an analysis of 2.8 million patients in the American College of Cardiology's National Cardiovascular Data Registry (ACC-NCDR) CathPCI Registry and noted that adoption of a transradial approach has increased almost 16-fold, from 1.2% in 2007 to 16.1% in 2012, and it now accounts for 6.3% of total procedures. The main advantage for TR access appears to be dramatic reductions in vascular access complications and bleeding, as shown in the Radial Versus Femoral Access for Coronary Intervention (RIVAL) trial,[34] which randomized 7021 acute coronary syndrome (ACS) patients to either TR ($n = 3507$) or transfemoral (TF; $n = 3514$) access and demonstrated no difference in the primary composite outcome of death, MI, stroke, or non–coronary artery bypass grafting (CABG) major bleeding at 30 days (3.7% vs. 4.0%, HR 0.92; 95% CI, 0.72 to 1.17) but showed a reduction in vascular access complications (1.4% vs. 3.7%, HR 0.37; 95% CI, 0.27 to 0.52) and Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) major bleeding (1.9% vs. 4.5%, HR 0.43; 95% CI, 0.32 to 0.57). Additional patient-centered benefits of TR access include easier hemostasis and earlier postprocedure ambulation. A radial approach has also been associated with lower cost of care and a shorter hospital stay.[35]

Although popular in the United States, the data for VCDs have been mixed. Randomized clinical trial data have shown limited benefit, and a recent NCDR analysis by Marso and colleagues[36] assessed the effects of different bleeding-avoidance strategies and found modestly decreased bleeding with VCDs, bivalirudin, or both compared with manual compression alone. Meta-analyses have been conflicting, with one study showing some benefit (pooled odds ratio [OR] 0.89; 95% CI, 0.86 to 0.91)[37] but another showing complication rates similar to those of VCDs and manual compression.[38]

Payer Expectations

As PCI has become safer and more effective, significant changes in payment structures have driven a shorter length of stay (LOS) and an increase in outpatient PCI. In 2007, the InterQual criteria (McKesson Corporation, San Francisco, CA), used by hospitals nationwide to offer guidance on admissions decisions, were modified such that PCI was no longer an inpatient procedure by default. Whereas procedures performed on an urgent or emergent basis, such as for acute MI, were still eligible for inpatient status, this change effectively made PCI predominantly an outpatient procedure.

Nevertheless, given differential reimbursement schedules, a significant incentive still existed to perform PCI and submit for reimbursement at the inpatient level. This was driven by the fact that the Centers for Medicare and Medicaid Services (CMS) reimburse outpatient procedures using the Ambulatory Payment Classification (APC) system and inpatient procedures using the more lucrative Diagnosis Related Group (DRG) framework, making the same procedure eligible for vastly different reimbursements based on admission status. For example, an uncomplicated PCI using a drug-eluting stent (MS-DRG 147) would be reimbursed $11,497 under the inpatient DRG system but only $7763 (APC 0656) under the outpatient APC system, a difference of more than $3700. As hospitals attempted to seek reimbursements for PCI procedures under the inpatient DRG system, CMS

instituted the Recovery Audit Contractors (RAC) program as part of the Medicare Modernization Act of 2003 to recover possible overpayments to hospitals, even retrospectively; to date, the program recovered more than $3.65 billion in 2013 alone. Facing increased scrutiny for inpatient billing of PCI, hospitals now perform the majority of nonacute PCIs in the outpatient setting.

In 2013, the inpatient and outpatient designations were further refined when CMS implemented the "two midnight" rule, stipulating that an acute inpatient admission requires a stay that spans at least two midnights, in effect classifying even more patient encounters as outpatient instead of inpatient. This has led to even further interest in same-day discharge programs.

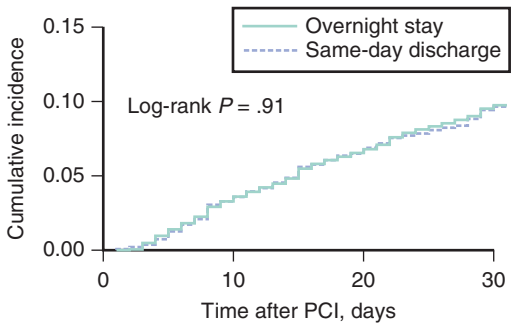
SAME-DAY DISCHARGE FOLLOWING PERCUTANEOUS CORONARY INTERVENTION

History and Background

The concept of same-day discharge (SDD) originated two decades ago, when Kiemeneij and colleagues,[39-41] pioneers of TR access, started patients on warfarin a priori, performed PCI via the TR approach, and discharged them the same day. Despite other early reports of the safety of SDD,[42,43] its adoption has been slow in the United States. In an analysis of the NCDR CathPCI Registry, Rao and colleagues[44] noted that the prevalence of SDD was only 1.25% among the 107,018 elective PCI patients hospitalized for 1 day or less between 2004 and 2008. Of note, although both strategies of SDD and overnight observation are outpatient admissions and discharges for the purposes of third-party payment, SDD occurs when the patient is discharged home on the same calendar day of the procedure, whereas overnight hospitalization requires at least one midnight of observation prior to discharge.

Safety of Same-Day Discharge

The safety of SDD compared with overnight observation has been demonstrated both in observational studies and randomized trials; however, results have been difficult to compare directly across studies given the variance in underlying patient populations, study settings, and outcomes of interest. The Rao[44] CathPCI analysis noted no significant difference in 30-day death or hospitalization between patients undergoing SDD or overnight hospitalization (Fig. 38-1). Abdelaal and colleagues[45] performed a meta-analysis of 13 studies (five randomized trials, eight observational analyses) that encompassed 111,830 patients and found similar complication rates between SDD and overnight observation in both the randomized (OR 1.20; 95% CI, 0.82 to 1.74) and observational (OR 0.67; 95% CI, 0.27 to 1.66) cohorts (Fig. 38-2). Another meta-analysis of 37 studies that included 12,803 patients found no difference between SDD and overnight observation with regard to death, MI, or target-vessel revascularization (OR 0.90; 95% CI, 0.43 to 1.87) among randomized patients and a low rate of the composite end point among the observational cohort (1.0%; 95% CI, 0.35% to 1.32%), suggesting that SDD is a safe and feasible strategy for patients undergoing elective PCI.[46]



No. at risk

Overnight stay	105,679	101,954	98,003	94,128
Same-day discharge	1,339	1,294	1,244	1,202

FIGURE 38-1 Cumulative incidence of 30-day mortality or rehospitalization between patients undergoing same-day discharge versus those hospitalized overnight. *PCI,* Percutaneous coronary intervention. (From Rao SV, Kaltenbach LA, Weintraub WS, et al: Prevalence and outcomes of same-day discharge after elective percutaneous coronary intervention among older patients. *JAMA* 306[13]:1461-1467, 2011.)

Patient Selection

Patient selection for SDD is controversial. An SCAI consensus document[47] released in 2009 suggested that the only patients eligible for an abbreviated observation period prior to discharge are (1) patients younger than 70 years; (2) those with stable angina on presentation who have no biomarker elevation; (3) asymptomatic patients with an abnormal stress test; (4) those with no significant comorbidities, including congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), bleeding predisposition, or contrast allergy; (5) those with normal renal function; (6) patients fully loaded on a thienopyridine and not using a GP IIb/IIIa inhibitor; (7) those with single-vessel PCI with a less than 28-mm stent and no periprocedural complications; and (8) patients and families who are willing. However, these criteria were criticized as being too conservative. Gilchrist and coworkers[48] reported safe SDD in 100 patients who underwent successful elective PCI without complications (defined as no unstable dissection, no major side-branch loss, no prolonged periprocedural ischemia); 85% of these patients would not have met SCAI criteria for SDD, with the main contraindications to discharge being age, distance from the hospital, and no pretreatment with a thienopyridine or GP IIb/IIIa inhibitor.

The dominant feature of safe SDD appears to be the absence of periprocedural or angiographic complications and not necessarily underlying patient characteristics. Hodkinson and colleagues[49] assessed prospective 30-day outcomes among patients undergoing SDD 6 hours after PCI using criteria that focused on the technical result of the procedure instead of clinical presentation or lesion complexity. Among the 1059 patients selected for SDD, 27.7% presented with an ACS and 40.8% had high-risk lesions as defined by the ACC/AHA definition. Almost all patients (98%) underwent PCI via a TR approach. In this group, the major adverse cardiovascular event (MACE) rate at 30 days was 0.85%, and the rate of subacute stent thrombosis was 0.4%; no MACEs were observed within 24 hours after discharge, suggesting minimal if any benefit from prolonged monitoring with regard to preventing short-term readmissions.

Selected Patient Populations

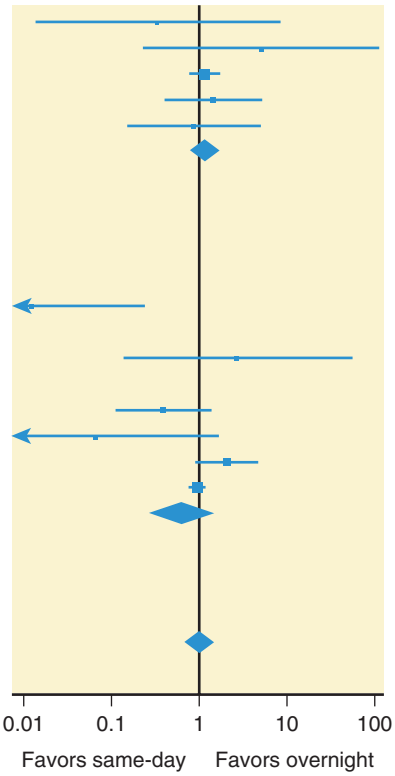
Acute Coronary Syndrome

Although most studies of SDD have excluded patients with ACS, a number of studies have demonstrated low event rates even in these high-risk patients. In the Early Discharge After Transradial Stenting of the Coronary Arteries (EASY) trial,[50] which randomized 1005 patients to bolus abciximab and SDD ($n = 504$) or to bolus plus 12-hour abciximab infusion and overnight monitoring ($n = 501$), 66% of patients presented with unstable angina and 18% to 19% presented with an acute MI; SDD discharge was noninferior to overnight monitoring at 30-day follow-up. Hodkinson and colleagues[49] describe a cohort of 1059 SDD patients, of which 293 (27.7%) were ACS patients, and described no MACEs within 24 hours after discharge and reported a 30-day MACE rate of 0.85%.

Transfemoral Access

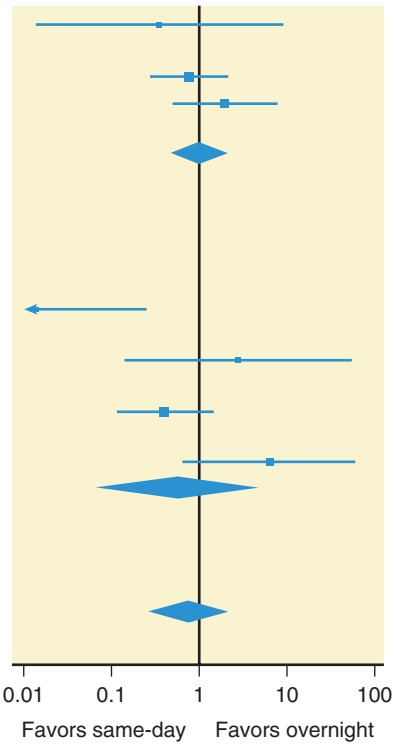
Given the low rates of adoption of the radial approach to PCI in the United States, many studies have demonstrated safe SDD among patients undergoing femoral access PCI with or without VCD use. In the Elective PCI in Outpatient Study (EPOS),[51] all 800 patients

Study or subgroup	Same-day discharge Events	Total	Overnight stay Events	Total	Weight	Odds ratio M-H, Random, 95% CI
Randomized trials						
Knopf et al 1999	0	43	1	47	1.7%	0.36 [0.01, 8.98]
Carere et al 2000	2	50	0	50	1.8%	5.21 [0.24, 111.24]
Bertrand et al 2006	56	504	48	501	24.5%	1.18 [0.79, 1.77]
Heyde et al 2007	6	403	4	397	8.3%	1.48 [0.42, 5.30]
Falcone et al 2011	3	23	3	21	5.1%	0.90 [0.16, 5.04]
Subtotal (95% CI)		**1023**		**1016**	**41.4%**	**1.20 [0.82, 1.74]**
Total events	67		56			
Heterogeneity: $T^2 = 0.00$; $\chi^2 = 1.65$, $df = 4$ ($P = 0.80$); $I^2 = 0\%$						
Test for overall effect: $Z = 0.94$ ($P = 0.35$)						
Observational studies						
Koch et al 2000	0	922	3	87	1.9%	0.01 [0.00, 0.26]
Slagboom et al 2001	0	106	0	53		Not estimable
Dalby et al 2003	3	51	0	19	1.9%	2.81 [0.14, 57.07]
Yee et al 2004	0	25	0	50		Not estimable
Slagboom et al 2005	4	375	7	269	8.6%	0.40 [0.12, 1.39]
Khater et al 2007	0	124	1	26	1.7%	0.07 [0.00, 1.72]
Chung et al 2010	12	214	12	446	14.6%	2.15 [0.95, 4.87]
Rao et al 2011	129	1339	10249	105,679	29.9%	0.99 [0.83, 1.19]
Subtotal (95% CI)		**3156**		**106,629**	**58.6%**	**0.67 [0.27, 1.66]**
Total events	148		10272			
Heterogeneity: $T^2 = 0.65$; $\chi^2 = 16.73$, $df = 5$ ($P = 0.005$); $I^2 = 70\%$						
Test for overall effect: $Z = 0.87$ ($P = 0.38$)						
Total (95% CI)		**4179**		**107,645**	**100.0%**	**1.00 [0.66, 1.54]**
Total events	215		10328			
Heterogeneity: $T^2 = 0.15$; $\chi^2 = 19.16$, $df = 10$ ($P = 0.04$); $I^2 = 48\%$						
Test for overall effect: $Z = 0.02$ ($P = 0.99$)						
Test for subgroup differences: $\chi^2 = 1.34$, $df = 1$ ($P = 0.25$), $I^2 = 25.6\%$						



A

Study or subgroup	Same-day discharge Events	Total	Overnight stay Events	Total	Weight	Odds ratio M-H, Random, 95% CI
Randomized trials						
Knopf et al 1999	0	43	1	47	7.9%	0.36 [0.01, 8.98]
Carere et al 2000	0	50	0	50		Not estimable
Bertrand et al 2006	7	504	9	501	22.6%	0.77 [0.28, 2.08]
Heyde et al 2007	6	403	3	397	19.0%	1.98 [0.49, 7.99]
Falcone et al 2011	0	23	0	21		Not estimable
Subtotal (95% CI)		**1023**		**1016**	**49.6%**	**0.99 [0.45, 2.18]**
Total events	13		13			
Heterogeneity: $T^2 = 0.00$; $\chi^2 = 1.59$, $df = 2$ ($P = .45$); $I^2 = 0\%$						
Test for overall effect: $Z = 0.01$ ($P = .99$)						
Observational studies						
Koch et al 2000	0	922	3	87	8.9%	0.01 [0.00, 0.26]
Slagboom et al 2001	0	106	0	53		Not estimable
Dalby et al 2003	3	51	0	19	8.7%	2.81 [0.14, 57.07]
Yee et al 2004	0	25	0	50		Not estimable
Slagboom et al 2005	4	375	7	269	20.4%	0.40 [0.12, 1.39]
Khater et al 2007	0	124	0	26		Not estimable
Chung et al 2010	3	214	1	446	12.4%	6.33 [0.65, 61.19]
Subtotal (95% CI)		**1817**		**950**	**50.4%**	**0.59 [0.06, 5.57]**
Total events	10		11			
Heterogeneity: $T^2 = 3.78$; $\chi^2 = 11.91$, $df = 3$ ($P = 0.008$); $I^2 = 75\%$						
Test for overall effect: $Z = 0.46$ ($P = 0.65$)						
Total (95% CI)		**2840**		**1966**	**100.0%**	**0.77 [0.26, 2.25]**
Total events	23		24			
Heterogeneity: $T^2 = 1.06$; $\chi^2 = 14.28$, $df = 6$ ($P = 0.03$); $I^2 = 58\%$						
Test for overall effect: $Z = 0.48$ ($P = 0.63$)						
Test for subgroup differences: $\chi^2 = 0.18$, $df = 1$ ($P = 0.67$), $I^2 = 0\%$						



B

FIGURE 38-2 Forest plot of the incidence of 30-day total complications (**A**) and 30-day major adverse cardiovascular event (MACE) rates (**B**) in patients undergoing same-day versus overnight hospitalization. *CI,* Confidence interval; *M-H,* Mantel-Haenszel. (From Abdelaal E, Rao SV, Gilchrist IC, et al: Same-day discharge compared with overnight hospitalization after uncomplicated percutaneous coronary intervention: a systematic review and meta-analysis. *JACC Cardiovasc Interv* 6[2]:99-112, 2013.)

randomized to SDD or overnight monitoring underwent elective PCI via a transfemoral approach; only three cases of access-site complications were reported. A meta-analysis showed no difference in major bleeding or vascular complications among patients randomized to SDD versus those monitored overnight (OR 0.75; 95% CI, 0.19 to 2.98).[46] In the CathPCI analysis, more than 96% of SDD cases incorporated femoral access, and a VCD was used in 65% of cases.[44] Patel and colleagues[52] assessed outcomes in 2400 patients discharged the same day after PCI and described low rates of bleeding (0.58%), fewer vascular complications (0.04%), and reduced major adverse cardiovascular and cerebrovascular event (MACCE) rates (0.96%) at 30 days among low-risk patients, the overwhelming majority of whom underwent PCI via a transfemoral approach (99.6%). This was further studied by Antonsen and colleagues[53] among 1809 low-risk patients undergoing PCI via a femoral approach and undergoing vascular closure using the AngioSeal device (St. Jude Medical, St. Paul, MN). In this study, it is worth noting that stable non–ST-elevation acute coronary syndrome (NSTE-ACS) was not an exclusion criterion for SDD. Among the 355 patients (19.6%) who underwent SDD, 78 (22.0%) presented with unstable angina (UA)/non–ST-elevation myocardial infarction (NSTEMI); no significant differences in MACCE rates were reported at 24 hours or 30 days after the procedure.

Elderly

Even among carefully selected elderly patients, SDD appears to be safe. Ziakas and coworkers[54] reported that despite high rates of minor access-site complications, no significant differences were found in major access-site complications, stent thrombosis, or readmission among elderly patients. Ranchord and colleagues[55] assessed the safety of SDD in 212 patients (13.4% of the study population) 75 years of age and older undergoing elective PCI and found no deaths, similar rates of readmission within 24 hours (<0.7%), and similar MACE rates (3.3% vs. 3.6%, $P = 1.0$) in both groups of patients. The analysis from the CathPCI registry was performed entirely in patients over the age of 65 years and showed similar rates of 30-day death or readmission between same-day discharge and overnight observation.[44]

Patient Satisfaction With Same-Day Discharge

Previous studies[56-58] have shown that many patients prefer SDD to overnight monitoring. Kim and colleagues[59] recently assessed patient preference with SDD versus overnight observation in a randomized trial of 298 patients undergoing elective PCI and found that perceived readiness for discharge assessed prior to discharge was high, and it was similar between SDD (97.9%) and next-day discharged patients (96.6%; $P = .69$). At 30-day follow-up, 79% of patients randomized to SDD, compared with 49% of patients randomized to overnight observation, were satisfied with the timing of their discharge. Whereas 9% of the SDD patients would have preferred to have stayed for longer observation, 37% of the overnight observation patients would have preferred to have been discharged sooner.

Economic Impact of Same-Day Discharge

The economic impact of SDD depends largely on the prevailing admissions and reimbursement criteria. Historically, a low rate of SDD has been attributed to the fee-for-service model, wherein additional services provided during the inpatient hospitalization were fully reimbursed. However, over the last decade, almost all elective PCI cases in the United States have been reimbursed at a fixed rate regardless of overall length of stay or resource utilization under the outpatient APC system. Given that one hospital day can cost up to $4000,[35] the opportunity exists to create care pathways that increase value by facilitating SDD among appropriately selected patients, by reducing costs associated with unnecessary overnight monitoring and prolonging the length of the patient's stay, if even by a matter of hours. Bundled payment schemes require providers to absorb costs related to postprocedure complications and preventable readmissions. In this context, a SDD system can only be cost saving if it reduces costs associated with post-PCI monitoring and maintains a low rate of complications.[60]

Providers who have created innovative new care pathways to appropriately select, monitor, and discharge stable, uncomplicated patients have noted significant decreases in resource utilization and increased bed capacity. Brewster and colleagues[61] describe the creation of an outpatient "radial lounge" for postprocedure monitoring of patients undergoing transradial coronary procedures, and they describe significantly increased rates of SDD after PCI procedures (from 2.3% to 51.2%, $P < .005$) with a concomitant reduction in inpatient bed utilization. An example of a successful radial lounge from Pilsen Hospital in the Czech Republic is shown in Figure 38-3.

The potential cost savings of SDD, compared with standard overnight monitoring, was studied by Rinfret and associates[62] in a post hoc analysis of the EASY Trial. This randomized, open-label study compared SDD and abciximab-only bolus with overnight monitoring and bolus in addition to a 12-hour infusion of abciximab and found that the SDD strategy was noninferior to overnight monitoring. The mean post-PCI hospital length of stay was 8.9 hours for the SDD patients but 26.5 hours for the overnight patients. Associated costs were $1117 (± $1,554) for SDD patients compared with $2258 (± $1328) for patients monitored overnight, a cost difference of $1141 that was primarily attributed to hospital costs related to post-PCI ward-related costs, estimated to be $65 per hour in this Canadian study. These savings may be higher in environments where costs are higher.

Recommendations for Safe Same-Day Discharge

Preprocedure Screening

Preprocedural screening should focus on baseline demographics and clinical and social factors that preclude SDD. Although older patients (>65 years of age) and those who present with an ACS have been discharged safely, most programs typically favor overnight management in these groups. Other patient factors that warrant overnight management include impaired renal function (glomerular filtration rate [GFR] <60 mL/min), severe LV dysfunction (<30%), or contrast allergy. Additionally, patients should live close to a medical facility in case of a medical emergency and have adequate social support.

Procedural Characteristics

The sine qua non of SDD is a successful procedure without complications. Most complications manifest within 6 hours of PCI and thus can be readily identified during postprocedure monitoring.[63] Although safely used in the EASY trial,[50] most operators feel that a postprocedure infusion of GP IIb/IIIa inhibitor warrants overnight monitoring. However, the use of an abbreviated infusion or bolus only, such as in the EASY trial, may be suitable for SDD. Other procedural factors that may warrant consideration of overnight monitoring include significant left main CAD, use of mechanical circulatory support (intraaortic balloon pump [IABP]), or complex PCI, including a bifurcation lesion, multivessel intervention, or atherectomy. Angiographic complications such as a significant dissection, side-branch loss, and slow or no-reflow phenomenon and procedural complications such as periprocedural ischemia or ventricular arrhythmias also warrant longer observation.

Postprocedural Monitoring

Patients are typically monitored for 4 to 8 hours after the procedure. Symptoms or signs of ischemia—including chest pain, shortness of breath, hemodynamic instability, or new or worsening ECG changes—should warrant careful management and longer observation. Patients should also be able to achieve their preprocedure level of ambulation without significant discomfort prior to discharge. Additionally, the access site should be evaluated carefully to ensure appropriate hemostasis and no early signs of distal vascular compromise. The role of checking biomarkers after PCI is controversial and is discussed elsewhere in this chapter. If the procedure was uncomplicated and no signs or symptoms of ischemia are present, checking cardiac biomarkers prior to SDD is not warranted; however, if an angiographic

FIGURE 38-3 The radial lounge at Pilsen Hospital in Pilsen, Czech Republic, which facilitates same-day discharge. (Photos courtesy Ivo Bernat MD.)

complication arose or signs of new myocardial dysfunction were apparent, a CK-MB or cTn should be checked 8 to 12 hours after the procedure and repeated if newly abnormal; in that situation, SDD is not a feasible strategy. Additionally, clear instructions should be provided prior to discharge that include medication changes and a plan for DAPT, activity recommendations, and clear contact information in the event of an adverse event. It is advisable to have the patient's family obtain at least a 30-day supply of DAPT medications prior to discharge. This is most feasible at hospitals that have on-site pharmacies.

After Discharge

SDD patients should be contacted within 24 hours of discharge to ensure no ischemic or vascular/bleeding complications have developed since their return home. Additionally, compliance with DAPT should be confirmed at this time along with plans for routine postprocedure follow-up. A proposed checklist for eligibility of SDD is provided in Table 38-3.

TABLE 38-3 Proposed Checklist for Eligibility for Same-Day Discharge

Preprocedural Factors
• No acute decompensated heart failure or shock
• No contrast allergy
• Nonemergent percutaneous coronary intervention
• Adequate social support is available
• Patient lives close to medical facility
Procedural/Angiographic Factors
• Uncomplicated access
• Uncomplicated lesion and procedure.
• Infusion glycoprotein IIb/IIIa inhibitor not used (bolus is acceptable)
• No angiographic complications (side-branch occlusion, dissection, no-reflow phenomenon)
Postprocedure Monitoring
• No signs or symptoms of ischemia
• No biomarker elevation (if checked)
• Patient able to ambulate without difficulty
• Patient able to tolerate oral intake
• Patient has $P2Y_{12}$ inhibitor on hand prior to discharge

CONCLUSIONS

The importance of appropriate postprocedure management in patients undergoing PCI cannot be understated and has taken on additional meaning as postprocedure length of stay has continued to decrease. Clear patient communication, both verbal and written, along with rigorous medication reconciliation that includes a plan for dual-antiplatelet therapy and a well-defined plan in case of complications may minimize adverse outcomes after PCI. The role of measuring cardiac biomarkers continues to evolve. Although current recommendations strongly support biomarker testing in patients with procedural complications or evidence of myocardial injury but offer only weak support for routine testing after the procedure, the clinical relevance of small levels of myocardial necrosis continues to be debated as newer and more sensitive assays to detect myocardial injury become available. Finally, as length of hospital stay after PCI continues to shorten, a valuable opportunity exists to design new, innovative care pathways to safely manage patients after PCI and to discharge eligible patients on the same day of their procedure, which, if performed safely and effectively, may lead to increased patient satisfaction in addition to cost savings.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, et al: Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation* 131(4):e29–e322, 2014.
2. Naidu SS, Rao SV, Blankenship J, et al: Clinical expert consensus statement on best practices in the cardiac catheterization laboratory: Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv* 80(3):456–464, 2012.
3. Lewin R: Return to work after MI, the roles of depression, health beliefs and rehabilitation. *Int J Cardiol* 72(1):49–51, 1999.
4. Levine GN, Steinke EE, Bakaeen FG, et al: Sexual activity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 125(8):1058–1072, 2012.
5. Parzeller M, Raschka C, Bratzke H: Sudden cardiovascular death during sexual intercourse—results of a legal medicine autopsy study]. *Z Kardiol* 88(1):44–48, 1999.
6. Ueno M: [The so-called coition death]. *Nihon Hoigaku Zasshi* 17:330–340, 1963.
7. Amsterdam EA, Wenger NK, Brindis RG, et al: 2014 AHA/ACC Guideline for the Management of Patients with Non–ST-Elevation Acute Coronary Syndromes; a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 64(24):e139–e228, 2014.
8. Levine GN, Bates ER, Blankenship JC, et al: 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 58(24):e44–e122, 2011.
9. O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 61(4):e78–e140, 2013.
10. Novack V, Pencina M, Cohen DJ, et al: Troponin criteria for myocardial infarction after percutaneous coronary intervention. *Arch Intern Med* 172(6):502–508, 2012.
11. Cutlip DE, Kuntz RE: Does creatinine kinase-MB elevation after percutaneous coronary intervention predict outcomes in 2005? Cardiac enzyme elevation after successful percutaneous coronary intervention is not an independent predictor of adverse outcomes. *Circulation* 112(6):916–922, discussion 922, 2005.
12. Jeremias A, Baim DS, Ho KK, et al: Differential mortality risk of postprocedural creatine kinase-MB elevation following successful versus unsuccessful stent procedures. *J Am Coll Cardiol* 44(6): 1210–1214, 2004.
13. Thygesen K, Alpert JS, White HD: Universal definition of myocardial infarction. *J Am Coll Cardiol* 50(22):2173–2195, 2007.
14. Thygesen K, Alpert JS, Jaffe AS, et al: Third universal definition of myocardial infarction. *J Am Coll Cardiol* 60(16):1581–1598, 2012.
15. Moussa ID, Klein LW, Shah B, et al: Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol* 62(17):1563–1570, 2013.
16. Breet NJ, van Werkum JW, Bouman HJ, et al: Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *JAMA* 303(8):754–762, 2010.
17. Buonamici P, Marcucci R, Migliorini A, et al: Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. *J Am Coll Cardiol* 49(24):2312–2317, 2007.
18. Hochholzer W, Trenk D, Bestehorn HP, et al: Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. *J Am Coll Cardiol* 48(9):1742–1750, 2006.
19. Price MJ, Berger PB, Teirstein PS, et al: Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 305(11):1097–1105, 2011.
20. Collet JP, Cuisset T, Range G, et al: Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med* 367(22): 2100–2109, 2012.
21. Kiemeneij F, Yoshimachi F, Matsukage T, et al: Focus on maximal miniaturisation of transradial coronary access materials and techniques by the Slender Club Japan and Europe: an overview and classification. *EuroIntervention* 10(11):1178–1186, 2015.
22. Wiviott SD, Braunwald E, McCabe CH, et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 357(20):2001–2015, 2007.
23. Wallentin L, Becker RC, Budaj A, et al: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 361(11):1045–1057, 2009.
24. Shahzad A, Kemp I, Mars C, et al: Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet* 384(9957):1849–1858, 2014.
25. Giugliano RP, White JA, Bode C, et al: Early versus delayed, provisional eptifibatide in acute coronary syndromes. *N Engl J Med* 360(21):2176–2190, 2009.
26. Stone GW, McLaurin BT, Cox DA, et al: Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 355(21):2203–2216, 2006.
27. Stone GW, Witzenbichler B, Guagliumi G, et al: Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 358(21):2218–2230, 2008.
28. Steg PG, van 't Hof A, Hamm CW, et al: Bivalirudin started during emergency transport for primary PCI. *N Engl J Med* 369(23):2207–2217, 2013.
29. Campeau L: Percutaneous radial artery approach for coronary angiography. *Cathet Cardiovasc Diagn* 16(1):3–7, 1989.
30. Otaki M: Percutaneous transradial approach for coronary angiography. *Cardiology* 81(6):330–333, 1992.
31. Kiemeneij F, Laarman GJ: Percutaneous transradial artery approach for coronary Palmaz-Schatz stent implantation. *Am Heart J* 128(1):167–174, 1994.
32. Kiemeneij F, Laarman GJ, de Melker E: Transradial artery coronary angioplasty. *Am Heart J* 129(1):1–7, 1995.
33. Feldman DN, Swaminathan RV, Kaltenbach LA, et al: Adoption of radial access and comparison of outcomes to femoral access in percutaneous coronary intervention: an updated report from the National Cardiovascular Data Registry (2007-2012). *Circulation* 127(23):2295–2306, 2013.
34. Jolly SS, Yusuf S, Cairns J, et al: Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet* 377(9775):1409–1420, 2011.
35. Amin AP, House JA, Safley DM, et al: Costs of transradial percutaneous coronary intervention. *JACC Cardiovasc Interv* 6(8):827–834, 2013.
36. Marso SP, Amin AP, House JA, et al: Association between use of bleeding avoidance strategies and risk of periprocedural bleeding among patients undergoing percutaneous coronary intervention. *JAMA* 303(21):2156–2164, 2010.
37. Vaitkus PT: A meta-analysis of percutaneous vascular closure devices after diagnostic catheterization and percutaneous coronary intervention. *J Invasive Cardiol* 16(5):243–246, 2004.
38. Nikolsky E, Mehran R, Halkin A, et al: Vascular complications associated with arteriotomy closure devices in patients undergoing percutaneous coronary procedures: a meta-analysis. *J Am Coll Cardiol* 44(6):1200–1209, 2004.
39. Kiemeneij F, Laarman GJ: Transradial artery Palmaz-Schatz coronary stent implantation: results of a single-center feasibility study. *Am Heart J* 130(1):14–21, 1995.
40. Kiemeneij F, Laarman GJ, Slagboom T, Stella P: Transradial Palmaz-Schatz coronary stenting on an outpatient basis: results of a prospective pilot study. *J Invasive Cardiol* 7(Suppl A):5a–11a, 1995.
41. Kiemeneij F, Laarman GJ, Slagboom T, van der Wieken R: Outpatient coronary stent implantation. *J Am Coll Cardiol* 29(2):323–327, 1997.
42. Gilchrist IC, Nickolaus MJ, Momplaisir T: Same-day transradial outpatient stenting with a 6-hr course of glycoprotein IIb/IIIa receptor blockade: a feasibility study. *Catheter Cardiovasc Interv* 56(1):10–13, 2002.
43. Wilentz JR, Mishkel G, McDermott D, et al: Outpatient coronary stenting using the femoral approach with vascular sealing. *J Invasive Cardiol* 11(12):709–717, 1999.
44. Rao SV, Kaltenbach LA, Weintraub WS, et al: Prevalence and outcomes of same-day discharge after elective percutaneous coronary intervention among older patients. *JAMA* 306(13):1461–1467, 2011.
45. Abdelaal E, Rao SV, Gilchrist IC, et al: Same-day discharge compared with overnight hospitalization after uncomplicated percutaneous coronary intervention: a systematic review and meta-analysis. *JACC Cardiovasc Interv* 6(2):99–112, 2013.
46. Brayton KM, Patel VG, Stave C, et al: Same-day discharge after percutaneous coronary intervention: a meta-analysis. *J Am Coll Cardiol* 62(4):275–285, 2013.
47. Chambers CE, Dehmer GJ, Cox DA, et al: Defining the length of stay following percutaneous coronary intervention: an expert consensus document from the Society for Cardiovascular Angiography and Interventions. Endorsed by the American College of Cardiology Foundation. *Catheter Cardiovasc Interv* 73(7):847–858, 2009.
48. Gilchrist IC, Rhodes DA, Zimmerman HE: A single center experience with same-day transradial-PCI patients: a contrast with published guidelines. *Catheter Cardiovasc Interv* 79(4):583–587, 2012.
49. Hodkinson EC, Ramsewak A, Murphy JC, et al: An audit of outcomes after same-day discharge post-PCI in acute coronary syndrome and elective patients. *J Interv Cardiol* 26(6):570–577, 2013.
50. Bertrand OF, De Larochelliere R, Rodes-Cabau J, et al: A randomized study comparing same-day home discharge and abciximab bolus only to overnight hospitalization and abciximab bolus and infusion after transradial coronary stent implantation. *Circulation* 114(24):2636–2643, 2006.
51. Heyde GS, Koch KT, de Winter RJ, et al: Randomized trial comparing same-day discharge with overnight hospital stay after percutaneous coronary intervention: results of the Elective PCI in Outpatient Study (EPOS). *Circulation* 115(17):2299–2306, 2007.
52. Patel M, Kim M, Karajgikar R, et al: Outcomes of patients discharged the same day following percutaneous coronary intervention. *JACC Cardiovasc Interv* 3(8):851–858, 2010.
53. Antonsen L, Jensen LO, Thayssen P: Outcome and safety of same-day-discharge percutaneous coronary interventions with femoral access: a single-center experience. *Am Heart J* 165(3):393–399, 2013.
54. Ziakas A, Klinke P, Mildenberger R, et al: Safety of same day discharge radial PCI in patients under and over 75 years of age. *Int Heart J* 48(5):569–578, 2007.
55. Ranchord AM, Prasad S, Seneviratne SK, et al: Same-day discharge is feasible and safe in the majority of elderly patients undergoing elective percutaneous coronary intervention. *J Invasive Cardiol* 22(7):301–305, 2010.
56. Glaser R, Gertz Z, Matthai WH, et al: Patient satisfaction is comparable to early discharge versus overnight observation after elective percutaneous coronary intervention. *J Invasive Cardiol* 21(9): 464–467, 2009.
57. Knopf WD, Cohen-Bernstein C, Ryan J, et al: Outpatient PTCA with same day discharge is safe and produces high patient satisfaction level. *J Invasive Cardiol* 11(5):290–295, 1999.
58. Ziakas A, Klinke P, Fretz E, et al: Same-day discharge is preferred by the majority of the patients undergoing radial PCI. *J Invasive Cardiol* 16(10):562–565, 2004.
59. Kim M, Muntner P, Sharma S, et al: Assessing patient-reported outcomes and preferences for same-day discharge after percutaneous coronary intervention: results from a pilot randomized, controlled trial. *Circ Cardiovasc Qual Outcomes* 6(2):186–192, 2013.
60. Gilchrist IC: Same day discharge after elective percutaneous coronary intervention. *Curr Cardiol Rep* 16(4):470, 2014.
61. Brewster S, Khimdas K, Cleary N, et al: Impact of a dedicated "radial lounge" for percutaneous coronary procedures on same-day discharge rates and bed utilization. *Am Heart J* 165(3):299–302, 2013.
62. Rinfret S, Kennedy WA, Lachaine J, et al: Economic impact of same-day home discharge after uncomplicated transradial percutaneous coronary intervention and bolus-only abciximab regimen. *JACC Cardiovasc Interv* 3(10):1011–1019, 2010.
63. Jabara R, Gadesam R, Pendyala L, et al: Ambulatory discharge after transradial coronary intervention: preliminary U.S. single-center experience (Same-day TransRadial Intervention and Discharge Evaluation, the STRIDE Study). *Am Heart J* 156(6): 1141–1146, 2008.

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39 Lower Extremity Interventions

DEBABRATA MUKHERJEE

KEY POINTS

- Individuals at risk for lower extremity peripheral artery disease (PAD) should undergo a vascular review of symptoms to assess walking impairment, claudication, ischemic rest pain, and the presence of nonhealing wounds.
- Despite recent advances in noninvasive evaluation of lower extremity PAD, contrast angiography remains the gold standard for definitive evaluation. Contrast angiography provides detailed information about arterial anatomy and is recommended for evaluation of patients with lower extremity PAD when revascularization is contemplated.
- Occlusive disease of the iliac arteries appears to occur in relatively young patients and may have a greater impact on productivity and lifestyle compared with infrainguinal lower extremity disease.
- The excellent intermediate- to long-term patency rates following percutaneous intervention of the lower extremity arteries has led to its emergence as an attractive alternative to surgery in patients with suitable lesions. Endovascular intervention is recommended as the preferred revascularization technique for TransAtlantic Inter-Society Consensus (TASC) type A iliac and femoropopliteal artery (FPA) lesions.
- Stenting is effective as primary therapy for common iliac and external iliac artery stenosis and occlusions.
- Technical and clinical success rates of endovascular interventions for iliac artery stenosis exceed 90% with a fairly comparable intermediate- and long-term patency to that of surgical revascularization, making them the initial therapy of choice for most iliac stenoses.
- Although controversial, surgery remains the preferred strategy for patients with common femoral and proximal profunda femoris obstructive PAD.
- Lower durability of percutaneous intervention may be offset by the less invasive nature of endovascular interventions and resultant decreased morbidity and mortality compared with vascular surgery.
- Interventions can be repeatedly done if they fail, but repeat surgery is technically more challenging and may be limited by availability of conduit.
- In patients with anatomically appropriate lesions, most practitioners use endovascular interventions preferentially as the initial therapy of choice.

EPIDEMIOLOGY AND NATURAL HISTORY

Peripheral arterial disease of the lower extremity is a common health problem.[1] Epidemiologic studies have mostly used intermittent claudication (IC) as a symptomatic marker of the disease and an abnormal ankle-brachial index (ABI) to define the burden of asymptomatic PAD. The prevalence of the disease is dependent on the age of the population studied and the underlying atherosclerotic risk profile of the cohort. It is estimated that the overall disease prevalence is in the range of 3% to 10%, increasing to about 15% to 20% in persons older than 70 years. More than half of all patients with lower extremity PAD may be asymptomatic.[2-8]

History that includes standardized questionnaires, such as the Rose Claudication Questionnaire used in the Framingham Heart Study, and physical examination may grossly underestimate the true burden of lower extremity PAD.[2] Criqui and colleagues[9] evaluated the prevalence of lower extremity PAD in a population of 613 men and women in southern California using four different modalities: the Rose Questionnaire, pulse examination, ABI, and pulse wave velocity. The detection rate of PAD with ABI and pulse-wave velocity was two to seven times higher than the detection rate of the Rose Questionnaire. Of interest, clinical examination of the pulse overestimated the prevalence of PAD by twofold.

To optimally manage patients with lower extremity PAD, whether symptomatic or asymptomatic, it is important to understand the global vascular disease burden, the natural history of the disease process, its impact on the patient's lifestyle, and the risk factors for an individual patient. Such knowledge is key to reducing the mortality and morbidity of the individual patient.

VASCULAR ANATOMY OF THE LOWER EXTREMITY

The abdominal aorta bifurcates at the level of the fourth lumbar vertebra into two branches, the right and the left common iliac arteries, which further divide into the *external iliac artery,* which normally follows the same axis of the common iliac artery, and the *internal iliac arteries,* which take a posteromedial track in relation to the common iliac artery. In addition to its terminal branches, the common iliac artery gives branches to the surrounding tissues, peritoneum, psoas muscle, ureter, and nerves. Occasionally, the common iliac artery provides accessory renal arteries to a normal or ectopic kidney. Figure 39-1 depicts the arterial circulation of the lower extremity.

The external iliac arteries are larger than the internal iliac arteries. They descend along the medial border of the psoas major muscle and enter the thigh posterior to the inguinal ligament to become the common femoral arteries. The inferior epigastric artery arises medially from the distal external iliac artery and ascends behind the rectus abdominis muscle. This vessel is a useful landmark in predicting higher bleeding risk in arterial punctures proximal to its origin.[10] The external iliac artery gives off other branches—namely, the deep circumflex, cremasteric, and several muscular and cutaneous branches—before it continues as the common femoral artery (CFA). Together the common iliac and the external iliac arteries contribute to the inflow of the lower extremity.

The CFA starts as a continuation of the external iliac artery, giving multiple branches to surrounding tissues, such as the pudendal arteries

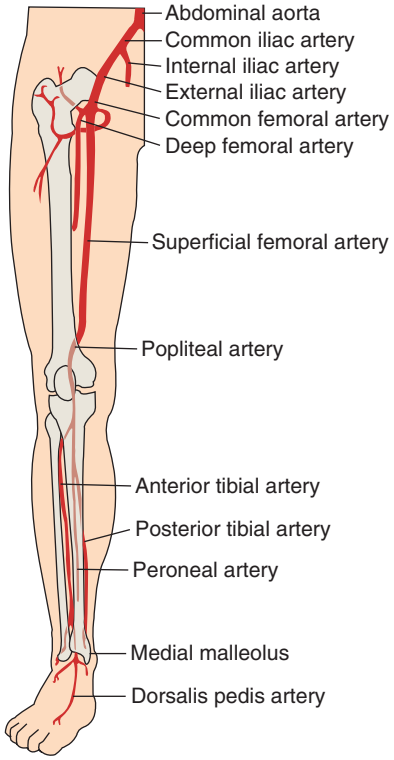

FIGURE 39-1 Arterial tree of the lower extremity.

and the superficial circumflex artery; then it becomes the superficial femoral artery (SFA) after giving rise to the deep femoral artery (DFA) roughly 3.5 cm distal to the inguinal ligament. The DFA arises laterally and posteriorly from the CFA, whereas the SFA continues its pathway to end as the popliteal artery when it passes through the abductor canal. The DFA gives off perforating branches, usually three—the lateral and medial circumflex arteries and muscular branches—and the end of the DFA is the fourth perforating branch. The popliteal artery continues through the abductor's canal, and after giving muscular, cutaneous, genicular, and sural branches, it terminates into the anterior tibial artery and the tibioperoneal trunk. The CFA, SFA, DFA, and the popliteal artery comprise the outflow of the lower extremity.

The anterior tibial artery runs between the two heads of the tibialis posterior muscle and then through the upper part of the interosseous membrane to the front of the leg medial to the head of the fibula. It descends down to the ankle and then continues to the dorsum of the foot, where it becomes the dorsalis pedis artery. The posterior tibial artery arises from the popliteal artery distal to the origin of the anterior tibial artery as the tibioperoneal trunk. After giving rise to the peroneal artery, the tibioperoneal trunk continues as the posterior tibial artery behind the leg and passes behind the medial malleolus to end by giving rise to the arteries of the foot, namely the calcaneal, which anastomoses with the calcaneal and malleolar branches of the peroneal and medial and lateral planter arteries. The anterior tibial artery, posterior tibial artery, and the peroneal artery are considered the runoff vessels.

DIAGNOSIS OF LOWER EXTREMITY PERIPHERAL ARTERIAL DISEASE

History and Physical Examination

Patients with lower extremity PAD may be asymptomatic (disease is detected during physical examination or screening tests), or they may present with intermittent claudication, rest pain, nonhealing ulcers, or intractable foot infections. In light of the limitations of clinical assessment in defining patients with asymptomatic PAD, additional assessment of patients with risk factors for atherosclerosis may be required in identifying patients with asymptomatic advanced PAD. Symptomatic patients can be classified based on the severity of ischemia based on either the Fontaine or Rutherford categories (Table 39-1).

TABLE 39-1 Classification of Lower Extremity Peripheral Artery Disease by the Fontaine Stages and Rutherford Categories

FONTAINE		RUTHERFORD		
Stage	Clinical	Grade	Category	Clinical
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate to severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
		III	5	Minor tissue loss
IV	Ulceration or gangrene	IV	6	Ulceration or gangrene

From Dormandy JA, Rutherford RB: Management of peripheral arterial disease (PAD). TASC Working Group. Trans-Atlantic Inter-Society Consensus (TASC). *J Vasc Surg* 31:S1-S296, 2000.

Ankle-Brachial Index

The ankle-brachial index (ABI) is a ratio of the blood pressure in the dorsalis pedis or the posterior tibial artery, whichever is higher, to the blood pressure in the brachial arteries. ABI measurement is one of the most cost-effective methods for assessing PAD of the lower extremity, and it typically is done with a handheld Doppler ultrasound device. This is a noninvasive, fairly reproducible, and inexpensive test. The resting ABI should be used to establish the lower extremity PAD diagnosis in patients with *suspected* lower extremity PAD, defined as individuals with one or more of the following: exertional leg symptoms, nonhealing wounds, age 65 and older, or 50 years and older with a history of smoking or diabetes.[11] The ABI should also be measured in both legs in all new patients with PAD of any severity to confirm the diagnosis of lower extremity PAD and establish a baseline.[11] ABI results should be uniformly reported: *noncompressible* values are defined as greater than 1.40, *normal* values are 1.00 to 1.40, *borderline* is 0.91 to 0.99, and *abnormal* is 0.90 or less. The most widely accepted definition of lower extremity PAD is a resting ABI of less than 0.9, which is usually associated with 50% or greater angiographic arterial stenosis with a reported sensitivity of 95% and close to 100% specificity.[8] A resting ABI of 0.4 to 0.9 is suggestive of mild to moderate PAD, and a resting ABI below 0.4 is suggestive of severe PAD (Table 39-2). Resting ABI measurement can be artifactually high in the setting of tibial artery calcification usually seen in diabetics. The toe-brachial index (TBI) should be used to establish a diagnosis in patients in whom lower extremity PAD is clinically suspected but in whom the ABI test is not reliable because of noncompressible vessels (usually patients with long-standing diabetes or advanced age). A TBI below 0.7 is considered abnormal.

The use of exercise ABI may be helpful in equivocal cases. For this the patient walks on the treadmill at a constant speed of 1 to 2 miles per hour and at a 10% to 12% incline for 5 minutes, or the exercise can be done with active pedal plantar flexion. A decrease of at least 15 mm Hg in the ankle systolic pressure following the exercise challenge is considered an abnormal test. Patients with no significant PAD are expected to have an increase or no change in their ankle systolic pressure. Exercise treadmill tests may also be performed in individuals with claudication who are to undergo exercise training (lower extremity PAD rehabilitation) so as to determine functional capacity, assess nonvascular exercise limitations, and demonstrate the safety of exercise.

Pulse Volume Recording

Plethysmography is used to detect volumetric changes in the lower extremity blood flow and is performed with pressure cuffs inflated to 60 to 65 mm Hg at various segments of the lower extremity. A normal tracing will have a rapid systolic upstroke and downstroke with a prominent dicrotic notch. This pattern changes as PAD develops and progresses, with a noted attenuation and widening of the arterial waveform. Ultimately, the waveform becomes flat (nonpulsatile) in patients with advanced PAD (Fig. 39-2). Pulse volume recordings are reasonable to establish the initial lower extremity PAD diagnosis, assess localization and severity, and follow the status of lower extremity revascularization procedures.

TABLE 39-2 Grading Lower Extremity Peripheral Arterial Disease by Ankle-Brachial Index

	Supine Resting ABI	Postexercise ABI
Normal	>1.0	>1.0
Mild	0.8 to 0.9	>0.4
Moderate	0.4 to 0.8	>0.2
Severe	<0.4	<0.2

From Mukherjee D, Yadav JS: Update on peripheral vascular diseases: from smoking cessation to stenting. *Cleveland Clinic J Med* 68(8):723-733, 2001; Table 2.
*Postexercise ankle-brachial index (ABI) is measured following treadmill exercise at 1 to 2 mph, 10% to 12% grade, for 5 minutes or is symptom limited.

Segmental Blood Pressure

For this test, a series of blood pressure cuffs are placed at the level of the thigh (one or two cuffs), calf, ankle, foot, and the big toe. These cuffs are then inflated sequentially to about 20 mm Hg above the systolic pressure in that segment. The cuff pressure is then released slowly and a continuous-wave Doppler probe is used to obtain the pressure at each segment. A decrease between two consecutive levels of 30 mm Hg or more indicates the presence of a stenosis in the segment proximal to the blood pressure cuff. Also, the presence of a 20- to 30-mm Hg difference in the pressure at one limb, when compared with the contralateral limb at the same level, is suggestive of significant PAD proximal to the cuff in that limb.

Duplex Ultrasonography

Duplex ultrasound uses a 5- to 7.5-MHz transducer to assess and characterize suprainguinal and infrainguinal PAD with a high sensitivity and specificity (over 90%). Doppler velocities are obtained (60-degree Doppler angle) to complement two-dimensional

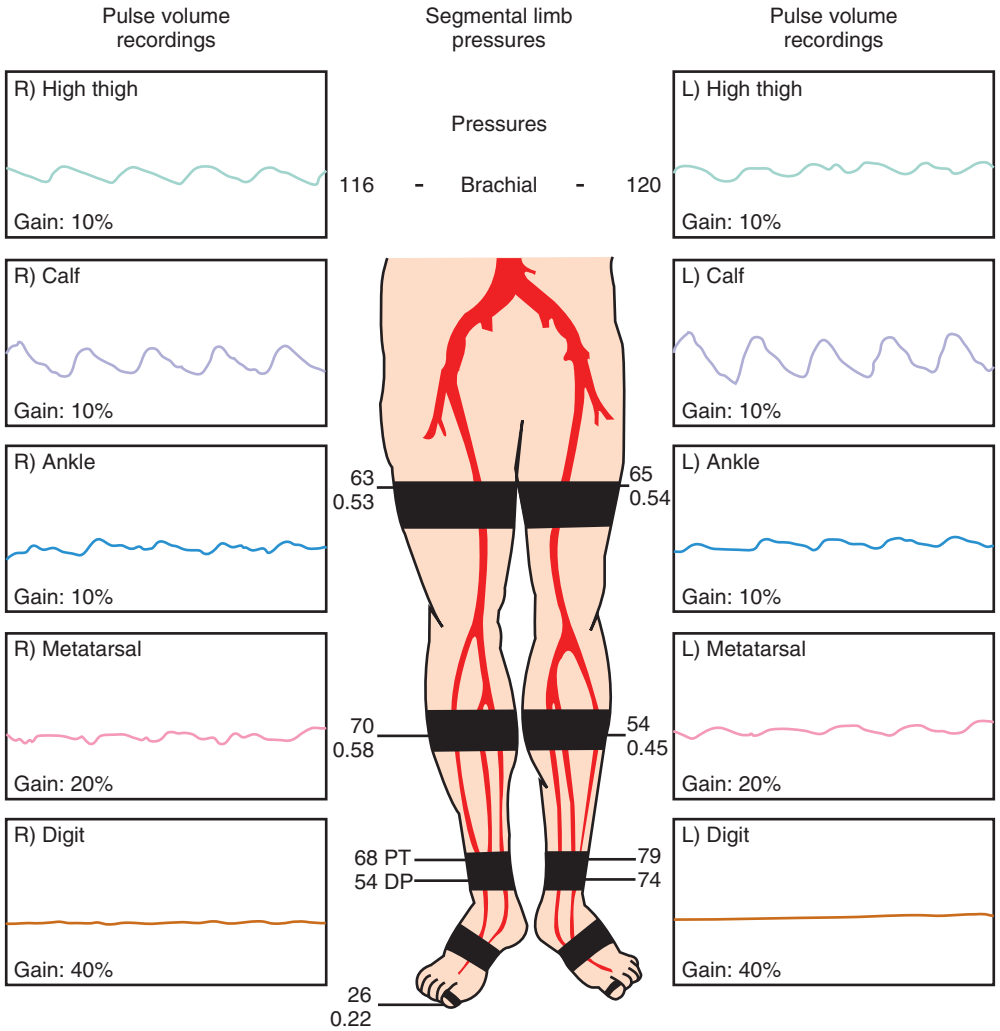

FIGURE 39-2 Segmental limb pressures and pulse volume recordings (PVRs) demonstrating aortoiliac disease. The PVR waveforms in the thigh segment are dampened, and the segmental pressures in the thigh are decreased when compared with the brachial pressures. (From Rajagopalan S, Mukherjee D, Mohler E, eds: *Manual of vascular diseases*. Philadelphia, 2004, Lippincott, Williams & Wilkins, p 17).

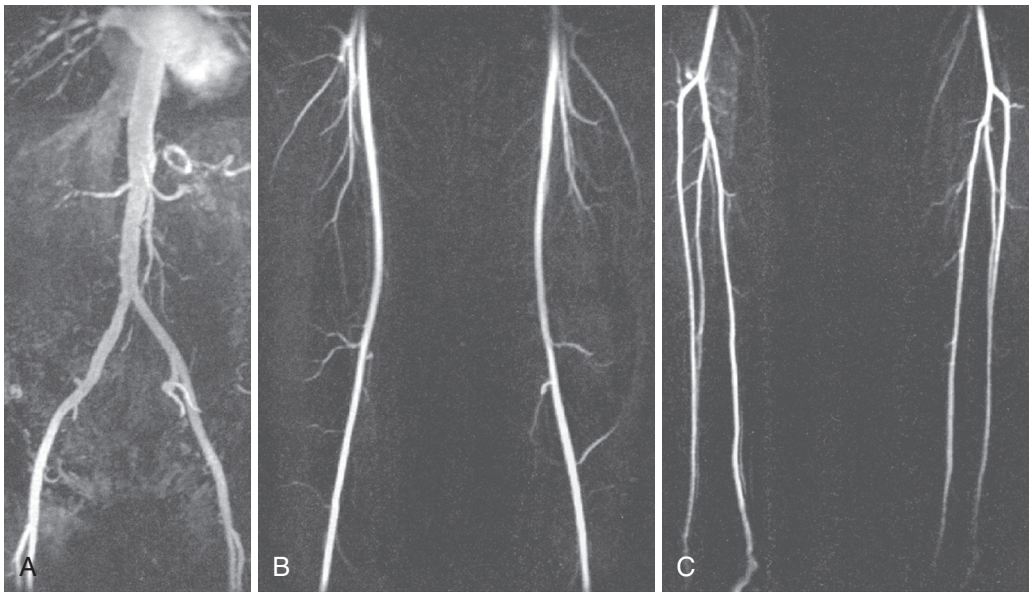

FIGURE 39-3 Maximal intensity projection images of a normal lower extremities runoff three-dimensional contrast-enhanced magnetic resonance angiography. (From Rajagopalan S, Mukherjee D, Mohler E, eds: *Manual of vascular diseases,* Philadelphia, 2004, Lippincott, Williams & Wilkins, p 65).

ultrasonography. Traditionally, arteries are classified into five categories based on the degree of stenosis: category 1 is considered normal, 2 indicates stenosis of 1% to 19%, 3 is stenosis of 20% to 49%, 4 indicates 50% to 99% stenosis, and 5 signifies total occlusion. Duplex ultrasonography may be useful to operators in planning access to a lesion that is amenable to endovascular therapy. It is also very helpful in identifying iatrogenic traumatic lesions and pseudoaneurysms. Direct ultrasound-guided compression or thrombin injection to repair femoral artery pseudoaneurysms is widely used in treating such lesions without the need for surgical procedures. One important limitation of Duplex ultrasonography is that it may overestimate residual stenosis following interventions, which limits its usefulness as a follow-up tool in this setting. Duplex ultrasound is recommended for routine surveillance after femoral-popliteal or femoral-tibial-pedal bypass with a venous conduit. Minimum surveillance intervals are approximately 3, 6, and 12 months and then yearly after graft placement.[11]

Computed Tomography Angiography

The use of spiral computed tomography angiography (CTA) in assessing lower extremity PAD has 93% sensitivity and 96% specificity in detecting greater than 50% stenosis with high accuracy when compared with digital subtraction angiography (DSA). A recent systematic review and meta-analysis[12] suggested that CTA is highly accurate for assessment of PAD in all regions of the lower extremity arteries. CTA correctly identified hemodynamically significant lesions and also accurately distinguished between greater than 50% stenoses and occlusions. Ninety-four percent of occlusions and 87% of nonoccluded segments with more than 50% stenosis detected by contrast angiography were correctly identified by CTA.[12] The accuracy of CTA may actually be even higher than reported in this study, because all studies used contrast angiography as the reference standard but did not report whether biplanar views were used routinely. Because CTA reconstructions allow three-dimensional (3-D) assessment, significant disease may be detected by CTA but may not be recognized by angiography, which may lead to underestimation of specificity. CTA has advantages over magnetic resonance angiography (MRA) in patients with pacemakers and defibrillators and in those with metal clips, stents, or prosthesis (no significant artifact is seen in CTA as opposed to MRA), and it is significantly faster to perform than MRA. However, CTA requires the use of iodinated contrast, and it entails exposure to ionizing radiation. Dose-saving algorithms are very effective in reducing radiation exposure and should be used whenever possible.[13]

Magnetic Resonance Angiography

The use of gadolinium-enhanced magnetic resonance angiography (GEMRA; Fig. 39-3) in the assessment of lower extremity PAD has been compared with standard catheter angiography with a reported sensitivity and specificity for detecting stenosis greater than 50% of about 90% and 100%, respectively. Most contemporary studies report an agreement of 91% to 97% between MRA and catheter angiography. GEMRA is superior to duplex ultrasound in detecting greater than 50% stenotic lesions (sensitivity of 98% vs. 88% and specificity of 96% vs. 95%).[8]

Limitations of this technology include the tendency to overestimate the severity of stenosis and the fact that metal clips may give the impression of total occlusion, and metal stents can obscure vascular flow as well. In addition to these limitations, certain subsets of patients may not be able to be studied with MRA, such as those with pacemakers and defibrillators and those with certain types of cerebral aneurysm clips.[8] The principle role of MRA is in the initial evaluation for PAD, especially in patients with inflow disease, using "bolus chase" 3-D imaging, in which a single bolus of contrast is followed to the foot.

Contrast Angiography

Despite recent advances in noninvasive evaluation of lower extremity PAD, contrast angiography remains the gold standard. Traditionally, a pelvic/abdominal aortogram in the anteroposterior projection is done using a straight pigtail catheter (5 or 6 Fr) placed at the level of the L1-L2 vertebrae. Approximately 10 to 15 mL of isoosmolar contrast is injected at a rate of 15 mL/second with DSA technology. This allows an excellent view of the distal aorta, the origin of the common iliac arteries, and the external iliac and common femoral arteries. Angulated views (left anterior oblique [LAO] of 30 degrees) can then be used to visualize the iliac and femoral bifurcations without overlap. Next, the pigtail catheter is placed above the aortic bifurcation (L3-L4) and DSA with bolus chase, 8 mL/second for 10 seconds, is used to assess the outflow and distal runoff. Selective injections and sheath injections can then be used to further define the territory of interest as needed. The use of "road map" technology can be used subsequently to help operators in their intervention and placement of balloons and stents.

Contrast angiography remains the most readily used and widely available imaging technique in patients with PAD of the lower extremity when revascularization is contemplated. The use of noninvasive technologies, such as MRA or CTA, may be used prior to contrast angiography to help identify the potential culprit lesion and plan the best approach (access point, catheter selection, etc.) to study such a lesion invasively.[8] Contrast angiography may be associated with vascular access complications (bleeding, infections, pseudoaneurysms, and vascular disruption), atheroembolism, contrast nephropathy, and contrast-induced anaphylactoid reactions. These complications, although rare, should be considered in the decision-making process with regard to the assessment of PAD.

Overall, contrast angiography provides detailed information about arterial anatomy and is recommended for evaluation of patients with lower extremity PAD when revascularization is contemplated. When conducting a diagnostic lower extremity arteriogram in which the significance of an obstructive lesion is ambiguous, transstenotic pressure gradients and supplementary angulated views should be obtained.[11]

INTERVENTIONS

Percutaneous or surgical interventions are indicated for severe lifestyle-limiting symptoms, to reduce tissue breakdown in the context of critical limb ischemia (CLI), or for salvage in the context of acute limb ischemia (ALI). In general, endovascular procedures are indicated for individuals with a vocational or lifestyle-limiting disability due to intermittent claudication when clinical features suggest a reasonable likelihood of symptomatic improvement with endovascular intervention and (1) the response to exercise or pharmacologic therapy has been inadequate or (2) the risk-benefit ratio is a very favorable (e.g., focal aortoiliac occlusive disease).

Iliac Artery Intervention for Inflow Disease

Indications

The indication for iliac artery (or aortoiliac) percutaneous intervention include (1) symptom relief in patients with IC who failed medical therapy; (2) management of CLI (rest pain, ulceration, or gangrene) prior to a planned distal lower extremity bypass surgery to restore or to preserve the inflow to the lower extremity; (3) in preparation for other invasive procedures, such as the placement of an intraaortic balloon pump (IABP); and (4) for treatment of flow-limiting dissection following invasive catheterization-based procedures.

Revascularization Options

Occlusive disease confined to the iliac arteries appears to occur in relatively young patients and may therefore have a greater impact on productivity and lifestyle. For instance, the mean age of the cohort in the Dutch Iliac Stent Trial was approximately 59 years.[14] These patients, over 90% of whom were smokers, were otherwise healthy compared with those with infrainguinal disease or more diffuse PAD. In general, any type of revascularization for this subset of patients can offer satisfactory long-term results. Historically, aortobifemoral bypass surgery has been the gold standard for PAD that involves the iliac arteries because this procedure is associated with excellent long-term patency rates (85% to 90% at 5 years, 75% to 80% at 10 years, and 60% at 20 years); however, it may be associated with an intraoperative mortality of roughly 1% to 3% and a major complication rate of 5% to 10%. This, combined with the excellent intermediate- to long-term patency rates following percutaneous intervention, has led to the emergence of percutaneous revascularization as an attractive alternative to surgery in patients with suitable lesions for such intervention. In a Swedish randomized controlled trial (RCT)[15] in which 37% of randomized patients had iliac artery stenosis, equivalence in outcomes was evident between percutaneous transluminal angioplasty (PTA) and surgery. In the iliac disease subgroup, the patency rate at 1 year was 90% in the PTA arm versus 94% in the surgical arm. Table 39-3 summarizes the recommendation of the Trans-Atlantic Inter-Society Consensus (TASC) working group for the revascularization strategy of iliac lesions.

TABLE 39-3 The Recommendation of the Trans-Atlantic Inter-Society Consensus (TASC) Working Group for the Revascularization Strategy of Aortoiliac Femoropopliteal Lesions

	Iliac Disease	Femoral Lesions
TASC A	Single, <3 cm of CIA or EIA (unilateral/bilateral)	Single, ≤3 cm in length, does not involve the SFA or popliteal artery
TASC B	1. Single, 3 to 10 cm, not extending into the CFA 2. Two stenoses <5 cm long in the CIA and/or EIA, does not extend to the CFA 3. Unilateral CIA occlusion	1. Single stenoses or occlusion 3 to 5 cm long, does not involve the distal popliteal artery 2. Heavily calcified, ≤3 cm, or multiple stenoses or occlusions each <3 cm 3. Single or multiple lesions in the absence of continuous tibial runoff
TASC C	1. Bilateral 5- to 10-cm stenosis of the CIA and/or EIA, does not extend to CFA 2. Unilateral EIA occlusion or stenosis, does not extend into the CFA 3. Bilateral CIA occlusion	1. Single stenosis/occlusion >5 cm 2. Multiple stenoses or occlusions 3 to 5 cm, with or without heavy calcification
TASC D	1. >10-cm lesions or diffuse, multiple, unilateral stenoses that involve the CIA, EIA, and CFA 2. Unilateral occlusion that involves both the CIA and EIA 3. Bilateral EIA occlusions 4. Diffuse disease that involves the aorta and both iliac arteries or lesions in a patient that require aortic or iliac surgery (AAA)	Complete CFA or SFA occlusions

From Dormandy JA, Rutherford RB: Management of peripheral arterial disease (PAD). TASC Working Group. Trans-Atlantic Inter-Society Consensus (TASC). *J Vasc Surg* 2000; 31: S1-S296.

An endovascular procedure is the treatment of choice for type A, and surgery is the procedure of choice for type D. At present, endovascular treatment is more commonly used in type B lesions, and surgical treatment is more commonly used in type C lesions. Evidence is insufficient to make firm recommendations, particularly in cases with type B and C lesions. *AAA,* Abdominal aortic aneurysm; *CFA,* common femoral artery; *CIA,* common iliac artery; *EIA,* external iliac artery; *SFA,* superficial femoral artery.

Techniques

Access and Recanalization Techniques

In patients with a unilateral stenotic iliac lesion that does not involve the common femoral artery (CFA), ipsilateral access through the CFA with retrograde PTA is usually preferred because it provides direct access to the diseased segment and provides a coaxial alignment of the equipment (Fig. 39-4). Contralateral access with the use of a crossover sheath is reserved for patients with disease that involves the ipsilateral CFA (Fig. 39-5) when the surgeon plans to intervene on more distal lesions in the same limb or when jeopardizing flow to the affected limb by placement of the sheath in the ipsilateral CFA is a concern. Various crossover sheaths are available; the ArrowFlex sheath (Arrow International, Reading, PA) is more flexible and can be helpful in crossing over acute aortic bifurcation angles, but it provides less support than the Flexor Ansel, Raabe, and Balkin sheaths (Cook Medical, Bloomington, IN); these provide more support but are less compliant. If the iliac

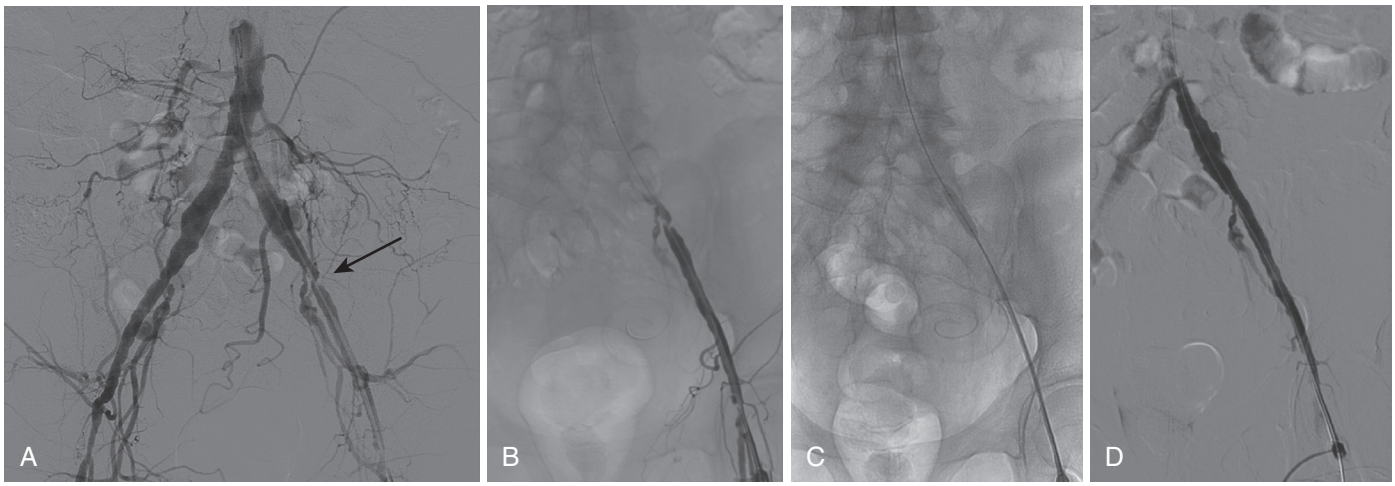

FIGURE 39-4 Left external iliac artery intervention. **A,** Abdominal aortogram with runoffs where the lesion is noted (*arrow*). **B,** Using an ipsilateral approach, the lesion is crossed with a guidewire. **C,** Angioplasty is done. **D,** Successful final result with resolution of the obstructive lesion and no flow-limiting dissection or significant elastic recoil.

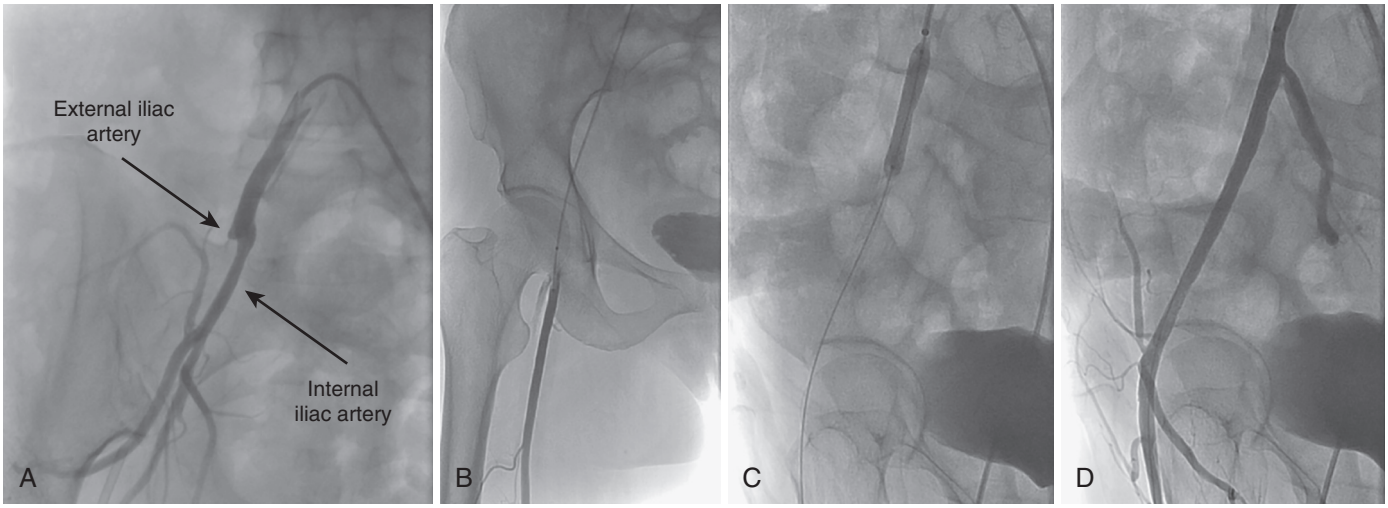

FIGURE 39-5 Ostial external iliac artery occlusion. **A,** The lesion is approached from a contralateral access point utilizing a crossover sheath. **B,** The lesion is crossed with a hydrophilic guidewire, a balloon is placed at the level of the noted distal external iliac artery lesion, and angioplasty is done. **C,** The first stent is deployed and a second, more proximal stent is placed. **D,** Final result after stent placement.

artery is occluded, both approaches may be needed. For aortic bifurcation lesions, a bilateral retrograde approach is used; the placement of kissing balloons—and, subsequently, kissing stents—is the optimal approach in this setting.

In lesions distal to the aortic bifurcation (in the body of the common iliac artery or the external iliac artery), PTA is attempted, and if satisfactory results are achieved (<5 mm Hg residual gradient and <30% residual stenosis with no flow-limiting dissection), stenting may not be indicated. However, ostial lesions of the common iliac arteries (i.e., aortoiliac bifurcation lesions) are preferably stented with kissing stents. In general, 0.035-inch guidewires are used in PTA and in stenting of the iliac arteries, but 0.018- or 0.014-inch guidewires may be used as well. In nonocclusive lesions, a regular nonhydrophilic guidewire can be used; however, if crossing such lesions is difficult, the use of a hydrophilic wire is indicated.

Stent Choice

Both balloon- and self-expandable stents can be used in aortoiliac disease. The balloon-expandable stent is advantageous in the context of an aortic bifurcation lesion, in which kissing stents are usually placed. It is also superior to self-expandable stents when precision in stent placement is needed. The self-expanding stent provides the flexibility in flexion points, which reduces the risk of stent deformity and fracture and is ideal in the setting of common iliac lesions that do not involve the ostium and those in the external iliac artery. Self-expanding stents were generally favored for the external iliac artery because they reduce the perforation risk.

Clinical Data

In the management of patients with IC secondary to iliofemoral disease, percutaneous revascularization (specifically PTA without stenting) has been compared with conservative management (specifically with exercise training, smoking cessation counseling, and antiplatelet therapy with aspirin). The results revealed two important findings: First, PTA can effectively alleviate patients' symptoms, improve treadmill distance, and improve ABI during a short-term follow-up period, although these benefits are mostly lost by 2 years. Second, although PTA improves perfusion to the feet, which may confer protection—particularly for populations at higher risk for limb loss, such as diabetics—supervised exercise improves functional

outcome and at the same time enhances global conditioning. These two strategies should therefore be considered complementary to each other because they address different but interrelated issues.[16-18]

Overall, for iliofemoral lesions, the clinical results of percutaneous revascularization are generally comparable to those of surgical bypass or reconstruction. A Swedish trial[19] randomized patients with threatened limb loss (40% with rest pain or gangrene) or claudication who did not improve with exercise training (60%) to either PTA or surgical revascularization. The study population had a mean age of 70 years, a 26% prevalence of diabetes, and an average symptom duration of 18 months. No differences were found between the PTA or surgery treatment groups with regard to 1-year primary and secondary patency rates, which were 61% and approximately 72%, respectively. The complication rates were not statistically different between treatment groups, although most of the adverse events involved patients who presented with rest pain or gangrene, which highlights the impact of baseline limb status on subsequent outcomes. Adverse events included a 1-year death rate of about 10% and a reocclusion rate of 5% (both treatment groups), a major amputation rate of 5.7% versus 16%, and a hematoma rate of 7.5% versus 4.1% (PTA vs. surgery, respectively). The infection and embolization rates were 8.2% each and were seen only in the surgical group, not with PTA. These findings were corroborated by the Veterans Administration (VA) Cooperative study,[20] which randomized 255 male patients with iliac or femoropopliteal disease and claudication or rest pain. To be eligible, patients had to be suitable for either PTA or surgery, which may have resulted in a case mix with less diffuse disease compared with the typical vascular surgery population. The average age was 61.5 years, 29% had diabetes, 20% had a history of myocardial infarction (MI), more than 25% had previous surgery or PTA for PAD, and 99% were current or previous smokers (~48 pack-years each). Three study-related deaths occurred, all in the surgery group ($n = 126$). Of the 129 patients randomized to PTA, 20 procedural failures (15.5%) were reported but no deaths; also noted were an inability to cross the lesion with a wire in 7.8%, inability to dilate the lesion in 2.3%, thrombosis within 24 hours in 3.9%, and no hemodynamic improvement after PTA in 1.6%. No stents were available for this trial. Seventeen of the patients who failed PTA subsequently underwent successful surgical revascularization. At a median follow-up of 2 years, no statistically significant difference was found between the PTA and surgery groups with regard to death and major amputations. This pattern of equivalent outcome held true at 4 years follow-up. However, the 2-year target-limb repeat revascularization rate was higher after PTA compared with surgery.[16] In a review of the available literature from 1989 through 1997, Bosch and Hunink[21] reported a higher technical success with stenting with no difference in complication rates and 30-day mortality rates in their meta-analysis of six studies that included 2116 patients with IC secondary to aortoiliac disease. The severity-adjusted primary patency rates were 65% with PTA versus 77% with stenting for stenotic lesions and 54% for PTA versus 61% with stenting for occlusions.

A strategy of primary stenting, as opposed to provisional stenting, is generally recommended for aortoostial lesions. Although an equivalent outcome between primary versus provisional stenting was reported in the Dutch Iliac Stent Trial,[22] only 57% of patients randomized to PTA did *not* require stenting. In comparison, a strategy of routine implantation of the same stent (a Palmaz balloon-expandable stent) gave results that were superior to PTA in an RCT of 185 patients by Richter and colleagues.[23] The authors reported a 4-year patency rate of 94% in the stent arm versus 69% with PTA. Cumulative clinical success, defined as improvement of clinical stage of one level or more, was 89% for stenting and 67% for PTA, respectively. Major periprocedural complications were noted in four patients in the stent group as opposed to three in the PTA group (3.7% overall). These findings were confirmed in the meta-analysis by Bosch and Hunink[21] because stenting offered superior technical success rates and long-term patency compared with PTA in occluded arteries. The outcome of two different self-expanding stents, the stainless steel Wallstent (Boston Scientific, Natick, MA) and the nitinol S.M.A.R.T. stent (Cordis Endovascular, Warren, NJ), for the treatment of iliac artery lesions was compared in a multicenter prospective randomized trial.[24] The acute procedural success was higher with the S.M.A.R.T. stent (98.2%, vs. 87.5% with the Wallstent; $P = .002$). At 1 year, the patency rate was similar for both stents (91.1% with the Wallstent and 94.7% with the S.M.A.R.T. stent) with similar complication rates (5.9% vs. 5.9%, respectively; P = nonsignificant [NS]).

Overall, the technical and clinical success rates of endovascular interventions for iliac artery stenosis exceeds 90% and approaches almost 100% in focal iliac lesions, with a fairly comparable intermediate- and long-term patency to that of surgical revascularization. Factors that negatively affect the long-term patency for either modality are the quality of the distal runoff vessels, the severity of ischemia, and the length of the diseased segment.[25,26] Female sex has also been associated with decreased patency following external iliac stents.[27] Technical success is commonly defined as less than 30% residual stenosis (*anatomic success*), a postintervention mean translesion gradient of 5 mm Hg or less and an increase in the ABI of more than 0.1, or a decrease in symptoms by one category (*hemodynamic success*). Another criterion that has been suggested is an improvement of at least one category of symptoms (*clinical success*).[28] At this time, stenting is an effective primary therapy for common iliac artery and external iliac artery stenoses and occlusions.

Complications and Their Management

Complications rates are generally low in aortoiliac interventions. These include access-site complications (such as groin hematoma, retroperitoneal bleeding, pseudoaneurysm, and arteriovenous fistula [AVF] formation), thrombosis at the intervention site, arterial rupture, and distal embolization. These complications happen at a rate of less than 5% to 6% in most series.[29] Death, contrast-induced nephropathy, MI, and cerebrovascular accident (CVA) occur at a rate of less than 0.5%. The need for urgent vascular repair is reported to be around 2%. With regard to serious complications, rupture—particularly of the external iliac artery—seems to be reported more frequently with the iliac arteries than with percutaneous interventions in other lower extremity arteries.[29,30]

When to Refer to Surgery

Surgery is usually reserved for patients with diffuse disease or those with long total occlusions. It is also the appropriate approach in those with associated infrarenal aortic aneurysms. Table 39-3 summarizes the recommendations of the TASC working group for the appropriate revascularization strategy of iliac lesions.

Femoropopliteal Intervention for Outflow Disease

Common Femoral Artery

Although controversial, many believe CFA revascularization should be done surgically. Concerns about elastic recoil and dissection following PTA and concerns about mechanical compression of stents and acute stent thrombosis have limited endovascular intervention to this territory. PTA has been used in cases of severe fibrotic lesions following previous surgery.

The superficial femoral artery (SFA) and the proximal popliteal artery are the most common anatomic sites of stenosis and occlusion in patients with IC. It is estimated that slightly more than a quarter of diseased SFAs progress over a 3-year period, and 17% may go on to occlusion. Predictors of progression are continued smoking, worsening symptoms, and the presence of an already occluded contralateral SFA.[27] For patients who have disease confined to the SFA, a supervised exercise program might offer a functional outcome that is equivalent or even superior to percutaneous revascularization. This could be due to preserved iliac inflow and the DFA, which is a common and important source of collaterals for patients with SFA stenoses or occlusion. Surgery remains the gold standard when therapy is indicated, and primary femoropopliteal graft patency rates of about 80% at 5 years have been documented.[27] Continued improvements in technology include metal alloys with shape memory and superelastic properties

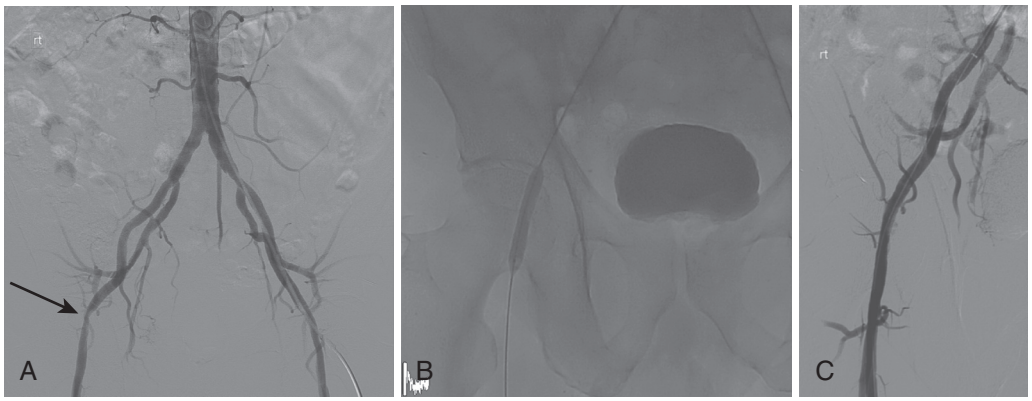

FIGURE 39-6 Right superficial femoral artery (SFA) intervention. **A,** Abdominal aortogram reveals the right SFA lesion (*arrow*). **B,** The lesion is crossed and angioplasty is done using a contralateral access point. **C,** Successful percutaneous transluminal angioplasty (PTA) result with no significant residual lesion or flow-limiting dissection.

and stents coated with antiproliferative agents, and these are helping to surmount the problem of poor long-term durability, which is currently the main limitation of endovascular techniques. Femoropopliteal angioplasty can be considered for discrete single lesions less than 10 cm, less than 5 cm for calcified stenosis, or less than 3 cm for multiple lesions, so long as the SFA origin or distal popliteal artery is not involved. Endovascular treatment of longer SFA lesions is more controversial. Factors that have been found to adversely impact long-term patency are CLI (gangrene or rest pain), multiple stenoses or diffuse disease, and poor distal runoff.[31,32]

Indications

The low morbidity and mortality of endovascular intervention makes this the strategy of choice in patients with suitable lesions (see Table 39-3). It is an appropriate option in the management of symptomatic patients with (1) femoropopliteal lesions less than 10 cm in length (unilateral or bilateral), (2) multiple stenoses or occlusions less than 5 cm (not involving the trifurcation), (3) a single stenosis less than 15 cm (not involving the trifurcation), and (4) prior to surgery in patients with no continuous tibial runoffs in order to improve inflow for surgical bypass.

Techniques

Common Femoral Artery

Access is usually obtained via the contralateral femoral artery (with a crossover sheath) or via the brachial artery. Lesions that involve the bifurcation of the common femoral artery (CFA) represent a challenging problem, and sometimes kissing balloons are needed to achieve desirable angiographic outcome.

Stents have historically not been recommended; however, the use of self-expanding nitinol stents is gaining popularity among some interventionalists. Stents are routinely used in salvage situations, and the flexible self-expanding stent is the appropriate choice in this vessel. Stenting, however, poses many concerns because stent compression or fracture can occur and may render future surgical repair more complicated. It is important to point out that although restenosis rates are high in the CFA (>50%), restenosis may be associated with less limiting symptoms in patients who needed the PTA for persistent or critical symptoms.

Deep Femoral Artery

Revascularization of the DFA may be needed in the setting of total occlusion of the SFA, or of a femoropopliteal bypass graft, because the DFA plays an important role as a source of collaterals to the lower extremity. Surgery is the preferred strategy in this vessel; however, PTA may be tried in the setting of severe limb-threatening ischemia when surgery is contraindicated or if the disease involves the distal portion of the descending branch of the DFA, which is less accessible to surgeons.

Access via the contralateral femoral artery (with a crossover sheath) or from the brachial artery can be used. Interventions are usually done in the context of limb-threatening ischemia; thus it is important to emphasize that a rather conservative approach with regard to balloon sizing is best in this setting, especially with no data available regarding the placement of stents in the DFA. Stents are used provisionally in the context of flow-limiting dissections or severe residual lesions.

Superficial Femoral Artery

Four approaches are possible to access the SFA, through (1) a contralateral femoral artery (with a crossover sheath), (2) an ipsilateral antegrade common femoral approach, (3) a retrograde popliteal approach, or (4) a brachial artery approach. By accessing the contralateral CFA and then using a curved catheter—such as an internal mammary (IM), Judkins right, Cobra, or Simmons catheter—to engage the ostium of the common iliac artery of the diseased limb, a long, kink-resistant sheath (e.g., Balkin, Raabe, ArrowFlex) is placed. The contralateral approach is more popular because it provides excellent support and helps access other segments (iliac or infrainguinal vessels) on the same limb; however, the antegrade CFA access—which is relatively more challenging than the retrograde approach—is still widely used. An antegrade brachial approach might be the only viable option in patients with bilateral iliofemoral disease. The popliteal approach is the least used because it is associated with a higher risk of complications associated with the smaller size of the popliteal artery and the nearby vital structures that may be injured and because it is uncomfortable for the patient. In general, a familiarity with all the different approaches is necessary because the underlying anatomy of each patient will determine what would be a feasible vascular access point. Figure 39-6 shows an example of an SFA intervention.

Stent Choice

Stenting as the primary approach for femoropopliteal lesions is typically not indicated. Stents and other adjunctive techniques such as lasers, cutting balloons, atherectomy devices, and thermal devices can be useful in the femoral, popliteal, and tibial arteries as salvage therapy for a suboptimal or failed result from balloon dilation (e.g., persistent translesional gradient, residual diameter stenosis >50%, or flow-limiting dissection).[11,33] If stenting is indicated, self-expanding nitinol stents are generally used in SFA lesions in light of the high risk of stent compression and fracture. One small randomized study of 104 patients suggested that treatment of SFA disease by primary implantation of a self-expanding nitinol stent yielded results superior to those with the currently recommended approach of balloon angioplasty with optional secondary stenting at 6 to 12 months.[34] Another study in 73 patients

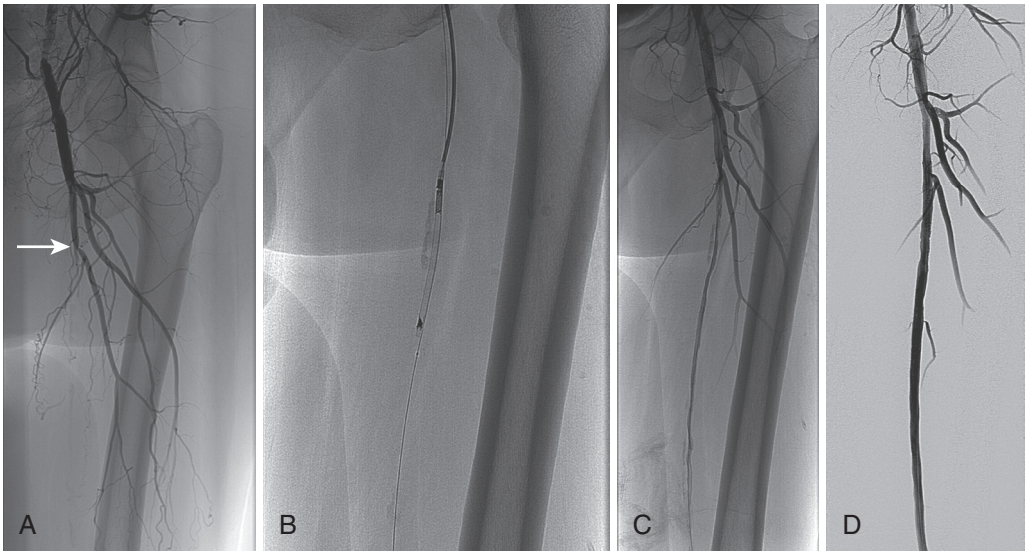

FIGURE 39-7 Superficial femoral artery (SFA) ostial bifurcation lesion. **A,** Angiogram reveald the right SFA ostial occlusion (*arrow*). **B,** The lesion is crossed and atherectomy is done using a contralateral access point. **C,** Percutaneous transluminal angioplasty (PTA) result with significant residual lesion. **D,** Stenting is performed with no residual stenosis, and normal flow is noted in the deep femoral artery.

confirmed that primary stenting with a self-expanding nitinol stent for treatment of intermediate-length SFA disease resulted in morphologically and clinically superior midterm results compared with balloon angioplasty with optional secondary stenting.[35] However, in a meta-analysis of 934 patients, Mwipatayi and colleagues[36] concluded that stent placement in femoropopliteal occlusive disease does not increase the patency rate when compared with PTA alone at 1 year.

The use of sirolimus-eluting S.M.A.R.T. stents for SFA occlusion was evaluated in the Sirolimus-Eluting Versus Bare Nitinol Stent for Obstructive Superficial Femoral Artery Disease (SIROCCO II)[37] study and did not show any significant differences in clinical outcome compared with bare-metal stents (BMSs). At 24 months, the restenosis rate in the sirolimus group was slightly higher in the BMS group (22.9% vs. 21.1%, $P > .05$). Stent fractures, defined as one or more broken struts, were detected by the independent angiographic and radiographic core laboratory in eight patients in the BMS group and nine in the sirolimus stent group.[37] The Zilver PTX paclitaxel-eluting stent (Cook Medical)—a polymer-free, paclitaxel-coated, nitinol drug-eluting stent (DES)—was also evaluated in several clinical studies.[38,39] Dake and colleagues[38] compared the 12-month safety and effectiveness of the Zilver PTX with PTA and provisional BMS placement in patients with femoropopliteal PAD. Compared with the PTA group, the primary DES group exhibited superior 12-month event-free survival (90.4% vs. 82.6%, $P = .004$) and primary patency (83.1% vs. 32.8%, $P < .001$). Overall, femoropopliteal PAD treatment with the paclitaxel-eluting stent was associated with superior 12-month outcomes compared with PTA and provisional BMS placement. Longer term follow up of this cohort at 2 years demonstrated that outcomes with the paclitaxel-eluting stent support its sustained safety and effectiveness in patients with femoropopliteal artery (FPA) disease, including the long-term superiority of the DES to PTA and to provisional BMS placement.[39] Based on outcome data, the Zilver PTX is the first and only DES approved by the U.S. Food and Drug Administration (FDA) for SFA lesions. The IntraCoil (Sulzer IntraTherapeutics, St. Paul, MN) self-expanding peripheral stent; the LifeStent FlexStar (Bard, Murray Hill, NJ) peripheral vascular stent; the Complete SE (Medtronic Vascular, Santa Rosa, CA) vascular stent system; the Supera (Abbott Vascular, Abbott Park, IL) peripheral stent; the Viabahn (W.L. Gore, Flagstaff, AZ) endoprosthesis; and the Ever-Flex (Covidien, Mansfield, MA) self-expanding stent are examples of some FDA-approved BMSs used in the femoral and peripheral arteries.

Specific Techniques: Laser, Atherectomy, SilverHawk

Although anecdotal experiences and reported case series have suggested some benefits, the use of directional atherectomy and laser angioplasty has not been shown to offer any clear advantage over PTA in femoropopliteal PAD.[40,41] A prospective database of 275 patients suggested that the SilverHawk device (Fox Hollow Technologies, Redwood City, CA) was an effective endovascular therapy for peripheral arterial intervention with a low mortality, low complication rate, low amputation rate, and rare need for conversion to surgical bypass.[42] Atherectomy devices may be particularly useful for ostial SFA bifurcation lesions (Fig. 39-7) and calcified lesions.

Clinical Data

RCTs in patients with IC and FPA disease that compared medical therapy with PTA consistently revealed that PTA offers early symptomatic relief at 3 to 6 months compared with medical therapy, and outcomes were similar at 2 years.[41,43] Clinical acute success rates of PTA of FPA disease in the contemporary era exceeds 95%.[33] Contemporary endovascular approaches that include stenting offer acute technical success rates of up to 99%, and short- to medium-term patency rates are superior to PTA alone.[34] The mid- to long-term data of endovascular interventions in patients with IC or CLI and FPA disease are summarized in Tables 39-4 and 39-5.

The advantage of placing a sent in the SFA is that it limits elastic recoil, scaffolds flow-limiting dissection, and provides a higher acute technical support; however, these advantages are counterbalanced by a stent-induced enhanced endothelial hyperplasic response that can result in in-stent restenosis (ISR) and negate the noted advantages of stenting on long-term follow-up. Restenosis following endovascular interventions depends on the severity of the disease (total occlusion vs. patent vessel with a high-grade lesion), the status of the distal runoffs, and the length of the lesion. Whether different stent material and/or drug elution with antiproliferative agents would result in improved outcomes will remain to be seen in future investigations.

Restenosis remains a limiting factor in achieving optimal intermediate to long-term patency. The use of brachytherapy in treating ISR resulted in a 50% reduction in the restenosis rate with no noted increased risk of late thrombosis. The use of sirolimus-eluting stents was not associated with superior results when compared with BMSs.[37] However, the Zilver PTX, a DES that elutes paclitaxel, showed sustained

TABLE 39-4 Estimated Pooled Primary Patency Rates Following Balloon Dilation and Stent Implantation in Patients With Intermittent Claudication Secondary to Femoropopliteal Stenoses

		BALLOON DILATION		STENT IMPLANTATION	
Lesion Type and Year After Treatment		Patency (%)*	Range (%)	Patency (%)*	Range (%)
Stenosis:	0	100 (1.0)	98-100	100 (1.2)	99-100
	1	77 (1.7)	78-80	75 (2.2)	73-79
	2	66 (2.0)	63-71	67 (2.4)	65-71
	3	61 (2.2)	55-68	66 (2.7)	64-70
	4	57 (2.5)	54-63	NA	NA
	5	55 (2.8)	52-62	NA	NA
Occlusion:	0	88 (2.9)	81-94	99 (2.3)	92-100
	1	65 (3.0)	55-71	73 (2.8)	69-75
	2	54 (3.1)	45-61	66 (3.0)	61-68
	3	48 (3.3)	40-55	64 (3.2)	59-67
	4	44 (3.5)	36-53	NA	NA
	5	42 (3.7)	33-51	NA	NA

From Muradin GS, Bosch JL, Stijnen T, Hunink MG: Balloon dilation and stent implantation for treatment of femoropopliteal arterial disease: meta-analysis. *Radiology* 221(1):137-145, 2001.
Note: Ranges are derived from sensitivity analyses.
*Numbers in parentheses represent the standard error.
NA, Not available.

TABLE 39-5 Estimated Pooled Primary Patency Rates Following Balloon Dilation and Stent Implantation in Patients With Critical Limb Ischemia Secondary to Femoropopliteal Stenoses

		BALLOON DILATION		STENT IMPLANTATION	
Lesion Type and Year After Treatment		Patency (%)*	Range (%)	Patency (%)*	Range (%)
Stenosis:	0	83 (3.7)	69-88	100 (3.3)	94-100
	1	60 (4.0)	46-63	74 (3.8)	68-80
	2	49 (4.0)	35-54	66 (3.9)	59-72
	3	43 (4.1)	30-51	65 (4.1)	58-71
	4	40 (4.3)	26-46	NA	NA
	5	38 (4.5)	24-44	NA	NA
Occlusion:	0	70 (3.5)	62-75	98 (3.2)	94-100
	1	47 (3.5)	41-51	73 (3.6)	68-75
	2	36 (3.6)	28-41	65 (3.7)	60-68
	3	30 (3.7)	20-37	63 (3.9)	58-68
	4	27 (3.9)	16-34	NA	NA
	5	25 (4.1)	13-32	NA	NA

From Muradin GS, Bosch JL, Stijnen T, Hunink MG: Balloon dilation and stent implantation for treatment of femoropopliteal arterial disease: meta-analysis. *Radiology* 221(1):137-145, 2001.
Note: Ranges are derived from sensitivity analyses.
*Number in parentheses is the standard error.
NA, Not available.

safety and effectiveness in patients with FPA disease and has been approved by the FDA for use in the SFA.[39] Nitinol, an alloy of nickel and titanium, is flexible and more likely to recover from being crushed when compared with stainless steel. A small single-center clinical trial compared the use of a self-expanding nitinol stent versus PTA with optional stenting (32% in this arm received stents) in symptomatic SFA disease (i.e., severe IC or CLI). In this trial, the use of stents was associated with lower rates of angiographic restenosis at 6 months (24% vs. 43%, $P = .05$) and improved treadmill time at 6 to 12 months. This study is limited by its small size and short-term follow-up.[34] Figure 39-8 lists the overall success and patency rates of PTA (with and without stenting) versus surgery in all claudicants.

Drug-eluting balloons (DEBs) have shown promise in patients undergoing intervention for FPA disease. In the Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries (THUNDER) trial,[44] investigators randomly allocated patients undergoing FPA intervention to a paclitaxel-iopromide drug-eluting balloon or standard balloon angioplasty and found a significant reduction in the primary end point of late lumen loss with the DEB strategy (0.4 ± 1.2 mm vs. 1.7 ± 1.8 mm; $P < .001$). Positive results were also observed in the randomized Femoral Paclitaxel (FemPac) trial, in which late lumen loss was significantly lower with a paclitaxel-iopromide DEB compared with balloon angioplasty (0.5 ± 1.1 vs. 1.0 ± 1.1 mm; $P = .031$).[45] The Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis Trial (LEVANT I) sought to evaluate the safety and efficacy of the Lutonix drug-coated balloon (DCB), which is coated with 2 $\mu g/mm^2$ paclitaxel and a polysorbate-sorbitol carrier for treatment of FPA lesions.[46] At 6 months, late lumen loss was 58% lower for the Lutonix DCB group (0.46 ± 1.13 mm) than for the control group (1.09 ± 1.07 mm; $P = .016$).[46] Similarly encouraging data were

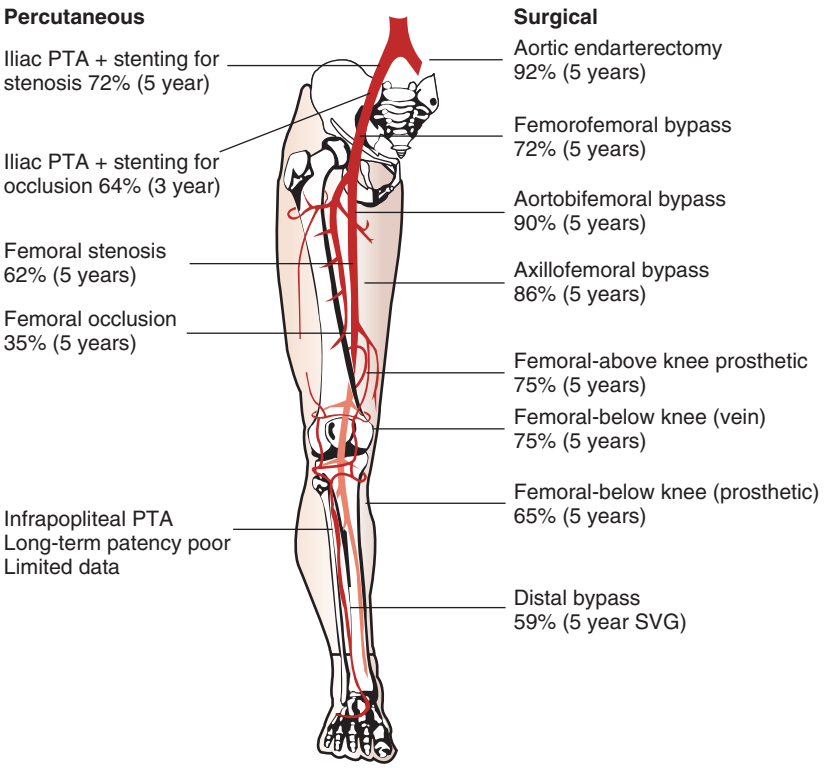

FIGURE 39-8 Patency rates for percutaneous and bypass procedures in intermittent claudication. (Data adapted from the TransAtlantic Inter-Society Consensus [TASC] recommendation.)

seen with a paclitaxel-urea DEB (IN.PACT Pacific; Medtronic Vascular).[47] A meta-analysis of the available data from randomized trials shows a significant improvement in clinical and angiographic outcomes with DCBs.[48] Another recent study compared a paclitaxel-eluting balloon (PEB) with conventional PTA, followed by systematic implantation of a self-expanding nitinol BMS in patients at risk for restenosis.[49] A total of 104 patients (110 FPA lesions in 110 limbs) were randomly assigned to either a PEB plus a BMS or regular balloon angioplasty plus a BMS. The primary end point was 12-month binary restenosis, and secondary end points were freedom from target-lesion revascularization (TLR) and major amputation. Post hoc subanalyses were performed for the comparison of long (≥100 mm) versus short lesions and true lumen versus a subintimal approach. The study found that predilation with DEB angioplasty prior to BMS implantation, compared with a regular balloon plus BMS in complex FPA lesions, reduces restenosis and target-lesion revascularization (TLR) at 12-month follow-up.[49] DEBs are likely to become available in the United States for clinical use in 2015 or 2016.

RCTs that compare PTA with surgery in the management of infrainguinal PAD are limited. This is partly because the choice of the revascularization modality will depend on how extensive the disease is in the individual patient, surgery being the most likely route of action in the setting of extensive long lesions and in those with CLI. In a multicenter RCT of 263 men, Wolf and associates[16] reported three operative deaths in the surgical arm ($n = 126$) and none in the PTA arm ($n = 129$). No difference in survival was noted, although a trend was seen in favor of the PTA arm. Although patients in both arms had sustained improvement in both hemodynamics and quality of life, the success rate was higher in the surgical arm, and more limb salvage was reported than in the PTA arm. No differences were reported in clinical outcome on median follow up of 4 years. In a small randomized trial, a 1-year patency rate of 43% in the PTA arm ($n = 30$) versus 82% in the surgical arm ($n = 24$) was reported.[50]

Complications and Their Management

Dissection, perforation, and distal embolization are the complications encountered in femoropopliteal interventions. Although the use of stenting is discouraged as a primary strategy, its use as a bailout strategy in the context of flow-limiting dissections and perforations has been well established. The appropriate use of anticoagulation and antiplatelet therapy safeguard against acute and subacute thrombosis and may limit the incidence and the consequences of distal embolization.

When to Refer to Surgery

Although somewhat controversial, surgery remains the preferred strategy for patients with common femoral and proximal DFA obstructive PAD. It is also the preferred strategy for patients with a heavily calcified or completely occluded CFA, femoropopliteal calcified stenosis, occlusions more than 15 cm in length, total occlusions (TOs) of the SFA that are more than 20 cm, and TOs of the popliteal artery or of the proximal trifurcation.[2,8] It is important to point out that a strategy of initial PTA in lieu of surgery in selected patients is reasonable.[19]

Infrapopliteal (Runoff) Disease

Indications

Despite the fact that the first reported cases of endovascular interventions in the management of infrapopliteal PAD was in 1964 by Dotter and Judkins, endovascular therapy has had a limited role in the management of infrapopliteal PAD. In patients with IC secondary to infrapopliteal PAD, medical therapy is the most appropriate initial strategy.[8] Tibioperoneal angioplasty is limited by recurrence and also by the need for highly skilled operators, because the need for emergency surgical bailout is associated with considerable risk that cannot be justified in patients with stable IC, especially when medical management is known to produce similar outcomes with limited risk.[2] However, in carefully selected patients, and in the hands of experienced operators, an acute success rate of 95% (98% for stenosis, 86% for TO) with less than 1% significant complication rates can be achieved.[26,51-53] The role of angioplasty in patients with CLI is more promising and justified because its results are comparable, if not superior, to infrapopliteal/tibial bypass surgery.[53] Endovascular techniques can thus be used as a primary therapy or as an adjunctive therapy to bypass surgery to improve inflow

in a diseased segment or to improve the outflow. Up to a quarter of patients with CLI have lesions isolated to arteries below the knee, and these occur mostly in patients with diabetes and other comorbid conditions. Historically, the main concerns with regard to endovascular interventions of the infrapopliteal vessels were the long-term patency, complications, and technical failure of such interventions. With improved equipment, appropriate patient selection, and meticulous technical approach, acute success rates of over 90% and 5-year limb salvage rates of close to 90% are now possible on a more consistent basis, particularly in the context of a comprehensive strategy that includes medical, endovascular, and surgical modalities, as well as lesion surveillance long term.[51] Local delivery of paclitaxel via DEBs has recently shown promising results in the treatment of femoropopliteal disease,[48] and in the infrapopliteal area, a reduction in 3-month binary restenosis has been observed compared with historic controls treated with PTA.[54]

Techniques

Access and Recanalization Techniques and Devices

Antegrade ipsilateral femoral access is usually used for infrapopliteal interventions. The advantages of such access include a straight-line approach to the lesion and that it allows a shorter length of catheter or balloon shaft, more torque control, and a better mechanical advantage and "pushability" for occlusions or lesions that are difficult to cross. This approach requires experience to minimize complications at the access site. If combined below- and above-knee PTA is necessary, angioplasty of the tibioperoneal arteries initially might lower the risk of peripheral embolization. In the Uppsala series, six of the initial 40 procedures had embolization that required either transcatheter embolectomy or local streptokinase infusion. After altering their practice so that distal angioplasty was performed prior to more proximal lower limb angioplasty, no embolization was seen in the subsequent 54 procedures.

Because occlusion of these end arteries jeopardizes the feet and leaves no surgical bail-out options, the characteristics of reported successful series must be carefully considered. In Dorros and colleagues' series,[53] tibioperoneal lesions had to be less than 10 cm in length, and distal vessels were visualized. Occlusions were less successfully opened than stenoses (73% vs. 98%), and a residual stenosis of up to 50% was acceptable for these relatively small vessels. Complete multivessel revascularization may not be necessary, especially when a significant improvement in ABI is already documented. If angioplasty results in straight-line flow to the foot, clinical success rates of up to 80% at 24 months have been reported; conversely, the lack of straight-line flow portends failure within 11 months. Vasospasm usually abates with intraarterial nitroglycerin or verapamil.

Stent Choice

Stents are not recommended in the management of infrapopliteal disease; however, stent placement may be used as a bailout in the context of flow-limiting dissections. The Percutaneous Transluminal Angioplasty and Drug-Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia (PADI) trial[55] is a prospective, multicenter, randomized, controlled, double-arm study to investigate the safety and efficacy of primary paclitaxel-eluting stent (PES) implantation versus PTA in infrapopliteal lesions in CLI, and it was anticipated to report results in 2015. The primary end point will be primary patency of the treated site at 6 months.

Specific Techniques

Previous case series detailing the use of atherectomy in treatment of tibial lesions has had dismal results.[56] Zeller and colleagues[57] reported that below-knee native vessel lesions with a diameter of at least 2 mm can be treated with the SilverHawk catheter with a high success rate and a low complication rate. Orbital atherectomy was recently tested as a unique approach to infrapopliteal disease and provided predictable and safe lumen enlargement.[58] Short-term data demonstrated substantial symptomatic improvement and infrequent need for further revascularization or amputation, but additional studies are needed.

Clinical Data

Despite advances in modern aggressive revascularization techniques, the mortality and morbidity rates for this cohort of patients have remained substantial, with 30-day mortality rates of around 4% to 10%, a 6% to 14% amputation rate, and 90-day graft failure rates of close to 5%.[59] The 5-year patency rate for femoral below-knee bypass is about 75% (vein graft) to 60% (prosthetic grafts), whereas for distal bypass, it is about 50%.[2] An important contributor to these poor outcomes is the substantial disease burden in this cohort of patients, who have a preponderance of coronary artery disease (CAD), diabetes mellitus, and baseline tissue loss (foot ulcer, gangrene, or nonhealing wound).[2,59,60]

No RCTs have compared strategies for the treatment of below-knee arterial occlusive disease. Dorros and colleagues[60] reported the largest prospective series of infrapopliteal angioplasty on 284 limbs with CLI (Fontaine stages III and IV) in 235 patients between 1983 and 1996. The mean age was 67 years, 69% were males, half had diabetes, more than a quarter had previous MI, a third had prior coronary artery bypass surgery, and 39% had prior peripheral vascular surgery. The overall acute technical success rate was 100% for inflow lesions and 92% for infrapopliteal lesions. The success rate was 98% for stenoses but only 73% for occlusions. Complications were infrequent: 0.7% in-hospital all-cause mortality; 0.7% emergency vascular surgery; 9% in-hospital major amputation; and 0.4%, or one case each, of compartment syndrome, major infection, and transfusion were reported. A more contemporary series ($n = 60$) reported by Söder and associates[51] involved an older (mean age, 72 yr) and sicker cohort: more than 75% had diabetes, almost 25% had baseline renal insufficiency, 90% presented with minor (81%) or major (9.7%) tissue loss, and the majority were not eligible for distal bypass surgery (no runoff in 70 limbs, single-vessel runoff in two limbs). This group reported a primary angiographic success rate of 84% (102 of 121) for stenosis and 61% (41 of 67) for occlusions with corresponding restenosis rates of 32% and 52% at follow-up angiography performed at a mean of 10 months after primary PTA. The rate of major complications was 2.8% (access-site pseudoaneurysms in two patients). The primary clinical success was 63% (45 of 72). A 48% cumulative primary patency rate, a 56% secondary patency rate, and an 80% cumulative limb-salvage rate were reported at 18 months. Factors that independently correlated with continued lesion patency up to 12 months were angiographic improvement to the site of most severe ischemia (6-month primary patency of 68% vs. 16%; $P = .001$) and absence of renal insufficiency (patency of 63% vs. 24%; $P = .06$%). Clinical success, defined as relief of claudication or avoidance of major amputation, was achieved in only 45 of 72 limbs (63%) acutely, but this is comparable to results from surgical series. No patient in this series had a subsequent surgical bypass operation for the limbs, largely because of poor distal targets or pedal arteries. The Drug-Eluting Balloon in Peripheral Intervention for Below the Knee Angioplasty Evaluation (DEBATE-BTK)[61] investigated the efficacy of a paclitaxel DEB versus conventional PTA for the reduction of restenosis in diabetic patients with CLI undergoing endovascular intervention of below-the-knee arteries. This was a randomized, open-label, single-center study to compare DEBs and PTA. Inclusion criteria were diabetes mellitus, CLI (Rutherford class 4 or higher), significant stenosis or occlusion greater than 40 mm of at least one below-the-knee vessel with distal runoff, and life expectancy greater than 1 year. Binary in-segment restenosis at a 1-year angiographic or ultrasonographic follow-up was the primary end point. Clinically driven TLR, major amputation, and target-vessel occlusion were the secondary end points. This study reported that compared with PTA, DEBs strikingly reduce 1-year restenosis, TLR, and target vessel occlusion in the treatment of below-the-knee lesions in diabetic patients with CLI.[61]

When to Refer to Surgery

In the management of infrapopliteal disease, bypass surgery has been associated with disappointing results. Just as with PTA, the patency rate of bypass grafting remains inferior to that of bypass grafting in

more proximal PAD as shown in Figure 39-7.[2] Success in achieving limb salvage with minimal periprocedual complication is dependent on the status of distal circulation and on the overall risk profile of the patient. Amputation—primary, when no antecedent attempt is made on revascularization, or secondary, following failure of revascularization—may be necessary in patients with CLI complicated by intractable infections or uncontrollable rest pain.

ACUTE LIMB ISCHEMIA

Acute limb ischemia (ALI) is defined as a sudden or rapidly developing loss of limb perfusion that results in the development or worsening of symptoms and signs of limb ischemia with an eminent threat to limb viability. ALI may be the first manifestation of PAD in previously asymptomatic patients.[8] More commonly, patients with IC will experience progression in their disease with development of rest pain, ischemic ulcers, and eventually gangrene. Although it may be gradual, this progression is usually the result of recurrent acute ischemic events. Two mechanisms are implicated in ALI: embolism and in-situ thrombosis. Differentiation based on history and clinical examination alone may be clinically impossible in 10% to 15% of cases. Although little information is available on the incidence of ALI in the general population, it is estimated to be 14 per 100,000 and is the indication for 10% to 16% of all vascular procedures performed. Patients with embolic ALI are more likely to die than those with thrombosis, usually secondary to underlying cardiac disease, whereas patients with thrombotic ALI are more likely to lose their limbs when compared with those who have embolic ALI.

The natural history of ALI has remained largely unchanged despite the advances in the surgical, endovascular, and pharmacologic therapies. Patients who present with ALI continue to have a particularly poor short-term outlook both in terms of loss of the leg and mortality, with 30-day amputation rates of between 10% and 30% and a mortality rate of 15%. The fact that overall mortality rates after intervention for acute ischemia have not improved dramatically over the past 20 years reflects the severity of the underlying atherosclerotic burden in these high-risk patients.[2,8,62]

An embolic event complicates atrial fibrillation, MI with left ventricular thrombus, or peripheral pseudoaneurysm. Thrombosis in situ is usually encountered in patients with PAD and tenuous collateral circulation, or it may be seen in patients with prior bypass surgery with an acute thrombosis of the graft. Also of importance are other mechanisms of ALI such as septic or cardiac tumor emboli; trauma, such as popliteal artery disruption; and dissection of large vessels with distal progression, such as aortic dissection with iliac artery occlusion. Table 39-6 shows a recommended classification of ALI, which is useful in estimating the impact for the individual patient and in determining the prognosis of the limb at presentation.[63]

TABLE 39-6 Classification of Acute Limb Ischemia

	NEUROMUSCULAR		
Category	Description	Findings	Doppler
I	Viable	No sensory or muscle weakness	Audible arterial and venous
IIa	Threatened (marginally)	Minimal	Often inaudible arterial, audible venous
IIb	Threatened (immediately)	Mild to moderate, associated with pain	Usually inaudible arterial, audible venous
III	Irreversible	Profound deficit	No signals

From Weaver FA, Comerota AJ, Youngblood M, et al: Surgical revascularization versus thrombolysis for nonembolic lower extremity native artery occlusions: results of a prospective randomized trial. The STILE Investigators. Surgery versus thrombolysis for ischemia of the lower extremity. *J Vasc Surg* 24(4):513-521, discussion 521-523, 1996.

Management Strategies of Acute Limb Ischemia

In approaching patients with suspected ALI, history and physical examination should be focused on establishing the underlying mechanism of the ALI to categorize the patient based on the underlying leg symptoms and signs in addition to the Doppler assessment of the peripheral pulses. Once the diagnosis of ALI is made, the objective should be to prevent thrombus propagation and worsening ischemia. Thus anticoagulation with heparin, if not contraindicated, is the first step in management. Restoration of the flow as soon as possible is the next step (for viable limbs in Fontaine class I and II) using either pharmacologic or endovascular versus open catheter thromboembolectomy. If the patient has a true late nonviable limb (class III), amputation is the only option because revascularization of such limbs is of no benefit but rather is associated with a high risk of mortality. Table 39-7 gives the recommended medications and doses of thrombolytic therapy. In general, patients with clear embolic etiology and a discernible location of obstruction by physical exam are taken to surgery for open embolectomy. If there is no clear embolic etiology, an arteriogram should be performed and the decision made, based on the findings, regarding endovascular versus surgical interventions.

Interventional Treatment

Pharmacologic Thrombolysis

Although systemic thrombolysis has no role in the management of ALI, catheter-directed thrombolytic therapy is effective in the management of patients with class I and IIa ischemia. This approach is clearly less invasive, has less morbidity and mortality when compared with open surgery, and may reduce the risk of reperfusion injury. The choice of lytic therapy will depend on the location, anatomy, and patient comorbidities. Contraindication to thrombolysis should be observed.

Percutaneous Aspiration Thrombectomy

Percutaneous aspiration thrombectomy (PAT) is an alternative nonsurgical modality to treat ALI that uses large-lumen catheters and suction with a 50-mL syringe to remove embolus or thrombus from native vessels, bypass grafts, and runoff vessels. PAT devices such as the Amplatz Clot Buster (BARD-Microvena, White Bear Lake, MN) and the Straub Rotarex System (Straub Medical, Wangs, Switzerland) have been used with fibrinolysis to reduce the time and dose of the fibrinolytic agent or as a stand-alone procedure.

TABLE 39-7 Recommended Doses of Antiplatelet, Antithrombotic, and Thrombolytic Medications for Management of Acute Limb Ischemia

Medication	Route	Dosage	Laboratory
Aspirin	PO/PR	325 mg	None
Clopidogrel	PO	300 to 600 mg loading dose 75 mg maintenance dose	None
Heparin	IV	600 U/kg bolus then 12 U/kg/hr	aPTT, plts, Hct
Mannitol	IV	12.5 to 25 g	Creatinine
Plasminogen activator	IA	Depends on agent*	Hct, fibrinogen, FSP
Urokinase	IA	80 to 200,000 U/hr tapered infusion	Hct, fibrinogen, FSP

From Rajagopalan S, Mukherjee D, Mohler E, eds: *Manual of vascular diseases,* Philadelphia, 2004, Lippincott, Wilkins & Williams, p 92.
*Depends on thrombolytic (retaplase 0.25 to 1.0 U/hr; alteplase 0.2 to 1.0 mg/hr; tenecteplase 0.25 to 0.5 mg/hr).
aPTT, Activated partial thromboplastin time; *FSP,* fibrin split products; *Hct,* hematocrit; *IA,* intraarterial; *IV,* intravenous; *plts,* platelet count; *PO,* per os (orally); *PR,* per rectum (rectally).

Percutaneous Mechanical Thrombectomy

The concept of creating a "hydrodynamic recirculation vortex" that would dissolve a thrombus and remove its fragments is the underlying thought behind most percutaneous mechanical thrombectomy (PMT) devices, such as AngioJet (Possis Medical, Minneapolis, MN), Hydrolyser (Cordis, Warren, NJ), and Oasis (Boston Scientific/Medi-tech, Natick, MA) thrombectomy systems. The efficacy of PMT depends on the age of the thrombus because fresh thrombi can be efficiently removed, unlike old, organized thrombi.

Surgery

The indications for surgery include patients with clear embolic etiology, where an open embolectomy can be performed, and patients with CLI (classes IIb and III). Surgery is associated with the risk of infection, hemorrhage, and periprocedural cardiovascular adverse events.

CRITICAL LEG ISCHEMIA

Critical leg (or limb) ischemia (CLI) is characterized by persistent rest pain with or without ongoing tissue loss, ischemic ulceration, or gangrene. The term *critical limb ischemia* is traditionally used to describe patients with ischemic symptoms of more than 2 weeks duration. Patients with CLI usually have ankle systolic pressure below 40 mm Hg, toe systolic pressure below 30 mm Hg, reduced transcutaneous oxygen concentration ($TCPO_2$) of less than 50 mm Hg, or combinations of these.

In general, the underlying etiology is almost exclusively atherosclerosis, and frequently it is a multivessel and multisegment disease. Smoking and diabetes are the most potent risk factors and are associated with higher rates of amputation. The prognosis in patients with CLI is poor secondary to comorbid conditions: mortality rates approach 10% per year, and amputation rates of 25% to 45% at 1 year.[2,8]

Interventional Treatment and Surgery

Management of CLI depends on the patient's *risk profile* (expected operative mortality, underlying renal function, and the risk of contrast nephropathy, etc.) and *anatomic profile* (multisegment, multivessel, the number of runoffs, the suitability of the disease to PTA vs. surgery, etc.). Figure 39-9 outlines a general approach to the management of CLI.

Periprocedural Antithrombotic Therapy

PTA and stenting are usually conducted with weight-based heparinization to achieve an ACT of 200 to 250 seconds. A front load of aspirin and clopidogrel (300 to 600 mg) at least 12 hours prior to intervention is widely used. The use of glycoprotein IIb/IIIa may be useful in the context of diabetes or evidence of angiographic thrombus or ulceration and in patients with poor runoff (one vessel or none) to prevent distal embolization. After PTA and stenting, life-long aspirin therapy is recommended in light of the high cardiovascular event rate in patients with advanced PAD. Most clinicians prescribe adjunctive clopidogrel for 1 to 12 months after a lower extremity percutaneous intervention.

Post Peripheral Bypass Surgery Patient

Various types of vascular bypass grafts are used in the management of lower extremity PAD. A detailed discussion of this subject is beyond the scope of this chapter; however, interventionalists are likely to

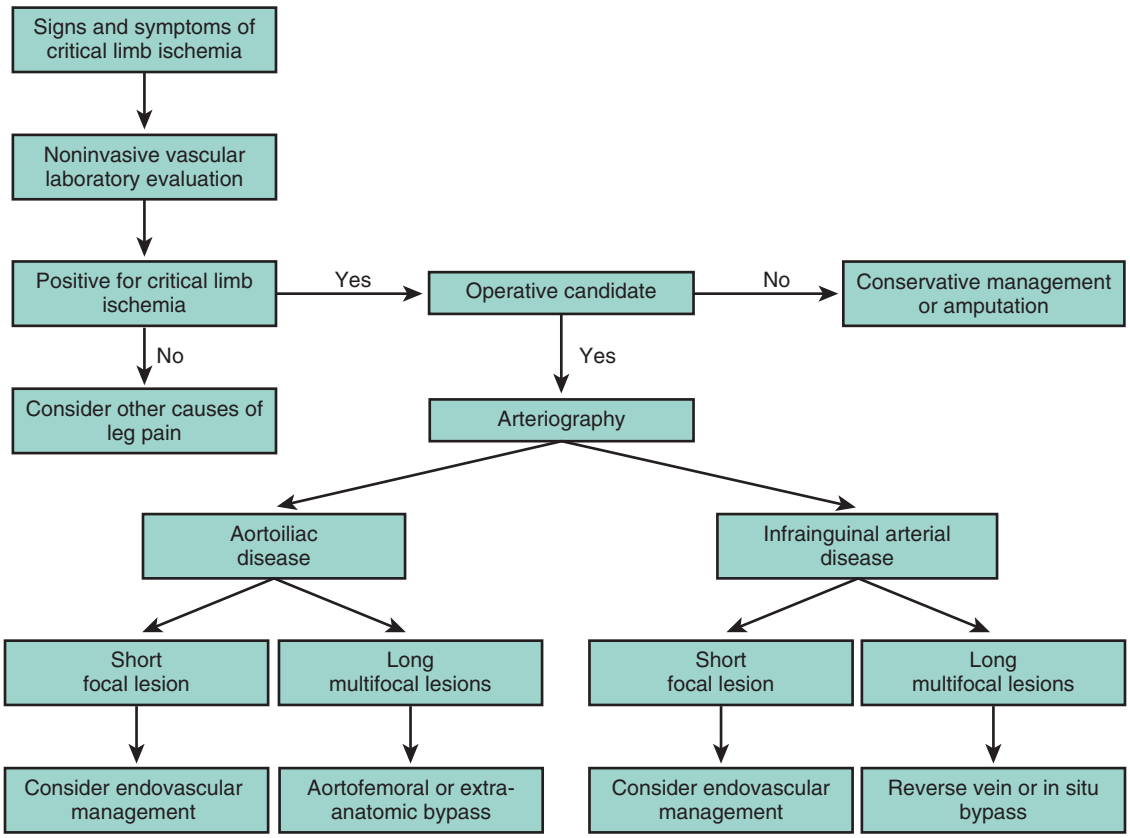

FIGURE 39-9 Treatment algorithm for patients with critical limb ischemia. (From Rajagopalan S, Mukherjee D, Mohler E, eds: *Manual of vascular diseases,* Philadelphia, 2004, Lippincott, Williams & Wilkins, p 92).

encounter graft-related complications, the most serious of which is ALI secondary to graft thrombosis.

In general, acute thrombosis of bypass grafts is secondary to technical problems and usually presents in the early postoperative period and requires an urgent intervention. In this setting, patients should be anticoagulated and then evaluated for balloon catheter thrombectomy. Mature graft thrombosis occurs at a rate of 10% at 5 years and rarely presents with ALI. Such patients are managed with thrombolytic therapy to clear the thrombus burden, and then the underlying etiology should be addressed either through an endovascular approach or by open surgery.[64]

MISCELLANEOUS CONDITIONS

Buerger Disease (Thromboangiitis)

Buerger disease is a nonatherosclerotic inflammatory vasculitis of the small and medium-sized arteries, veins, and nerves. It can affect upper and lower extremities and occurs most commonly in young male smokers. The etiology is uncertain, although a clear and strong association exists with smoking and tobacco use. The mainstay of therapy is smoking cessation, and in fact without complete cessation of smoking and tobacco use, the prognosis for limb salvage is dismal.[65] Medical therapy with antiplatelets, immunosuppressants (cyclophosophamide), and analgesics has been used.

Surgical revascularization of the lower extremity in the context of Buerger disease has a limited role in light of the diffuse nature of the disease and its tendency to involve distal small vessels before progressing proximally. Bypass surgery, when feasible, should be done with an autologous vein and veins not affected by the disease process. Percutaneous intervention has no clear role in the management of patients with Buerger disease.

Peripheral Aneurysm

The most common cause of peripheral aneurysm formation is atherosclerosis. Other predisposing factors include hypertension, inflammatory and infectious processes, trauma, connective tissue diseases, and familial tendencies. Whereas most aneurysms are asymptomatic, they can become the source of distal embolization, they can become infected, they may compress surrounding tissues, or they may rupture. Aneurysms of the lower extremity have particular complications depending on their location.

Iliac artery aneurysms are associated with atheroembolism, obstructive uropathies, iliac vein obstruction, and perineal or groin pain. The use of magnetic resonance angiography (MRA) or multidetector contrast computed tomography (CT) is the preferred strategy for diagnosis. Traditionally speaking, surgical resection is indicated if the aneurysm is symptomatic or is more than 3 cm in diameter. Endovascular treatment using a variety of options available today, such as coil embolization or stent-graft placement, may be an alternative to surgery. Early experience indicates that endovascular treatment is safe and effective in the hands of skilled operators; however, large long-term follow-up studies are needed to determine whether this approach is a practical alternative to open surgery.[66]

Femoral artery aneurysm is associated with atheroembolism and venous obstruction. It can be diagnosed with ultrasound and is managed surgically if symptomatic. Case series of endovascular interventions have been reported, but the data are limited, and larger studies with long-term follow-up are needed to help identify the role of this approach in the setting of femoral artery aneurysm.[67]

Popliteal artery aneurysm is associated with thrombosis, atheroembolism, venous obstruction, popliteal neuropathy, and infection. It can be bilateral in 50% of patients. Ultrasound can be used to make the diagnosis, although contrast angiography is generally needed prior to surgery to assess the proximal and distal circulation (Fig. 39-10). Once diagnosed, popliteal artery aneurysm should be resected to prevent its potentially devastating thromboembolic complications. Endovascular repair of popliteal artery aneurysms is a new technique that has emerged as an alternative to open surgical bypass. The evidence to support its use is limited, and long-term follow-up data are lacking; however, early results have been promising and have shown high rates of initial treatment success.[67,68]

Atheroembolism

Atheroembolism refers to the occlusion of arteries secondary to the detachment and embolization of atheromatous debris, which includes cholesterol crystals, platelets, fibrin, and calcium. Atheroemboli can originate from any atherosclerotic segment, although typically they originate from aortic atheromas and from aneurysms of the large and medium-sized arteries. They tend to occlude small end arteries and arterioles such as those of the kidneys, retina, brain, and extremities.

Clinical features of this disorder are usually reflective of acute ischemic complications and depend on the affected organ. Atheroembolic events in the lower extremity would result in painful cyanotic toes (blue toe syndrome) and are associated with digital and foot ulcerations in addition to multiorgan dysfunction depending on the extent of the embolic burden. Levido reticularis is common in patients with atheroembolism and is encountered in up to 50% of patients. It is important to point out that distal pulses will remain intact, unlike with CLI and ALI secondary to thromboembolism, in which pulses are usually abnormal because atheroemboli occlude smaller, more distal vessels. The differential diagnosis includes many conditions such as vasculitis and prothrombotic conditions, such as antiphospholipid syndrome and heparin-induced thrombocytopenia (HIT).

Affected patients may have an elevated erythrocyte sedimentation rate (ESR), thrombocytopenia, eosinophilia, eosinophiluria, and hypocomplementemia. The finding of cholesterol crystals in small arteries is a pathognomonic sign when found in skin or muscle biopsies. Transesophageal echocardiography (TEE), CT scan, and MRA can be used to visualize the aorta (searching for shaggy, mobile atheromas), and

FIGURE 39-10 Digital substraction angiography of left popliteal artery showing aneurysm.

assessment of aneurysms by ultrasound and angiography is part of the workup to identify the source of the emboli if possible.

If the source cannot be identified, no definitive therapy exists, but antiplatelet therapy with aspirin has been advocated. If the source is identified, surgical removal or endovascular isolation of the source of the emboli is the only definitive therapy.[69]

CONCLUSIONS AND FUTURE DIRECTIONS

PAD of the lower extremity is a serious health problem associated with significant morbidity, and it is a reflection of advanced atherosclerosis that often affects other vascular trees. Although the management of patients with IC is based on an integrated exercise program and pharmacologic modification of the associated risk factors, percutaneous interventions have emerged as an alternative to surgical revascularization in patients who remain symptomatic or those who progress to CLI. Advances in technology will likely continue to optimize the role of percutaneous interventions in the management of PAD, and whereas such interventions are already very effective in the management of IC caused by iliofemoral disease, room for improvement remains in the use of such interventions in the management of infrapopliteal disease and of ALI and CLI. The use of drug-eluting balloon therapy for de novo peripheral artery disease is quite promising. Although studies to date have been small in scale, the data from these trials are consistent in showing benefit over conventional balloon angioplasty.[70] Pending issues that need to be resolved include (1) the development of devices of an appropriate length to facilitate treatment of disease that is often diffuse, (2) the long-term clinical outcomes of patients treated with drug-eluting balloons, and (3) the optimal duration of dual-antiplatelet therapy.

REFERENCES

1. Mukherjee D, Yadav JS: Update on peripheral vascular diseases: from smoking cessation to stenting. *Cleve Clin J Med* 68(8):723–733, 2001.
2. Dormandy JA, Rutherford RB: Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg* 31(1 Pt 2):S1–S296, 2000.
3. Management of peripheral arterial disease (PAD): TransAtlantic Inter-Society Consensus (TASC). Section D: chronic critical limb ischaemia. *Eur J Vasc Endovasc Surg* 19(Suppl A):S144–S243, 2000.
4. Hirsch AT, Halverson SL, Treat-Jacobson D, et al: The Minnesota Regional Peripheral Arterial Disease Screening Program: toward a definition of community standards of care. *Vasc Med* 6(2):87–96, 2001.
5. Selvin E, Erlinger TP: Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation* 110(6):738–743, 2004.
6. Fowkes FG, Housley E, Cawood EH, et al: Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 20(2):384–392, 1991.
7. Willigendael EM, Teijink JA, Bartelink ML, et al: Peripheral arterial disease: public and patient awareness in The Netherlands. *Eur J Vasc Endovasc Surg* 27(6):622–628, 2004.
8. Hirsch AT, Haskal ZJ, Hertzer NR, et al: ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation* 113(11):e463–e654, 2006.
9. Criqui MH, Fronek A, Barrett-Connor E, et al: The prevalence of peripheral arterial disease in a defined population. *Circulation* 71(3):510–515, 1985.
10. Sherev DA, Shaw RE, Brent BN: Angiographic predictors of femoral access site complications: implication for planned percutaneous coronary intervention. *Catheter Cardiovasc Interv* 65(2):196–202, 2005.
11. Anderson JL, Halperin JL, Albert NM, et al: Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 127(13):1425–1443, 2013.
12. Met R, Bipat S, Legemate DA, et al: Diagnostic performance of computed tomography angiography in peripheral arterial disease: a systematic review and meta-analysis. *JAMA* 301(4):415–424, 2009.
13. Hausleiter J, Meyer T, Hadamitzky M, et al: Radiation dose estimates from cardiac multislice computed tomography in daily practice: impact of different scanning protocols on effective dose estimates. *Circulation* 113(10):1305–1310, 2006.
14. Whyman MR, Fowkes FG, Kerracher EM, et al: Randomised controlled trial of percutaneous transluminal angioplasty for intermittent claudication. *Eur J Vasc Endovasc Surg* 12(2):167–172, 1996.
15. Whyman MR, Fowkes FG, Kerracher EM, et al: Is intermittent claudication improved by percutaneous transluminal angioplasty? A randomized controlled trial. *J Vasc Surg* 26(4):551–557, 1997.
16. Wolf GL, Wilson SE, Cross AP, et al: Surgery or balloon angioplasty for peripheral vascular disease: a randomized clinical trial. Principal investigators and their Associates of Veterans Administration Cooperative Study Number 199. *J Vasc Interv Radiol* 4(5):639–648, 1993.
17. Lundgren F, Dahllöf AG, Lundholm K, et al: Intermittent claudication–surgical reconstruction or physical training? A prospective randomized trial of treatment efficiency. *Ann Surg* 209(3):346–355, 1989.
18. Perkins JM, Collin J, Creasy TS, et al: Exercise training versus angioplasty for stable claudication. Long and medium term results of a prospective, randomised trial. *Eur J Vasc Endovasc Surg* 11(4):409–413, 1996.
19. Holm J, Arfvidsson B, Jivegård L, et al: Chronic lower limb ischaemia. A prospective randomised controlled study comparing the 1-year results of vascular surgery and percutaneous transluminal angioplasty (PTA). *Eur J Vasc Surg* 5(5):517–522, 1991.
20. Wilson SE, Wolf GL, Cross AP: Percutaneous transluminal angioplasty versus operation for peripheral arteriosclerosis. Report of a prospective randomized trial in a selected group of patients. *J Vasc Surg* 9(1):1–9, 1989.
21. Bosch JL, Hunink MG: Meta-analysis of the results of percutaneous transluminal angioplasty and stent placement for aortoiliac occlusive disease. *Radiology* 204(1):87–96, 1997.
22. Tetteroo E, ven der Graaf Y, Bosch JL, et al: Randomised comparison of primary stent placement versus primary angioplasty followed by selective stent placement in patients with iliac-artery occlusive disease. Dutch Iliac Stent Trial Study Group. *Lancet* 351(9110):1153–1159, 1998.
23. Richter GM, Roeren T, Noeldge G, et al: [Initial long-term results of a randomized 5-year study: iliac stent implantation versus PTA]. *Vasa Suppl* [Article in German] 35:192–193, 1992.
24. Ponec D, Jaf MR, Swischuk J, et al: The Nitinol SMART stent vs Wallstent for suboptimal iliac artery angioplasty: CRISP-US trial results. *J Vasc Interv Radiol* 15(9):911–918, 2004.
25. Sacks D, Marinelli DL, Martin LG, Spies JB: Reporting standards for clinical evaluation of new peripheral arterial revascularization devices. Technology Assessment Committee. *J Vasc Interv Radiol* 8(1 Pt 1):137–149, 1997.
26. Management of peripheral arterial disease (PAD): TransAtlantic Inter-Society Consensus (TASC). *Int Angiol* 19(1 Suppl 1):I–XXIV, 1–304, 2000.
27. Taylor LM, Jr, Porter JM: Clinical and anatomic considerations for surgery in femoropopliteal disease and the results of surgery. *Circulation* 83(2 Suppl):I63–I69, 1991.
28. Walsh DB, Gilbertson JJ, Zwolak RM, et al: The natural history of superficial femoral artery stenoses. *J Vasc Surg* 14(3):299–304, 1991.
29. Ballard JL, Sparks SR, Taylor FC, et al: Complications of iliac artery stent deployment. *J Vasc Surg* 24(4):545–553, discussion 553–555, 1996.
30. Creasy TS, McMillan PJ, Fletcher EW, et al: Is percutaneous transluminal angioplasty better than exercise for claudication? Preliminary results from a prospective randomised trial. *Eur J Vasc Surg* 4(2):135–140, 1990.
31. Matsi P: Percutaneous transluminal angioplasty in critical limb ischaemia. *Ann Chir Gynaecol* 84(4):359–362, 1995.
32. Ljungman C, Ulus AT, Almgren B, et al: A multivariate analysis of factors affecting patency of femoropopliteal and femorodistal bypass grafting. *Vasa* 29(3):215–220, 2000.
33. Muradin GS, Bosch JL, Stijnen T, Hunink MG: Balloon dilation and stent implantation for treatment of femoropopliteal arterial disease: meta-analysis. *Radiology* 221(1):137–145, 2001.
34. Schillinger M, Sabeti S, Loewe C, et al: Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. *N Engl J Med* 354(18):1879–1888, 2006.
35. Dick P, Wallner H, Sabeti S, et al: Balloon angioplasty versus stenting with nitinol stents in intermediate length superficial femoral artery lesions. *Catheter Cardiovasc Interv* 74(7):1090–1095, 2009.
36. Mwipatayi BP, Hockings A, Hofmann M, et al: Balloon angioplasty compared with stenting for treatment of femoropopliteal occlusive disease: a meta-analysis. *J Vasc Surg* 47(2):461–469, 2008.
37. Duda SH, Bosiers M, Lammer J, et al: Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. *J Endovasc Ther* 13(6):701–710, 2006.
38. Dake MD, Ansel GM, Jaff MR, et al: Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. *Circ Cardiovasc Interv* 4(5):495–504, 2011.
39. Dake MD, Ansel GM, Jaff MR, et al: Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions: 2-year follow-up from the Zilver PTX randomized and single-arm clinical studies. *J Am Coll Cardiol* 61(24):2417–2427, 2013.
40. Nakamura S, Conroy RM, Gordon IL, et al: A randomized trial of transcutaneous extraction atherectomy in femoral arteries: intravascular ultrasound observations. *J Clin Ultrasound* 23(8):461–471, 1995.
41. Vroegindeweij D, Tielbeek AV, Buth J, et al: Directional atherectomy versus balloon angioplasty in segmental femoropopliteal artery disease: two-year follow-up with color-flow duplex scanning. *J Vasc Surg* 21(2):255–268, discussion 268–269, 1995.
42. McKinsey JF, Goldstein L, Khan HU, et al: Novel treatment of patients with lower extremity ischemia: use of percutaneous atherectomy in 579 lesions. *Ann Surg* 248(4):519–528, 2008.
43. Vroegindeweij D, Vos LD, Tielbeek AV, et al: Balloon angioplasty combined with primary stenting versus balloon angioplasty alone in femoropopliteal obstructions: A comparative randomized study. *Cardiovasc Intervent Radiol* 20(6):420–425, 1997.
44. Tepe G, Zeller T, Albrecht T, et al: Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med* 358(7):689–699, 2008.
45. Werk M, Langner S, Reinkensmeier B, et al: Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. *Circulation* 118(13):1358–1365, 2008.
46. Scheinert D, Duda S, Zeller T, et al: The LEVANT I (Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis) trial for femoropopliteal revascularization: first-in-human randomized trial of low-dose drug-coated balloon versus uncoated balloon angioplasty. *JACC Cardiovasc Interv* 7(1):10–19, 2014.
47. Werk M, Albrecht T, Meyer DR, et al: Paclitaxel-coated balloons reduce restenosis after femoro-popliteal angioplasty: evidence from the randomized PACIFIER trial. *Circ Cardiovasc Interv* 5(6):831–840, 2012.
48. Cassese S, Byrne RA, Ott I, et al: Paclitaxel-coated versus uncoated balloon angioplasty reduces target lesion revascularization in patients with femoropopliteal arterial disease: a meta-analysis of randomized trials. *Circ Cardiovasc Interv* 5(4):582–589, 2012.
49. Liistro F, Grotti S, Porto I, et al: Drug-eluting balloon in peripheral intervention for the superficial femoral artery: the DEBATE-SFA randomized trial (drug-eluting balloon in peripheral intervention for the superficial femoral artery). *JACC Cardiovasc Interv* 6(12):1295–1302, 2013.
50. van der Zaag ES, Legemate DA, Prins MH, et al: Angioplasty or bypass for superficial femoral artery disease? A randomised controlled trial. *Eur J Vasc Endovasc Surg* 28(2):132–137, 2004.
51. Söder HK, Manninen HI, Jaakkola P, et al: Prospective trial of infrapopliteal artery balloon angioplasty for critical limb ischemia: angiographic and clinical results. *J Vasc Interv Radiol* 11(8):1021–1031, 2000.
52. Matsi PJ, Manninen HI, Suhonen MT, et al: Chronic critical lower-limb ischemia: prospective trial of angioplasty with 1-36 months follow-up. *Radiology* 188(2):381–387, 1993.
53. Dorros G, Jaff MR, Murphy KJ, Mathiak L: The acute outcome of tibioperoneal vessel angioplasty in 417 cases with claudication and critical limb ischemia. *Cathet Cardiovasc Diagn* 45(3):251–256, 1998.

54. Schmidt A, Piorkowski M, Werner M, et al: First experience with drug-eluting balloons in infrapopliteal arteries: restenosis rate and clinical outcome. *J Am Coll Cardiol* 58(11):1105–1109, 2011.
55. Martens JM, Knippenberg B, Vos JA, et al: Update on PADI trial: percutaneous transluminal angioplasty and drug-eluting stents for infrapopliteal lesions in critical limb ischemia. *J Vasc Surg* 50(3):687–689, 2009.
56. Grimm J, Müller-Hülsbeck S, Jahnke T, et al: Randomized study to compare PTA alone versus PTA with Palmaz stent placement for femoropopliteal lesions. *J Vasc Interv Radiol* 12(8):935–942, 2001.
57. Zeller T, Rastan A, Schwarzwälder U, et al: Midterm results after atherectomy-assisted angioplasty of below-knee arteries with use of the SilverHawk device. *J Vasc Interv Radiol* 15(12):1391–1397, 2004.
58. Safian RD, Niazi K, Runyon JP, et al: Orbital atherectomy for infrapopliteal disease: device concept and outcome data for the OASIS trial. *Catheter Cardiovasc Interv* 73(3):406–412, 2009.
59. Holdsworth RJ, McCollum PT: Results and resource implications of treating end-stage limb ischaemia. *Eur J Vasc Endovasc Surg* 13(2):164–173, 1997.
60. Dorros G, Jaff MR, Dorros AM, et al: Tibioperoneal (outflow lesion) angioplasty can be used as primary treatment in 235 patients with critical limb ischemia: five-year follow-up. *Circulation* 104(17):2057–2062, 2001.
61. Liistro F, Porto I, Angioli P, et al: Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischemia. *Circulation* 128(6):615–621, 2013.
62. Dormandy J, Heeck L, Vig S: Predictors of early disease in the lower limbs. *Semin Vasc Surg* 12(2):109–117, 1999.
63. Working Party on Thrombolysis in the Management of Limb Ischemia: Thrombolysis in the management of lower limb peripheral arterial occlusion–a consensus document. *J Vasc Interv Radiol* 14(9 Pt 2):S337–S349, 2003.
64. Weaver FA, Comerota AJ, Youngblood M, et al: Surgical revascularization versus thrombolysis for nonembolic lower extremity native artery occlusions: results of a prospective randomized trial. The STILE Investigators. Surgery versus Thrombolysis for Ischemia of the Lower Extremity. *J Vasc Surg* 24(4):513–521, discussion 521–523, 1996.
65. Olin JW, Shih A: Thromboangiitis obliterans (Buerger's disease). *Curr Opin Rheumatol* 18(1):18–24, 2006.
66. Sakamoto I, Sueyoshi E, Hazama S, et al: Endovascular treatment of iliac artery aneurysms. *Radiographics* 25(Suppl 1):S213–S227, 2005.
67. Saxon RR, Coffman JM, Gooding JM, Ponec DJ: Endograft use in the femoral and popliteal arteries. *Tech Vasc Interv Radiol* 7(1):6–15, 2004.
68. Siauw R, Koh EH, Walker SR: Endovascular repair of popliteal artery aneurysms: techniques, current evidence and recent experience. *ANZ J Surg* 76(6):505–511, 2006.
69. Smyth JS, Scoble JE: Atheroembolism. *Curr Treat Options Cardiovasc Med* 4(3):255–265, 2002.
70. Byrne RA, Joner M, Alfonso F, Kastrati A: Drug-coated balloon therapy in coronary and peripheral artery disease. *Nat Rev Cardiol* 11(1):13–23, 2014.

40 Upper Extremities and Aortic Arch

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KEY POINTS

- Arterial disease in one vascular bed is a harbinger of disease in other vascular beds.
- The differential diagnosis of diseases involving the upper extremity (UE) and aortic arch branch vessels is vast and requires extensive knowledge and a thorough history and physical examination.
- In patients with suspected arterial disease, blood pressure should be measured in both UEs, and if Takayasu arteritis is suspected, blood pressure should be measured in all four extremities.
- Anatomic variation in the UE vessels and aortic arch occurs in 20% to 30% of the population, and the pathologic significance depends on the anomaly.
- The physical examination of a patient with UE disease is incomplete in the absence of performing diagnostic maneuvers to evaluate for thoracic outlet syndrome.
- Before performing percutaneous intervention for UE large vessel disease, the relationship of branch vessels to the lesion and ostial involvement of the lesion should be thoroughly evaluated.
- Percutaneous intervention in the brachiocephalic artery is more complicated than revascularization of the subclavian artery due to the potential for embolization to the anterior cerebral circulation.
- Percutaneous revascularization has become first-line therapy instead of surgery for treating atherosclerotic brachiocephalic or subclavian stenosis because of the high technical success rates, the low restenosis and high patency rates, and lower cost with quicker recovery times.
- Management of UE arterial and aortic arch vascular disease requires discernment of when to refer patients to surgery and an understanding of the management of aneurysmal disease.

From the inception of the subspecialty of interventional cardiology, to the Centers for Medicare and Medicaid Services (CMS) physician specialty designation for interventional cardiology, the scope of interventional cardiology has continued to expand. The discipline has grown beyond percutaneous management of coronary artery disease to include therapy for valvular and structural heart disease and endovascular treatment of aortic aneurysm, venous disease, and peripheral arterial disease (PAD), including management of vascular disease in the upper extremity (UE) and proximal arch vessels.

The continued evolution of cardiology in the field of vascular medicine has been a natural extension because atherosclerosis is a systemic process that is not isolated to the coronary vasculature and a high degree of correlation exists between the extent of atherosclerosis in the coronary, carotid, and brachial arteries.[1] Coronary disease is associated with an increased risk of PAD, and among those with PAD, the risk of coronary and cerebrovascular ischemic events with significant morbidity and mortality is extremely high.[2-6] Most of the management concepts and techniques for coronary arterial disease are transferable to the treatment of PAD when a conservative medical strategy or percutaneous therapy is employed.

General and interventional cardiologists care for patients with coexistent coronary and peripheral vascular disease and those with significant risk factors for the development of arterial vascular disease. These clinicians must have a thorough understanding of PAD, including the application of screening tools and management strategies.

This chapter discusses the anatomy, epidemiology, risk factors, diagnosis, and treatment of PAD involving the UE (i.e., axillary and brachial arteries) and proximal arch vessel (i.e., subclavian artery). It excludes carotid arterial disease evaluation and management, which are discussed in Chapter 46.

EPIDEMIOLOGY AND RISK FACTORS FOR PERIPHERAL ARTERIAL DISEASE

Considering an age-adjusted prevalence of about 12%, PAD is estimated to affect at least 8 to 12 million individuals in the United States.[2,7] Advancing age is strongly associated with the increased prevalence of PAD, and approximately 20% of U.S. adults older than 70 years have PAD.[6,8]

PAD has been reported to affect males and females equally, but studies have demonstrated a greater predilection for PAD among blacks than non-Hispanic whites (38% vs. 25% of men), and the ethnic propensity is independent of traditional risk factors for cardiovascular disease such as hypertension, hyperlipidemia, diabetes, kidney disease, and tobacco use.[6,8,9] An estimated 25% to 40% of patients seen in the general cardiology clinic have PAD,[2,3,5] and up to 50% of patients with PAD may be asymptomatic, illustrating the need for careful evaluation of patients of advancing age and those with risk factors for cardiovascular and peripheral vascular disease.[6]

Unlike PAD involving the lower extremities, atherosclerosis is estimated to account for only about 5% of cases of upper extremity (UE) ischemia. Obstruction of the brachiocephalic (innominate) or subclavian (inflow) arteries accounts for most cases due to the propensity for atherosclerosis at those sites, with a fourfold higher occurrence on the left than the right.[10,11] However, not all UE ischemia is related to inflow obstruction. Because of the relatively uncommon occurrence of atherosclerosis distal to the inflow arteries, numerous causes of UE arterial disease involving the large or medium-sized arteries (proximal to the wrist) or small arteries (distal to the wrist) must be considered. Conditions such as vasculopathies, aneurysm or entrapment syndromes, embolic phenomena, medications, and chemical exposures can complicate the diagnosis due to the similarity of symptoms. Additional testing beyond the comprehensive history and physical examination may be required to elucidate the cause.[12] Table 40-1 provides the differential diseases, exposures, and other conditions that should be considered.[12,13]

VASCULAR ANATOMY OF THE UPPER EXTREMITY AND AORTIC ARCH

Normal Anatomy

The normal branching pattern of vessels coming off the aortic arch in approximately 70% of the population[14] includes the initial branch, the right brachiocephalic artery, the left common carotid artery, and the left subclavian artery. Variations from the typical branching pattern are discussed in the next section.

The right brachiocephalic artery (innominate) divides into the right subclavian and the right common carotid artery behind the right

TABLE 40-1 Differential Diagnosis of Upper Extremity Vessel Obstructive Disease

Vessel Size	Site, Disease State, and Substance	Symptoms and Physical Examination Findings	Symmetry and Acuity
Medium to Large			
Atherosclerosis	Brachiocephalic artery Subclavian artery Axillary artery	Arm claudication Hand or finger pain Bruit, pulse deficit	Typically unilateral Chronic and progressive
Aneurysm	Thoracic outlet syndrome Trauma, crutch syndrome Vasculitis Fibromuscular dysplasia	Pulsatile mass in the supraclavicular fossa, hoarseness, dyspnea, transient ischemic attack (subclavian artery)	Unilateral Chronic and progressive
Thromboembolism	Heart Aortic arch Proximal great vessels	Varies (e.g., ischemia, pallor) according to cause Skin ulcers Osler nodes Janeway lesions	Unilateral, can be bilateral Typically acute
Entrapment	Trauma Thoracic outlet syndrome Neoplasm	Pain, especially with movement or certain positions	Unilateral Chronic and progressive unless it is an acute injury
Vasculitis or arteritis	Giant cell (temporal) arteritis Kawasaki disease Takayasu arteritis Radiation-induced arteritis	Constitutional symptoms (e.g., fever, weight loss, fatigue, arthralgias, myalgias), rash, bruit, pulse deficit	Unilateral or bilateral
Vasospasm	Nicotine Cocaine Methamphetamine	Digital pallor Cyanosis	Unilateral or bilateral Acute on chronic
Small			
Hematologic disorders	Cryoglobulinemia (types I, II, III) Myeloproliferative syndrome Multiple myeloma Leukemia Primary macroglobulinemia	Constitutional symptoms	Unilateral or bilateral, typically bilateral Progressively worsening
Hypercoagulable states	Antiphospholipid syndrome Antithrombin III, protein C, or protein S deficiency Heparin-induced thrombocytopenia	Variable, typically mimicking thromboembolic disease	Unilateral or bilateral, typically bilateral Progressively worsening
Rheumatologic disorders (vasculitis)	Rheumatoid arthritis Systemic lupus erythematosus Scleroderma, CREST syndrome, mixed connective tissue disease Henoch-Schönlein purpura	Constitutional symptoms, dysphagia, nail pitting, prominent nailbed capillary loops, skin lesions (e.g., erythema nodosum, petechial rash, pyoderma gangrenosum, palpable purpura), sclerodactyly, telangiectasias	Unilateral or bilateral, typically bilateral Progressively worsening
Infectious diseases	Hepatitis C *Mycoplasma* pneumonia	Variable, typically mimicking thromboembolic disease	Unilateral or bilateral, typically bilateral Progressively worsening
Embolic and thrombotic diseases	Buerger disease Atheromatous disease Aneurysms Atrial fibrillation Atrial myxomas Left ventricular thrombus ASD/PFO Endocarditis or valvular disease	Varies according to cause Skin ulcers Osler nodes Janeway lesions	Bilateral Acute
Vasospasm	Raynaud phenomenon Medications or illicit substances	Finger pain, fixed cyanosis, ulcers, gangrene	Typically bilateral Acute, chronic, or acute on chronic
Exposures	Vinyl chloride	Digital pallor Cyanosis	Unilateral or bilateral Chronic and progressive

Data from Rajagopalan S, Mukherjee D, Mohler E: *Manual of vascular diseases,* Philadelphia, Lippincott Williams & Wilkins, 2005, p 216, and Stone JH: Immune complex-mediated small vessel vasculitis. In Firestein GS, Budd RC, Gabriel SE, et al, editors: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, Saunders, 2012.
ASD/PFO, Atrial septal defect or patent foramen ovale; *CREST,* calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia.

sternoclavicular joint. The right subclavian artery then becomes the axillary artery at the lateral border of the first rib. The brachial artery, a continuation of the axillary artery, begins at the lateral border of the teres major muscle and terminates at the neck of the radius as it divides into the radial and ulnar arteries. The radial artery continues in the hand as the deep palmar arch, whereas the ulnar artery continues in the hand as the superficial palmar arch, which gives rises to the digital arteries.[15] The left subclavian artery, the third branch off the aorta after the innominate and the left common carotid, has a branching pattern in the left UE that is analogous to the right. Figure 40-1 demonstrates normal anatomy angiographically.

Smaller vessels provide extensive collateral circuits in the shoulder, elbow, and palm regions and are protective in allowing perfusion to the UE despite significant obstruction. UE large vessel disease is typically asymptomatic until the collateral support is insufficient or exhausted. Despite having protective collateral circuits, the UE remains vulnerable to ischemia if the obstruction occurs proximally because the UE is supplied by only one artery from the aorta.

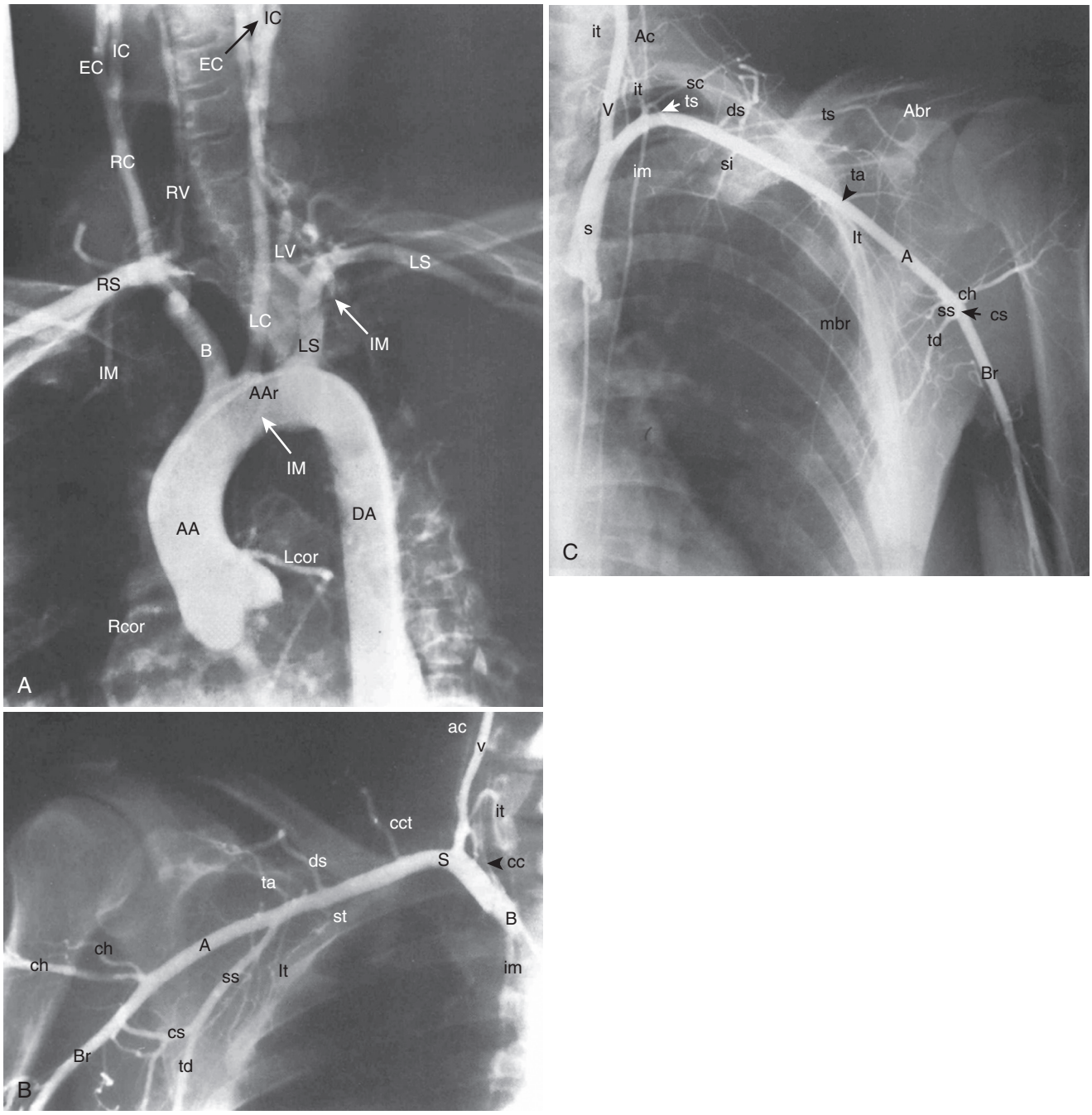

FIGURE 40-1 Normal anatomy. **A,** Left anterior oblique arch aortogram. **B,** Right subclavian arteriogram. **C,** Left subclavian arteriogram. *A,* Artery; *AA,* ascending aorta; *B,* brachiocephalic artery; *DA,* ductus arteriosus; *EC,* external carotid artery; *IC,* internal carotid artery; *IM,* internal mammary; *LC,* left carotid; *Lcor,* left coronary artery; *LS,* left subclavian artery; *RC,* right carotid; *Rcor,* right coronary artery; *RS,* right subclavian artery; *RV,* right ventricle; *ta,* truncus arteriosus; *V,* vein. (From Kadir S: *Atlas of normal and variant angiographic anatomy,* Philadelphia, WB Saunders; 1991.)

Anatomic Variants

The anomalous circulation in the UE and aortic arch primarily results from alterations in embryologic development (Fig. 40-2). Although an exhaustive review of embryologic development is beyond the scope of this chapter, the resultant aortic arch and proximal branching vessel variants are the consequence of aberrant formation, including persistence or abnormal regression, of the endocardial tube, the ventral and dorsal aortae, and the six paired branchial arch arteries or the intersegmental arteries.

Table 40-2 lists some of the more commonly encountered variants, their frequencies in the population, associated pathologic significance, and diagnostic physical examination findings.[12,14,16,17] The more common arterial variants in the forearm and collateral pathways that may form in the presence of main arterial obstruction are included. Figures 40-3 through 40-5 show examples of variant anatomy.

DIAGNOSTIC EVALUATION AND DISEASE CLASSIFICATION

History and Physical Examination

As with many other facets of medicine, the importance of a thorough history and physical examination in patients with suspected PAD

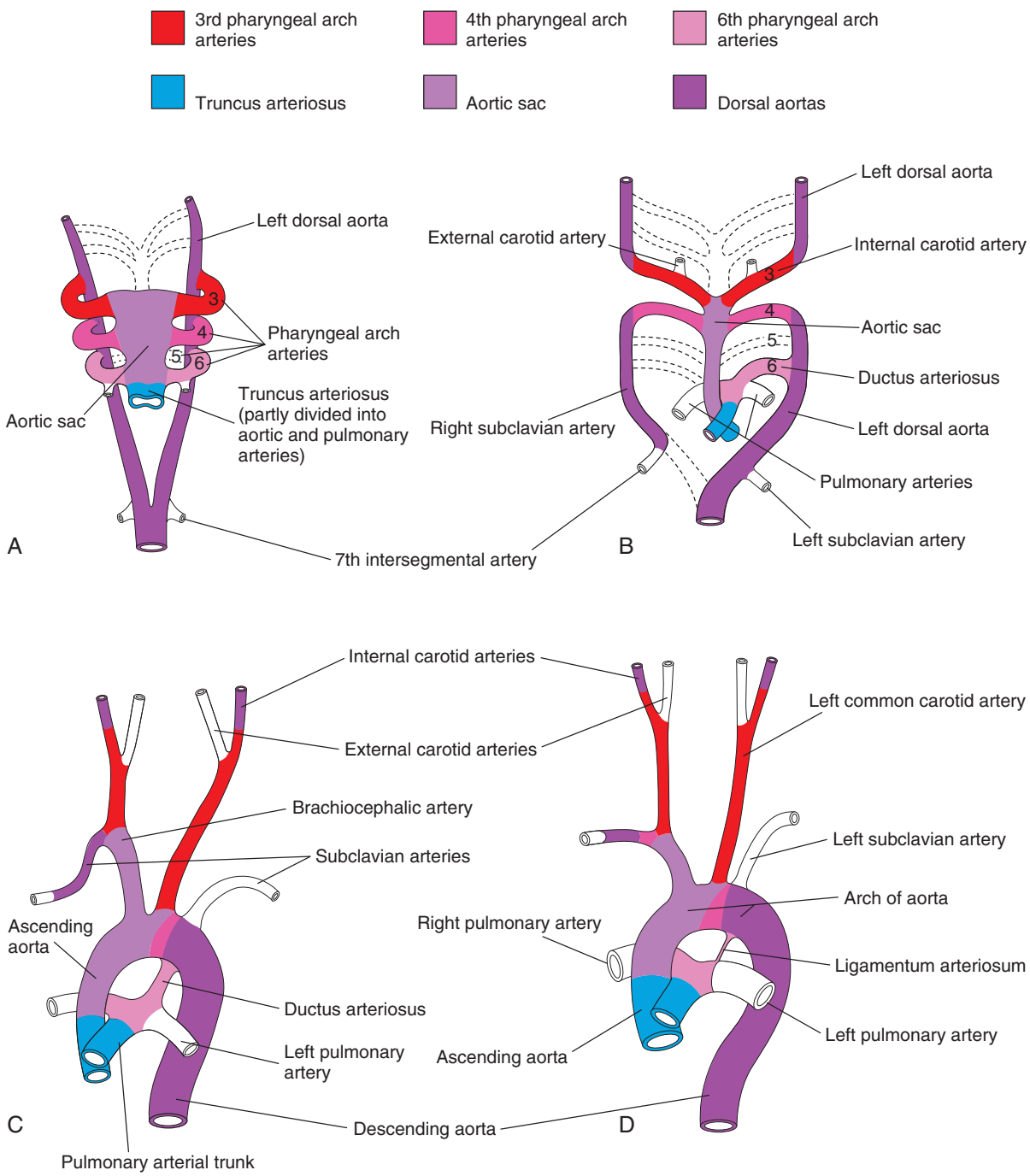

FIGURE 40-2 Embryologic transformation of the aorta to a normal adult pattern. The vessels that are not colored are not derived from these structures. **A,** Pharyngeal arch arteries at 6 weeks; by this stage, the first two pairs of arteries have largely disappeared. **B,** Pharyngeal arch arteries at 7 weeks; the parts of the dorsal aortae and pharyngeal arch arteries that normally disappear are indicated with broken lines. **C,** Arterial arrangement at 8 weeks. **D,** Sketch of the arterial vessels of a 6-month-old neonate. Note that the ascending aorta and pulmonary arteries are considerably smaller in **C** than in **D.** This represents the relative flow through these vessels at the different stages of development. Observe the large size of the ductus arteriosus (DA) in **C** and that it is essentially a direct continuation of the pulmonary trunk. The DA normally becomes closed within the first few days after birth. Eventually the DA becomes the ligamentum arteriosum, as shown in **D.** (From Moore K, Persaud TVN: The cardiovascular system. In Moore K, Persaud TVN, editors: *Before we are born: essentials of embryology and birth defects,* ed 6, Philadelphia, WB Saunders; 2003, p 264.)

TABLE 40-2 Arterial Variants and Collateral Pathways of the Upper Extremity and Aortic Arch

Anatomic Variants	Prevalence (%)	Pathologic Significance	Physical Examination Clues
Bovine arch: common origin of brachiocephalic and left common carotid arteries	22	None	No specific findings
Origin of left common carotid from the brachiocephalic (middle to upper)	8-10	None	No specific findings
Origin of left vertebral artery from the aorta	4-6	None	No specific findings
Origin of right subclavian from left aortic arch, distal to left subclavian (arteria lusoria)	2	Compression due to esophageal ring, prone to rupture and aneurysm (Kommerell diverticulum)	Dysphagia
Common origin of carotids	<1	None	No specific findings
Origin of radial artery from brachial or axillary artery	15-20	None	No specific findings
Origin of ulnar artery from brachial or axillary artery	2-3	None	No specific findings
Collateral Obstruction Site	**Donor Artery**	**Pathologic Significance**	**Physical Examination Clues**
Proximal subclavian or innominate obstruction	Vertebral, other neck, abdominal, or pelvic	Subclavian steal syndrome	Weak or absent pulse Decreased blood pressure Arm weakness or pain
Distal subclavian or axillary	Subscapular, intercostals, lateral thoracic	None, unless collateral supply insufficient, then ischemia	No specific findings
Brachial artery	Profunda brachialis, radial, ulnar	None, unless collateral supply insufficient, then ischemia	No specific findings

Data from references 12,14, 16, and 17.

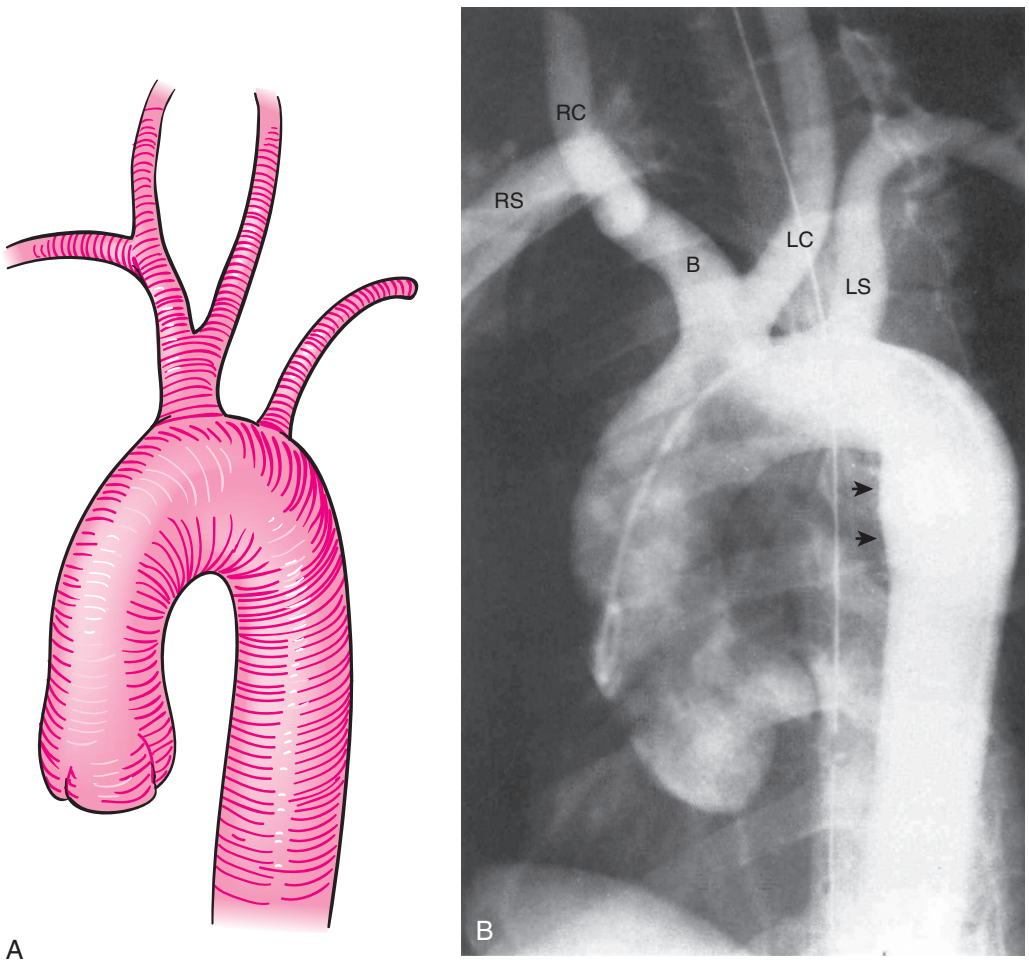

FIGURE 40-3 Common origin of left common carotid and brachiocephalic arteries (i.e., bovine arch). **A,** Schematic drawing. **B,** Left anterior oblique arch aortogram of a bovine arch. *B,* Brachiocephalic artery; *LC,* left carotid; *LS,* left subclavian artery; *RC,* right carotid; *RS,* right subclavian artery. (From Kadir S: *Atlas of normal and variant angiographic anatomy,* Philadelphia, WB Saunders; 1991.)

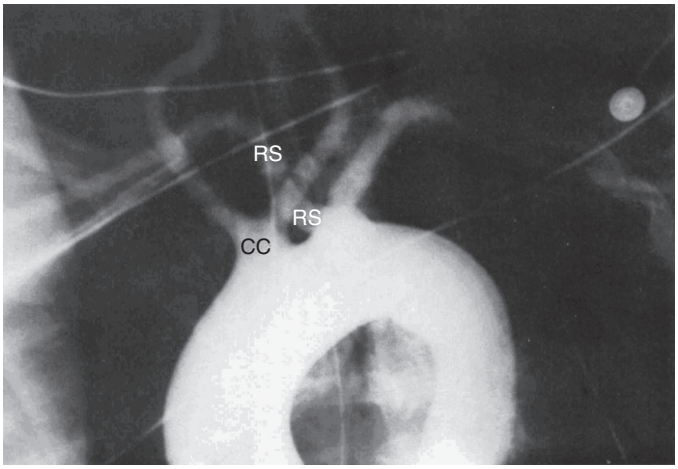

FIGURE 40-4 Aberrant right subclavian (RS) artery and a common carotid (CC) trunk. (From Kadir S: *Atlas of normal and variant angiographic anatomy,* Philadelphia, WB Saunders; 1991.)

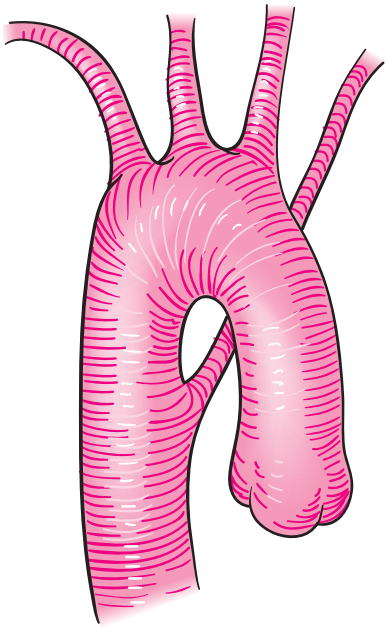

FIGURE 40-5 Schematic drawing of the right aortic arch with aberrant left subclavian artery. (From Kadir S: *Atlas of normal and variant angiographic anatomy,* Philadelphia, WB Saunders, 1991.)

cannot be overstated. Although they are often not sufficient to elucidate the diagnosis because of the broad differential, they should nonetheless be complete so as to narrow the focus and avoid extraneous testing or referrals.

Because of the broad differential for UE ischemia, the history and review of systems should be comprehensive and should include detailed descriptions of the symptoms, comorbidities, exposures (e.g., chemicals, vibratory tools, radiation), trauma, and a complete medication history including prescription drugs, illicit drugs, and tobacco use. Keys to narrowing the differential diagnosis include consideration of the previously described elements, the acuity of onset and time course (intermittent versus constant), exacerbating and alleviating factors, symmetry or asymmetry of symptoms, and physical examination findings (see Table 40-1).

Unilateral symptoms suggest a more localized process (e.g., entrapment, stenotic lesion), whereas bilateral symptoms are more

TABLE 40-3 Signs of Arterial Ischemia

Course	Signs
Acute	Pulselessness Palor Poikilotherima Pain Paresthesias
Chronic	Muscle atrophy Skin bronzing Focal hair loss Digital gangrene
Acute or chronic	Nonhealing ulcer

Data from Johnston, SL, Dieter RS: Upper extremities and aortic arch. In Topol EJ, Teirstein PS, editors: *Textbook of interventional cardiology,* ed 6, Philadelphia, Saunders, 2012, Chapter 38.

characteristic of a systemic disease process. The acuity or time course can be confusing because an acute onset of symptoms may be a manifestation of a chronic process with an acute exacerbation or simply an acute condition. In arterial ischemia, signs of acute or chronic arterial insufficiency can be distinct and aid in the diagnosis (Table 40-3).[18]

In vasospastic disease, the intermittent or constant nature of the symptoms helps to differentiate primary (nonobstructive) Raynaud disease from the secondary (obstructive) form. Primary Raynaud disease is typically intermittent, and the vasospastic symptoms resolve completely between bouts, whereas in secondary Raynaud disease, symptoms are persistent but may wax and wane in intensity. Normal vasomotor function must be differentiated from abnormal vasospastic disease. Normal physiologic arterial vasoconstriction of the cutaneous circulation in the hands and fingers occurs in response to stimuli such as cold exposure. During normal physiologic vasoconstriction, blood flow is continuous, whereas with vasospastic disease (i.e., Raynaud disease), there is cessation of blood flow.[12]

Blood pressure should be manually measured in both arms because a systolic gradient of greater than 15 to 20 mm Hg suggests a significant stenosis, with a gradient of 20 mm Hg or more having a specificity of 94%.[19] A systolic gradient of more than 10 mm Hg may indicate hemodynamic significance and justify further investigation.[11] If Takayasu (giant cell) arteritis is suspected, blood pressure should be measured in all four extremities to evaluate the differential pressure between the upper and lower extremities.

Palpation should begin in the supraclavicular fossa because a pulsatile mass suggests a subclavian artery aneurysm, and distal subclavian artery aneurysms are typically caused by compression over a cervical rib (i.e., thoracic outlet syndrome [TOS]). Tenderness in the supraclavicular fossa and along the scalene muscles also suggests TOS. The brachial, radial, and ulnar arteries should be palpated because pulse deficits, especially radial or brachial, in a younger and otherwise previously healthy patient suggests Takayasu arteritis, whereas a unilateral pulse deficit in an older adult patient with comorbidities of cardiovascular disease typically represents atherosclerotic disease.

The supraclavicular fossa should be auscultated for the presence of a bruit or murmur. A bruit suggests subclavian artery stenosis, whereas a continuous murmur suggests an arteriovenous fistula.[12] The skin should be inspected for ulcers (e.g., atherosclerosis, embolism, vasculitis, Buerger disease), rashes, petechiae, purpura (e.g., vasculitis, rheumatologic illnesses), and cyanosis (e.g., vasospasm, drug or chemical exposure). Examination of the nails for pitting and nail bed capillary loops or splinter hemorrhages, which suggest vasculitis or endocarditis, respectively.

Capillary refill (normal <5 seconds) should be evaluated bilaterally, and special techniques such as the Allen maneuver, the Halstead maneuver, or the Adson test can be performed if TOS is suspected. However, because the Adson sign (i.e., loss of the radial pulse in the arm) elicited by the test can be positive in asymptomatic patients, it should not be used as an independent indicator but considered in

TABLE 40-4 Vascular Diagnostic Testing

Test	Benefit	Limitations
WBI/FBI	Simple, economical, noninvasive	Inaccurate in heavily calcified, noncompressible vessels
Segmental limb pressures	Establishes presence, severity, and anatomic location of disease Useful for surveillance after revascularization	Inaccurate in heavily calcified, noncompressible vessels
Finger pulse volume recording with plethysmography	Differentiates normal from diseased limbs or obstructive from vasospastic disease Useful for surveillance after revascularization	Accuracy decreases with multilevel disease, less accurate in identifying level of disease, can be abnormal in low cardiac output states
Duplex ultrasound	Simple, economical, noninvasive High sensitivity and specificity (>90%) Color flow and spectral analysis used to identify flow reversal, turbulence at aneurysms or other arterial lesions, and stenosis vs. occlusion in low-flow states Useful for surveillance after revascularization	Highly operator dependent Diagnostic accuracy limited with dense calcification Difficult to image left proximal subclavian and other segments of the subclavian arteries under the clavicle
CTA	High-resolution definition of anatomy Allows visualization in multiple planes Used to determine candidacy for endovascular procedures	Radiation and contrast exposure Limited use in patients with contrast allergy or severe renal disease Acoustic shadowing artifact with pacemakers
Magnetic resonance angiography	Excellent anatomic resolution Lack of exposure to radiation Provides associated soft tissue definition, including vascular wall inflammation, cysts, aneurysms	Cannot be used if metal present (e.g., AICD, pacemaker) Time consuming, costly, requires prolonged breath holding Prone to artifacts (coil dropout and venous susceptibility) Gadolinium limits use in CKD stage 4 or 5
Catheter-based angiography	Allows direct visualization of vessels Allows for assessment of pressure gradients Allows structural and functional assessment with IVUS and FFR	Invasive Contrast and radiation exposure

Data from references 8, 10, 11, and 17.
AICD: Automatic implantable cardioverter defibrillator, *CTA*, computed tomography angiography; *CKD*: chronic kidney disease; *FFR*, fractional flow reserve; *FBI*: finger-brachial index; *IVUS*, intravascular ultrasound; *WBI*: wrist-brachial index.

conjunction with other objective findings.[20] If subclavian steal syndrome is suspected, the Dieter test, in which a blood pressure cuff is inflated and then rapidly deflated (on the limb with subclavian stenosis) to induce hyperemia, vertebral flow reversal, and provocation of posterior cerebral symptoms, can clinically establish the diagnosis.[21]

Laboratory Testing

Initial laboratory tests in the evaluation of UE ischemia include a complete blood cell count (CBC), comprehensive metabolic panel (CMP), lipid panel, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), activated partial thromboplastin time (aPPT), and prothrombin time (PT) or international normalized ratio (INR). Some authorities also recommend tests for rheumatoid factor (RF) and antinuclear antibodies (ANAs).

Based on the initial differential diagnosis, additional testing may be needed. For example, if an embolic phenomenon, an idiopathic thrombosis, or a hypercoagulable state is suspected, tests for factor V Leiden mutation, protein C and protein S deficiencies, antithrombin III deficiency, and prothrombin 20210A polymorphism may be useful. If an infectious cause is suspected, a hepatitis panel, rapid plasma reagin (RPR) test, and blood cultures may be needed. Similarly, if a rheumatologic disorder is likely, tests for antiphospholipid antibodies and lupus anticoagulant may be helpful in addition to tests for RF and ANA. Because the laboratory workup can be time-consuming and expensive, a comprehensive history and physical examination are essential for guiding the investigation and selecting patients who require a more extensive evaluation.[22]

Vascular Laboratory Testing

Various noninvasive and invasive vascular diagnostic tests and imaging studies may be used in assessing the cause and severity of disease. Measuring segmental limb pressures in the arm, analogous to testing performed for lower extremity arterial disease, can identify the level of obstruction and the severity of disease. A difference in blood pressures between the left and right sides of 10 mm Hg or more is considered abnormal, a pressure gradient between adjacent segments in the same limb of more than 20 mm Hg indicates significant obstructive disease, and a gradient of more than 30 mm Hg suggests an occlusion.[10] Similar to the ankle-brachial index in the lower extremity, a wrist-brachial index (WBI) or a finger-brachial index (FBI) of less than 0.85 or 0.70, respectively, is considered to be abnormal and indicates arterial insufficiency. Other diagnostic tools are listed in Table 40-4, along with the benefits and limitations of each study.[8,10,11,17]

Catheter-Based Angiography

Before performing selective angiography of the brachiocephalic or subclavian arteries, an aortic arch angiogram using a soft, multi-sidehole catheter (e.g., pigtail catheter) and 30 to 40 mL of contrast material delivered by autoinjection (e.g., 15 to 20 mL/sec delivered over 2 seconds, 0.3 to 0.5 seconds rate of rise, 900 psi) in a 30- to 40-degree left anterior oblique (LAO) projection using digital subtraction angiography (DSA) should be performed.[10,12,23] Based on improved tolerance, lower tonicity, and fewer side effects, the recommended contrast medium is iodixanol, an isoosmolar, nonionic agent.[10,24,25] Access is typically obtained from the common femoral artery (CFA) for catheter-based diagnostic angiography and for percutaneous intervention for stenosis, whereas radial and more commonly ipsilateral brachial artery access in combination with CFA access is used for treating occlusions. Indications for UE diagnostic angiography are given in Table 40-5.[10-12]

For selective engagement and angiography of the brachiocephalic and left subclavian arteries, various catheters can be used with hand-injected contrast of 5 to 10 mL on DSA. Commonly, the Judkins right 4 (JR4) catheter is selected, but alternatives include the internal mammary artery (IMA) and multipurpose (MP-A) catheter or specialty shaped catheters such as the Vitek (VTK), Simmons 1 or 2 (SIMS), or Headhunter-1 (H-1). Catheter selection should be guided by the arch aortogram, with the initial catheter choice matching the level of difficulty of the arch type. For example, a JR4 is appropriate for a type 1 arch, whereas a VTK or H-1 is recommended for type 2, and the SIMS is used for a type 3 arch.[10,12] Care should be taken when engaging, disengaging, or manipulating catheters to avoid vascular trauma or excessive scraping of the aorta (i.e., to minimize the risk of stroke).

After selective engagement, orthogonal oblique projections are recommended for proper delineation and reduction in overlap. The right anterior oblique (RAO) view is recommended for the brachiocephalic bifurcation, origin of the right subclavian artery, and origins of the left vertebral artery and IMA from the left subclavian artery. The LAO view is recommended for improved visualization of the right vertebral artery and IMA.[10,16] Patient positioning is neutral (i.e., anatomic position), but abduction and external rotation may be needed for the evaluation when TOS is suspected of causing vascular compression.

TABLE 40-5 Indications for Aortic Arch and Upper Extremity Diagnostic Angiography

Screening before planned coronary artery bypass grafting with internal mammary artery grafting in the following patients • Bilateral arm blood pressure differential >10 mm Hg • History of radiation therapy for the neck or chest • History of vasculitis or known peripheral arterial disease, especially angiographic aortic arch or iliofemoral disease, even if asymptomatic
Evaluation of acute symptoms • Cyanosis • Acute limb ischemia • Blue digit syndrome
After blunt or penetrating trauma with signs of vascular injury
Evaluation of symptomatic arm claudication
Evaluation for unilateral upper extremity embolization when a proximal arterial embolic source is suspected (e.g., vascular thoracic outlet syndrome)
Evaluation of suspected steal syndrome • Subclavian steal syndrome (i.e., vertebrobasilar insufficiency) • Coronary steal syndrome (i.e., angina from internal mammary graft insufficiency)

Data from references 10 through 12.

For axillary and brachial artery angiography, the diagnostic catheter should be placed in the distal subclavian artery. The anteroposterior projection, with the patient in the neutral position, is used to visualize the distal subclavian, axillary, and brachial arteries, although slight arm abduction may enhance visualization.[10,16]

TREATMENT

Management of UE disease ranges from medical management to percutaneous intervention or surgical treatment. Modification of risk factors and medical therapy for atherosclerotic disease are considered the standard of care for all patients, regardless of the degree of disease. When intervention is indicated, percutaneous management is favored over the surgical approach because of improved efficacy and patency rates with angioplasty and stenting in the modern era (Fig. 40-6) and the desire to avoid factors of surgery associated with increased morbidity and mortality, such as increased cost, general anesthesia, and longer hospitalization and recovery times.[11,12,26]

Before initiating a brachiocephalic or subclavian intervention, the diagnostic images should be studied to determine the proximity of the lesion to the vertebral, carotid, and internal mammary arteries and the vessel takeoff from the aortic arch (left subclavian) or the brachiocephalic (right subclavian).

Access for percutaneous angioplasty and stenting (PTAS) is typically obtained from the CFA for intervention in stenosis, whereas ipsilateral brachial (less commonly, radial) artery access in combination with CFA access is used for treating occlusions provided there is a lack of severe aortoiliac disease. If CFA access is prohibited by severe aortoiliac disease, brachial access is recommended for the treatment of stenosis and occlusive disease.[10]

All endovascular operators should be aware of the complexities and potential complications of PTAS involving the UE or proximal arch vessels (Table 40-6) and appreciate that intervention in the innominate artery is more complex than subclavian intervention

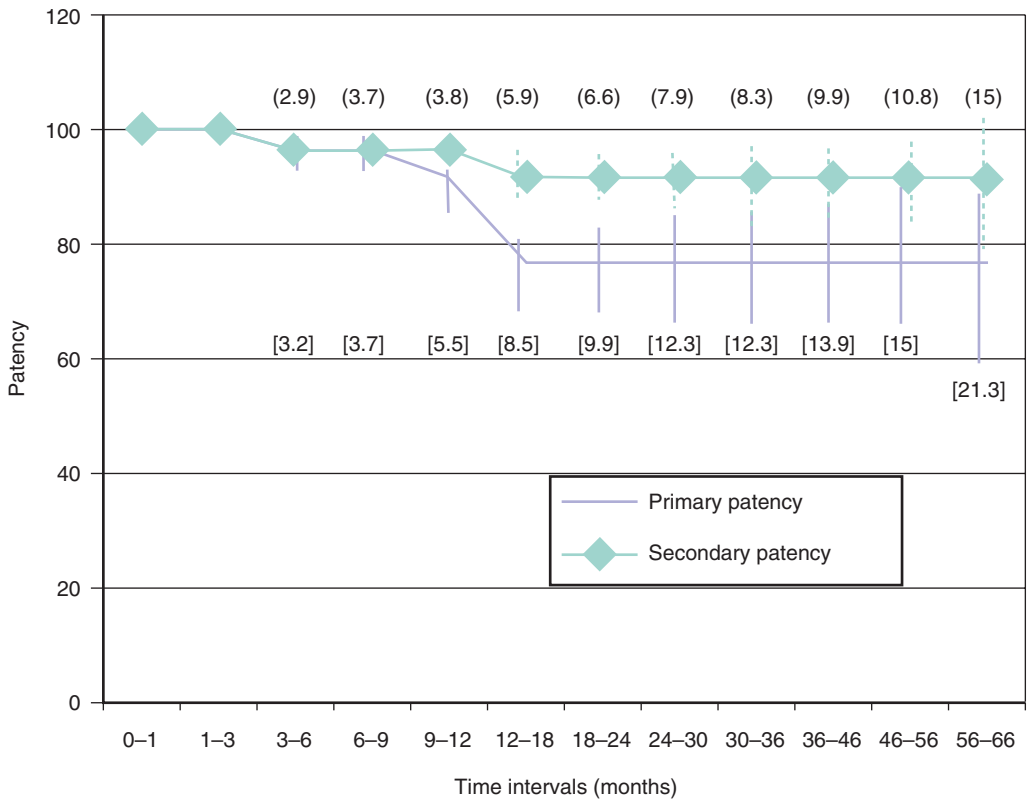

FIGURE 40-6 Long-term patency of innominate and subclavian artery stenting. (From Brountzos EN, Petersen B, Binkert C, Panagiotou I, Kaufman JA: Primary stenting of subclavian and innominate artery occlusive disease: a single center's experience. *Cardiovasc Intervent Radiol* 27:616-623, 2004.)

TABLE 40-6 Complications of Percutaneous Angioplasty and Stenting of the Upper Extremity or Proximal Arch Vessels

Vascular complications, including dissection, perforation, intrathoracic hemorrhage
Embolization, including thrombotic and atheroembolic material
Cerebrovascular accident or transient ischemic attack
Restenosis
Vascular access complications (e.g., hematoma, thrombosis, pseudoaneurysm, especially with brachial artery access)
Stent migration, malposition, dislodgement, or embolization

because of the potential for embolization to the anterior cerebral circulation through the right common carotid artery.[10-12] With that knowledge, use of a embolic protection device should be considered. Similarly, balloon angioplasty as a stand-alone therapy is rarely performed now because of the excellent, durable results obtained with the combination of balloon angioplasty and stenting.

A long sheath- or guide-based system can be used. The sheath or guide is parked proximal to the lesion, taking care to avoid atheroembolization, and the PTAS is carried out with an undersized balloon for predilation to avoid the risk of dissection (i.e., approximately 70% of the estimated vessel diameter). Balloon-expandable stents, which offer more accurate stent placement, are typically used for stenosis proximal to the vertebral artery. Self-expanding stents, which offer more flexibility and less deformability, are typically used to treat stenosis distal to the vertebral artery, where less placement accuracy is required but where flexion points related to the subclavian to axillary transition exist.

Because of the risk of dissection or rupture, conservative stent sizing is recommended. Typically, 6 to 8 mm is used for the subclavian, and 8 to 10 mm is used for the innominate artery.[10,12]

After stenting, lifelong aspirin and at least 4 weeks of clopidogrel are recommended with suggested follow-up intervals of 1 month, 6 months, 12 months, and then annually.[26] Bilateral cuff pressures should be taken at each visit, along with eliciting recurrent symptoms by the history and physical examination. Symptom recurrence or a more than 10 mm Hg change in the arm cuff pressure differential should be evaluated with duplex ultrasonography because early detection and intervention are important for maintaining patency.[10,26]

SPECIAL CONSIDERATIONS

The causes of large vessel disease of the UE are relatively limited and typically are categorized as embolic, aneurysmal, vasculopathic (including vasculitis and atherosclerosis), and entrapment syndromes. The following sections discuss common disease processes of the UE vessels that require specific knowledge and attention when suggested by the history or physical examination findings during evaluation.

Thoracic Outlet Syndrome

TOS is a term used to describe an array of symptoms that result from compression of the neurovascular structures passing through the scalene triangle (i.e., subclavian artery, subclavian vein, and brachial plexus), which has an anterior and posterior boundary of the anterior and middle scalene muscles, respectively, and a base of the cervical or first rib.[27] Compression may also occur at the costoclavicular space (i.e., costoclavicular space syndrome), which is bounded by the clavicle, first rib, costoclavicular ligament, and middle scalene muscle, or under the pectoralis minor and coracoid process (i.e., pectoralis minor space).[28]

Classification of symptoms is typically based on whether the brachial plexus (i.e., neurogenic TOS), the subclavian artery (i.e., arterial TOS), or rarely, the subclavian vein (i.e., venous TOS) accounts for the primary site of compression. Neurogenic TOS accounts for 90% to 95% of cases and is more common in women. Vascular TOS (arterial and venous), which account for the most serious morbidity associated with this condition due to a tendency for aneurysm formation, occurs in 5% to 10% of patients. Arterial TOS is equally distributed among males and female patients, whereas venous TOS tends to occur two times more often in men than women. Most patients with TOS tend to be 20 to 40 years of age and have a history of repetitive motion of the UE, especially overhead movements, or neck trauma, with whiplash being the most common cause.

Symptoms of arterial TOS include claudication, pallor, coolness, digital ischemia, and pain in the hand and are typically caused by aneurysm-induced emboli or embolization from thrombus formation distal to a subclavian stenosis. Arm heaviness, swelling of the arm, cyanosis, and paresthesias of the fingers or hand are symptoms suggesting venous TOS.[29] Arm swelling is an important discriminator because it is typically absent in neurogenic or arterial TOS. As previously described, various provocative maneuvers can be used to elicit symptoms, although all suffer from low specificity. When vascular TOS is suspected, further evaluation, including duplex ultrasound, magnetic resonance imaging (MRI), and angiography (arteriography or venography), may be useful.[10,18] Angiography should be performed initially in the neutral position and then repeated in the provocative position.

Treatment of vascular TOS is reserved for patients who are symptomatic or have evidence of embolization. Surgical intervention is considered for decompression in the setting of an acute vascular syndrome, whereas endovascular management using catheter-directed thrombolytics or embolectomy can be used if necessary in the setting of acute embolization.[10,12,29] However, other than thrombolysis, surgical decompression is considered mandatory for first-line, definitive therapy. Endovascular therapy is reserved for second-line treatment.

Subclavian Steal Syndrome

In the setting of a significant brachiocephalic or subclavian stenosis or obstruction, blood flow from the vertebrobasilar or posterior cerebral circulation can be redirected in a retrograde fashion along the ipsilateral vertebral artery toward the arm, causing symptoms of ischemia such as dizziness, unsteadiness, vertigo, ataxia, nystagmus, diplopia, or other visual changes. The condition, called *subclavian steal syndrome* (SSS), is somewhat controversial, and some argue that patients remain asymptomatic in the absence of concurrent cerebrovascular lesions such as contralateral carotid artery stenosis, contralateral vertebral artery stenosis, or hypoplastic posterior communicating arteries. In patients with those vascular lesions, there is inadequate blood flow to the posterior or vertebrobasilar circulation, resulting in ischemic symptoms, especially during vigorous arm activity.[12,30] Transient obstruction in the proximal subclavian (Fig. 40-7) with respiration (i.e., Dieter sign) has been reported.[21]

Only an estimated 2.5 % of patients are symptomatic, with 80% of them having concurrently contralateral carotid or vertebral artery stenosis. SSS has a threefold higher incidence in left subclavian artery stenosis compared with brachiocephalic artery lesions and is twice as likely to occur in 40- to 60-year-old men compared with women.[31] Further evaluation of symptomatic patients is indicated, and the recommended initial study is duplex ultrasonography of the carotid and vertebral arteries. Based on the results of the noninvasive studies, angiography of the aortic arch and the brachiocephalic, subclavian, carotid, and vertebral arteries may be warranted to confirm the diagnosis and for anatomic definition before intervention.

Intervention is indicated only for symptomatic patients. A fresh thrombus is the primary contraindication to brachiocephalic (subclavian) PTAS in this setting. In a study of 252 patients that compared endovascular treatment with extrathoracic bypass surgery, Song and colleagues found that endovascular treatment was safe and effective and had patency rates comparable to those of surgery in the short and medium terms, whereas surgery provided a more durable result in the long term.[32]

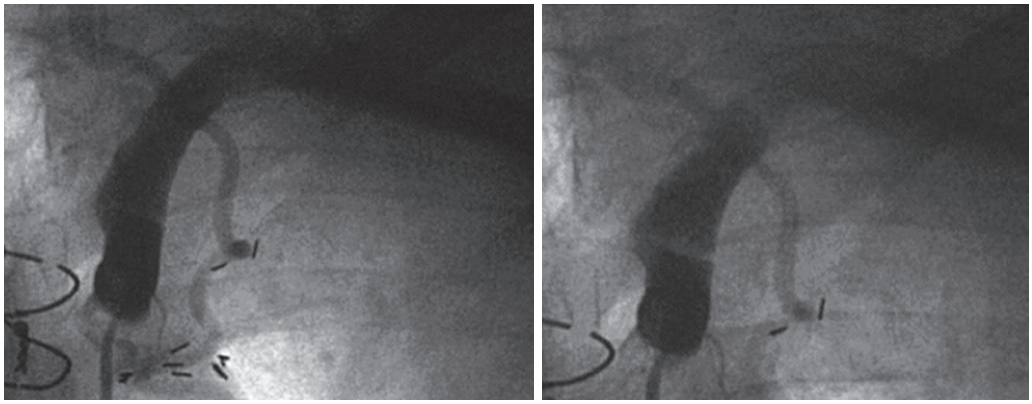

FIGURE 40-7 Dynamic left subclavian artery obstruction (i.e., Dieter sign) and exacerbation of a proximal subclavian artery kink with expiration. The subclavian arteriograms were obtained during inspiration *(left)* and expiration *(right)*. (From Dieter RS, Morshedi-Meibodi A, Ahmed MH, et al: Description of a new angiographic sign: dynamic left artery obstruction, *Vasc Dis Manage* 3:298-299, 2006.)

Coronary Steal Syndrome

Similar to SSS, *coronary steal syndrome* (CSS), is a phenomenon in which coronary ischemia results from coronary blood flowing retrograde through the IMA away from the heart to supply the arm with a proximal stenosis in the subclavian artery. CSS has become increasingly recognized over the past 2 decades because of the increased use of the IMA as a conduit in 75% to 90% of coronary arterial bypass graft operations.[33] Similar to SSS, catheter-based intervention is considered first-line therapy for symptomatic patients, and surgery for CSS is similar to that for SSS.[34,35]

CONCLUSIONS

Diagnosis and management of UE vascular disease is similar to that for lower extremity disease, with important differences in the differential diagnoses for UE disease, unique catheter-based interventional challenges based on the UE and aortic arch anatomy and important branch vessels, and the potential for rare but serious complications. Because of the high technical success rate, low restenosis or high patency rates, and minimal complications with careful catheter manipulation and conservative balloon and stent choices, percutaneous catheter-based intervention of symptomatic subclavian artery atherosclerotic disease remains the first-line therapy in the absence of acute thrombus.

Understanding when to refer patients to surgery is also important. Further reading regarding aneurysmal disease is recommended for practitioners managing UE or aortic arch vascular disease.

ACKNOWLEDGMENTS

We offer special thanks to Samuel L. Johnston for his contributions to this chapter in previous editions.

REFERENCES

1. Sorensen KE, Kristensen IB, Calermajer DS: Atherosclerosis in the human brachial artery. *J Am Coll Cardiol* 29(2):318–322, 1997.
2. Hirsch AT, Criqui MH, Treat-Jacobson D, et al: Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 286(11):1317–1324, 2001.
3. Hirsch AT, Gloviczki P, Drooz A, et al: *NHLBI Workshop on peripheral arterial disease (PAD): developing a public awareness campaign*, Bethesda, MD, 2003, National Heart, Lung, and Blood Institute.
4. Weitz JI, Byrne J, Clagett GP, et al: Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation* 94(11):3026–3049, 1996.
5. Dieter RS, Morshedi-Meibodi A, Ahmed MH, et al: Lower extremity peripheral arterial disease in hospitalized patients with coronary artery disease. *Vasc Med* 8(4):233–236, 2003.
6. Dhaliwal G, Mukherjee D: Peripheral arterial disease: epidemiology, natural history, diagnosis and treatment. *Int J Angiol* 16(2): 36–44, 2007.
7. American Heart Association: *Heart disease and stroke statistics—2014 update*, http://www.heart.org/idc/groups/ahamah-public/@wcm/@sop/@smd/documents/downloadable/ucm_459072.pdf (accessed December 29, 2014).
8. Olin JW, Sealove BA: Peripheral artery disease: current insights into the disease and its diagnosis and management. *Mayo Clin Proc* 85(7):678–692, 2010.
9. Criqui MH: Peripheral arterial disease: epidemiological aspects. *Vasc Med* 6(Suppl 1):3–7, 2001.
10. Casserly IP, Sachar R, Yadav JS: Chapters 2, 3, and 24. *Practical peripheral vascular intervention*, ed 2, Philadelphia, 2011, Lippincott Williams & Wilkins.
11. Ochoa VM, Yeghiazarians Y: Subclavian artery stenosis: a review for the vascular medicine practitioner. *Vasc Med* 16(1):29–34, 2010.
12. Rajagopalan S, Mukerjee D, Mohler E: *Manual of vascular diseases*, Philadelphia, 2005, Lippincott Williams & Wilkins, pp 39–43, 215.
13. Stone JH: Immune complex-mediated small vessel vasculitis. In Firestein GS, Budd RC, Gabriel SE, et al, editors: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2012, Saunders.
14. Kadir S: *Atlas of normal and variant angiographic anatomy*, Philadelphia, 1991, WB Saunders, p xi, 529.
15. Snell RS: *Clinical anatomy for medical students*, ed 5, Boston, 1995, Little Brown, pp 103–104, 391–392, 450–454.
16. Kaufman JA, Lee MJ: Chapter 6. *Vascular and interventional radiology: the requisites*, ed 2, Philadelphia, 2014, Elsevier.
17. Pellerito JS, Polak JF: Chapter 13. *Introduction to vascular ultrasonography*, ed 6, Philadelphia, 2012, Saunders.
18. Johnston SL, Dieter RS: Upper extremities and aortic arch, Chapter 38. In Topol EJ, Teirstein PS, editors: *Textbook of interventional cardiology*, ed 6, Philadelphia, 2012, Saunders.
19. English JA, Carell ES, Guidera SA, Tripp HF: Angiographic prevalence and clinical predictors of left subclavian stenosis in patients undergoing diagnostic cardiac catheterization. *Catheter Cardiovasc Interv* 54(1):8–11, 2001.
20. Jackson P: Thoracic outlet syndrome: evaluation and treatment. *Clin Manage* 7(6):6–10, 1987.
21. Dieter RS: The Dieter test. *Expert Rev Cardiovasc Ther* 7(3):221, 2009.
22. Bakerman S: *ABC's of interpretive laboratory data*, ed 4, Scottsdale, Ariz., 2002, Interpretive Laboratory Data Inc, pp 164–167, 173–178, 320–326.
23. Kern MJ: *The cardiac catheterization handbook*, ed 5, Philadelphia, 2011, Saunders, p 208.
24. Klein L, Sheldon MW, Brinker J, et al: The use of radiographic contrast media during PCI: a focused review. Position statement of the Society of Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv* 74:728–746, 2009.
25. Longnecker CR, Lim MJ: Basic radiation principles and contrast media. In Mukherjee D, Bavry AA, editors: *Interventional cardiology: essential clinician's guide*, New York, 2011, Oxford Press, p 11.
26. Brountzos EN, Petersen B, Binkert C, et al: Primary stenting of subclavian and innominate artery occlusive disease: a single center's experience. *Cardiovasc Intervent Radiol* 27(6):616–623, 2004.
27. Thompson RW, Petrinec D: Surgical treatment of thoracic outlet compressive syndromes: diagnostic considerations and transaxillary first rib resection. *Ann Vasc Surg* 11(3):315–323, 1997.
28. Magee DJ: *Orthopedic physical assessment*, ed 2, Philadelphia, 1992, WB Saunders, pp 91–92.
29. Sanders RJ, Hammond SL, Rao NM: Diagnosis of thoracic outlet syndrome. *J Vasc Surg* 46(3):601–604, 2007.
30. Lord RS, Adar R, Stein RL: Contribution of the circle of Willis to the subclavian steal syndrome. *Circulation* 40(6):871–878, 1969.
31. Fields WS, Lemak NA: Joint study of extracraninal arterial occlusion: VII, Subclavian steal: a review of 168 cases. *JAMA* 222(9): 1139–1143, 1972.
32. Song L, Zhang J, Li J, et al: Endovascular stenting vs. extrathoracic surgical bypass for symptomatic subclavian steal syndrome. *J Endovasc Ther* 19(1):44–51, 2012.
33. Ferguson TB, Jr, Coombs LP, Peterson ED: Internal thoracic artery grafting in the elderly patient undergoing coronary artery bypass grafting: room for process improvement? *J Thorac Cardiovasc Surg* 123(5):869–880, 2002.
34. Norsa A, Gamba G, Ivic N, et al: The coronary subclavian steal syndrome: an uncommon sequel to internal mammary-coronary artery bypass surgery. *Thorac Cardiovasc Surg* 42(6):351–354, 1994.
35. Saydjari R, Upp JR, Wolma FJ: Coronary-subclavian steal syndrome following coronary artery bypass grafting. *Cardiology* 78(1):53–57, 1991.

41 Chronic Mesenteric Ischemia: Diagnosis and Intervention

CHRISTOPHER J. WHITE

KEY POINTS

- Atherosclerotic stenoses commonly involve the major mesenteric arteries (celiac, superior mesenteric, and inferior mesenteric) but rarely cause symptomatic mesenteric ischemia because of the excellent collateral circulation that interconnects the visceral vascular beds.
- The classic presentation is postprandial abdominal pain with weight loss. Patients with functional bowel complaints rarely have significant weight loss.
- Patients with suspected chronic mesenteric ischemia (CMI) commonly have atherosclerosis involving other vascular territories such as coronary disease, stroke, renovascular disease, or lower extremity atherosclerotic disease.
- Symptomatic mesenteric ischemia usually results from disease affecting two or more vessels. Single-vessel disease of the mesenteric circulation is a rare cause of symptomatic mesenteric ischemia but may occur after an abdominal surgery that interrupts the collateral circulation.
- Noninvasive testing with ultrasound, computed tomographic angiography, or magnetic resonance angiography is an appropriate screening test in patients with suspected CMI.
- Invasive digital subtraction angiography requires a lateral view to visualize the origins of the mesenteric vessels as they arise anteriorly from the aorta.
- Catheter-based therapy with stents has largely replaced conventional open surgery as the treatment of choice for this disease.
- The clinical recurrence rate appears to be about 1 in 5 patients, so careful clinical and noninvasive follow-up is warranted.

BACKGROUND

Although the most common vascular disorder involving the intestines is ischemia, the clinical syndrome of chronic mesenteric ischemia (CMI), or chronic intestinal ischemia, is very unusual. Other etiologies associated with this uncommon syndrome include fibromuscular dysplasia, Buerger disease, and aortic dissection, but atherosclerosis is by the far the most frequent cause. Atherosclerotic disease of the aorta with associated aorto-ostial stenosis of the visceral vessels is a relatively common angiographic finding but an infrequent clinical problem.

In a population-based prevalence study of mesenteric artery stenosis, 553 healthy Medicare beneficiaries were screened with abdominal ultrasound for evidence of mesenteric disease.[1] In 17.5% of the total cohort, there was significant narrowing of a mesenteric vessel (>50% diameter stenosis), and more than 97% of these cases represented isolated celiac artery narrowing. There was no correlation with age, race, gender, or body mass index and the presence of mesenteric artery stenosis. Only 1.3% of the patients had involvement of more than one mesenteric vessel.

Another natural history study reported on a group of 980 asymptomatic patients with mesenteric ischemia who were monitored clinically.[2] Only three patients eventually developed symptoms, each with three mesenteric vessels severely affected. The most likely explanation for the infrequent occurrence of CMI in clinical practice is the redundancy of the visceral circulation, which has multiple interconnections between the superior mesenteric artery (SMA) and the inferior mesenteric artery (IMA).

CLINICAL PRESENTATION

Women are much more commonly affected (70%) than men. The classic presentation of this disease is postprandial abdominal discomfort with significant weight loss (Fig. 41-1). The abdominal discomfort associated with eating leads these patients to avoid food, causing them to lose weight. Patients with CMI typically avoid food and demonstrate significant weight loss. However, patients with ischemic gastropathy may have atypical presenting symptoms such as vomiting, diarrhea, constipation, ischemic colitis, or lower gastrointestinal bleeding. Most patients have evidence of atherosclerosis in other vascular beds and may have experienced prior myocardial infarction, stroke, or claudication.

Patients with atypical symptoms can be very difficult to diagnose, but a high degree of suspicion for CMI in patients with other manifestations of atherosclerosis and unexplained weight loss is appropriate. Often, the diagnosis is delayed in patients who are being evaluated for a possible malignancy as an explanation for their weight loss. Patients with functional bowel complaints rarely experience significant weight loss, which helps to differentiate them from CMI patients. Evidence of significant obstruction of two or more of these mesenteric vessels is often found when classic symptoms and endoscopy suggest bowel ischemia,[3] although single-vessel disease, usually of the SMA, has been described, particularly if collateral connections have been disrupted by prior abdominal surgery.

DIAGNOSIS

The diagnosis of CMI is a clinical one, based on symptoms and consistent anatomic findings. If there is a high clinical suspicion of CMI, patients should undergo Doppler ultrasound (duplex) imaging or noninvasive angiography with computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) to confirm their anatomy.

The ability to visualize the mesenteric vessels with duplex ultrasound is technically challenging and requires a skilled and dedicated sonographer. The reported accuracy for duplex imaging in identifying significant stenoses of the celiac artery and SMA approaches 90%.[4,5] With the relatively common application of CTA and MRA imaging for abdominal pathology, it is now possible to make the "anatomic" diagnosis without performing an invasive procedure.[6]

Invasive digital subtraction angiography is useful for diagnosis but requires a lateral aortogram to visualize the ostia of the mesenteric vessels (Fig. 41-2). Occasionally, an enlarged collateral vessel connecting a branch of the IMA with the SMA (arc of Riolan) is seen on the anteroposterior aortogram; it is an indication of proximal mesenteric artery disease. When critical stenoses (≥70%) in multiple vessels are found in symptomatic patients, revascularization is appropriate. However, in patients with borderline lesions or questionable symptoms, there is no stress test to confirm mesenteric ischemia.

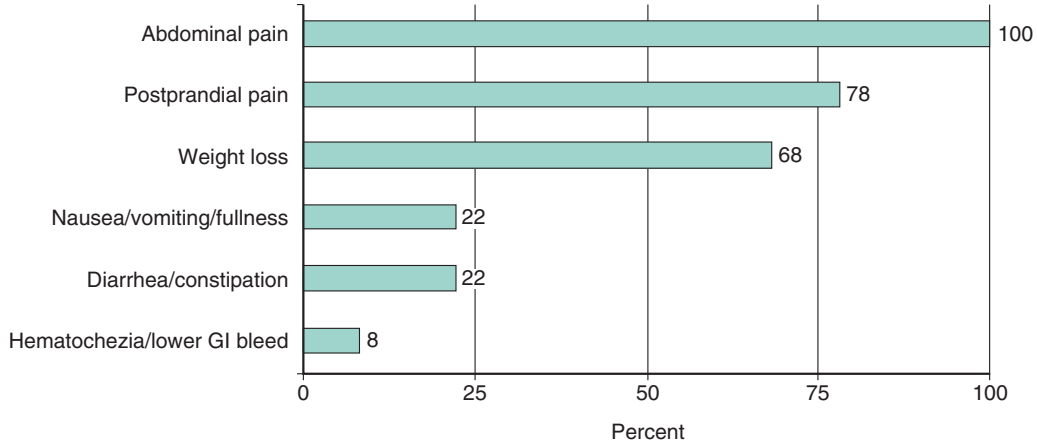

FIGURE 41-1 Initial clinical presentation of CMI patients. (From Silva JA, White CJ, Collins TJ, et al: Endovascular therapy for chronic mesenteric ischemia. *J Am Coll Cardiol* 47:944-950, 2006.)

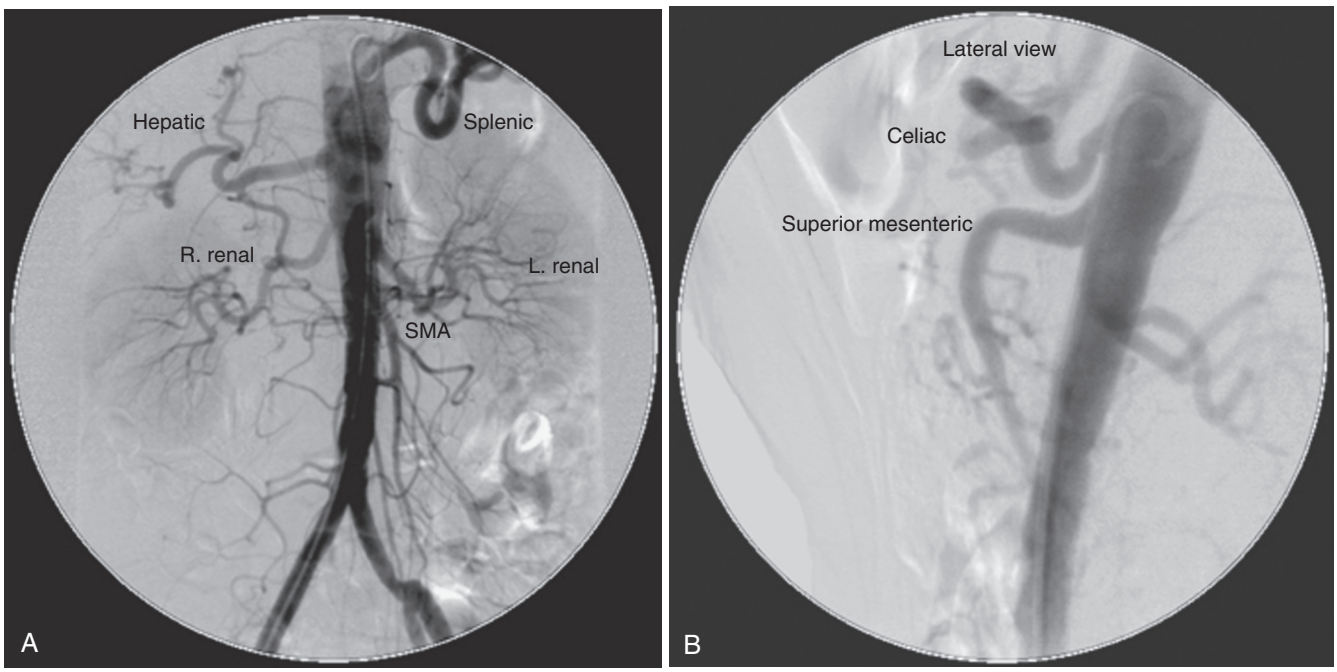

FIGURE 41-2 **A,** Anteroposterior view of an abdominal aortogram shows the branches of the celiac artery (hepatic and splenic), the right (R.) and left (L.) renal arteries, and the superior mesenteric artery (SMA). **B,** Lateral view of an abdominal aortogram shows the origin of the celiac and superior mesenteric arteries.

TREATMENT

Revascularization has traditionally been performed via open surgery with either endarterectomy or bypass grafting. However, this patient group has a high incidence of underlying coronary artery disease, and the perioperative surgical mortality rate ranges from 3.5% to 15% (Table 41-1),[7-22] with the highest incidence of complications occurring in patients older than 70 years of age.[23,24]

Atherosclerotic aorto-ostial obstructions of the visceral vessels are similar to those of the renal arteries, and the technical considerations for percutaneous transluminal angioplasty (PTA) with stent placement are similar to those for renal artery intervention (Fig. 41-3). As with renal interventions, stent placement offers a superior late patency compared to PTA alone.[25] The endovascular approach circumvents the need for general anesthesia and the operative trauma associated with open surgery, and it is believed to result in lower rates of acute mortality and morbidity (Table 41-2).[3,17,25-36]

Because of the relative infrequency of this disease, there are no randomized trials comparing surgery to endovascular treatment for CMI. The 20-year (1977-1997) Cleveland Clinic experience in 85 patients who had CMI treated with surgery demonstrated an 8% perioperative mortality rate, and one third of the patients had a major complication of surgery.[16] Advanced age, hypertension, coronary disease, and disease in other vascular beds correlated with surgical complications. At late follow-up, 23% ($n = 18$) had objective evidence of restenosis, 21% ($n = 16$) had recurrent CMI symptoms, and 12% ($n = 9$) underwent target-vessel revascularization). Use of vein conduit as graft material was associated with poorer patency, compared with

TABLE 41-1 Surgical Outcomes for Chronic Mesenteric Ischemia

Author	Year	No. Patients	No. Vessels	Technical Success (%)	30-Day Mortality (%)	Symptom Relief (%)	Restenosis (%)
Kieny et al[7]	1990	60	69	100	3.5	NA	25
Cormier et al[8]	1991	32	90	100	9	NA	9
Cunningham et al[9]	1991	74	194	100	12	86	NA
McAfee et al[10]	1992	58	119	100	10	90	10
Calderon et al[11]	1992	20	36	100	0	100	0
Christensen et al[12]	1994	90	109	100	13	NA	NA
Gentile et al[13]	1994	26	29	100	10	89	11
Johnston et al[14]	1995	21	43	100	0	NA	16
Moawad & Gewertz[15]	1997	24	38	100	4	78	23
Mateo et al[16]	1999	85	130	100	8	87	24
Sivamurthy et al[17]	2006	41	59	100	15	68	17
Atkins et al[41]	2007	49	88	100	4	88	20

NA, Not applicable.

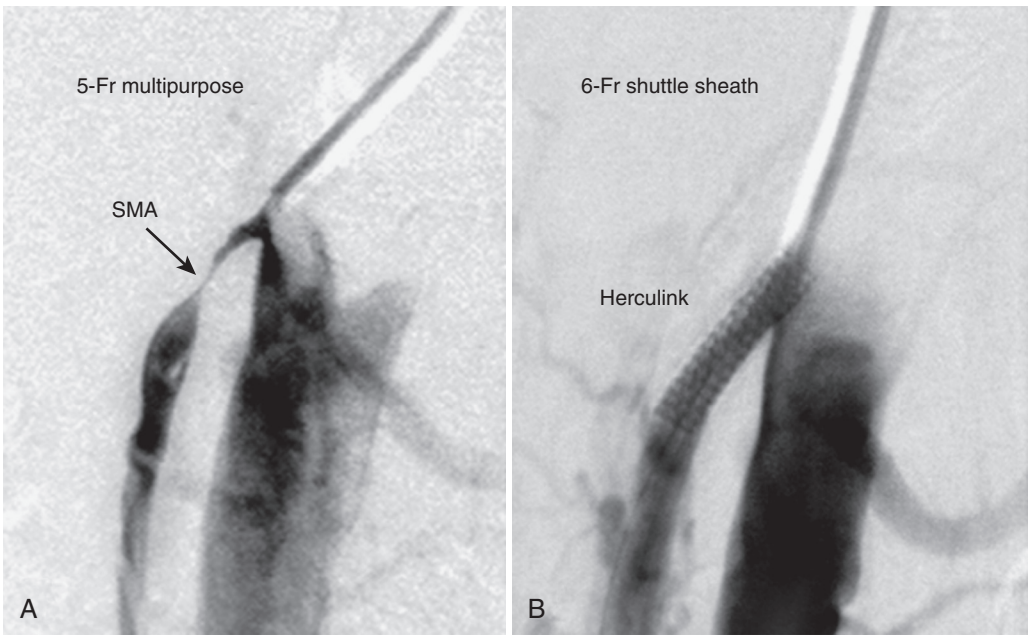

FIGURE 41-3 A, Baseline angiogram of tight proximal superior mesenteric artery (SMA) stenosis with brachial artery access. **B,** Final angiogram after deployment of balloon expandable stent.

Dacron graft material. The 5-year survival rate was 64% (95% confidence interval [CI], 53% to 75%), and the 3-year symptom-free survival rate was 81% (95% CI, 72% to 90%).

Data from Mayo Clinic on 229 consecutive CMI patients demonstrated a propensity for higher-risk patients with more comorbidities to be referred for angioplasty with stenting, whereas lower-risk patients tended to have open repair.[22] The researchers found that despite their lower-risk status, the surgical patients had greater morbidity and longer hospitalization compared with the endovascular group. They noted a higher restenosis rate for endovascular therapy, but there was no difference in secondary patency between surgery and stented patients.[16,22,31]

The largest single series of CMI patients included 59 patients and 79 vessels treated percutaneously at the Ochsner Medical Center.[34] The technical success rate was 96%, and symptom relief was achieved in 88% of the patients. There was one perioperative death (1.7%) and two access site complications. At a mean follow-up of 38 ± 15 months, 17% of the patients had recurrence of their symptoms, but none had developed acute mesenteric ischemia. All patients with recurrent symptoms underwent successful retreatment without complication. The in-stent restenosis rate at 14 ± 5 months, with 90% of the vessels imaged with CTA, invasive angiography, or duplex ultrasound, was 29% (Table 41-2). The target-vessel revascularization rate was 17%. The 5-year cumulative rates of freedom from death, symptom recurrence, or both were 72%, 79%, and 57%, respectively.

Complications of endovascular therapy can lead to serious consequences. In a series of 156 patients reported from Mayo Clinic, serious complications occurred in 7%, including branch perforation, distal embolization, vessel dissection, and stent embolization.[37] The use of antiplatelet therapy reduced the risk of embolization, and smaller platform equipment (0.014-inch versus 0.035-inch) reduced the risk of complications.

The Achilles heel of endovascular therapy has been restenosis. Recently, a nonrandomized 225-patient CMI case series suggested a

TABLE 41-2 Percutaneous Outcomes for Chronic Mesenteric Ischemia

Author	Year	No. Patients	No. Vessels	Technical Success (%)	30-Day Mortality (%)	Symptom Relief (%)	Restenosis (%)
Matsumoto et al[3]	1995	19	20	79	0	52	NA
Hallisey et al[26]	1995	16	25	84	6	75	25
Allen et al[27]	1996	19	24	95	5	79	NA
Maspes et al[28]	1997	23	41	90	0	75	12
Nyman et al[29]	1998	5	6	100	0	80	60
Sheeran et al[30]	1999	12	13	92	8	75	16
Kasirajan et al[31]	2001	28	32	100	11	66	27
AbuRahma et al[32]	2003	22	24	95	0	67	30
Sharafuddin et al[33]	2003	25	26	96	4	85	8
Landis et al[25]	2005	29	33	97	6.9	90	16.3
Sivamurthy et al[17]	2006	21	29	95.3	16	27	32
Silva et al[34]	2006	59	79	96	1.7	83	29
Atkins et al[41]	2007	31	42	97	3	84	20
Oderich et al[38]	2013	42	42	98	0	98	12

NA, Not applicable.

possible advantage for balloon expandable covered stents compared with bare metal stents.[38] Significant reduction in restenosis was seen in both de novo lesions and restenosis lesions. No potential for an increased risk of stent thrombosis was observed. The disadvantage of the balloon expandable covered stents is the requirement for a larger, 0.035-inch platform, rather than the smaller, safer, 0.014-inch stent platform. These encouraging data need confirmation in controlled trials.

Several papers have summarized noncontemporaneous comparisons of surgical therapy versus catheter-based therapies for CMI.[39-43] Complete surgical revascularization has benefits in terms of midterm patency, but usually at a cost of significant morbidity and mortality for the patients. Endovascular approaches are preferred in patients who are at increased risk for surgery, including those with severe comorbidities, including severe cachexia and a hostile abdomen. For lower-risk patients, either procedure is a reasonable alternative, and treatment selection should be governed by the patient's informed choice.

CONCLUSION

The infrequent occurrence of CMI has made randomized controlled trials comparing treatment outcomes very difficult to perform. Case series have shown that percutanous therapy with stent placement offers the lowest morbidity and roughly equivalent long-term outcomes compared to surgery. The current treatment recommendation is that patients who are candidates for either surgery or percutaneous therapy should receive percutaneous therapy with stent placement.

REFERENCES

1. Hansen KJ, Wilson DB, Craven TE, et al: Mesenteric artery disease in the elderly. *J Vasc Surg* 40:45–52, 2004.
2. Thomas JH, Blake K, Pierce GE, et al: The clinical course of asymptomatic mesenteric arterial stenosis. *J Vasc Surg* 27:840–844, 1998.
3. Matsumoto AH, Tegtmeyer CJ, Fitzcharles EK, et al: Percutaneous transluminal angioplasty of visceral arterial stenoses: results and long-term clinical follow-up. *J Vasc Interv Radiol* 6:165–174, 1995.
4. Bowersox JC, Zwolak RM, Walsh DB, et al: Duplex ultrasonography in the diagnosis of celiac and mesenteric artery occlusive disease. *J Vasc Surg* 14:780–786, discussion 786–788, 1991.
5. Zwolak RM, Fillinger MF, Walsh DB, et al: Mesenteric and celiac duplex scanning: a validation study. *J Vasc Surg* 27:1078–1087, discussion 1088, 1998.
6. Chow LC, Chan FP, Li KC: A comprehensive approach to MR imaging of mesenteric ischemia. *Abdom Imaging* 27:507–516, 2002.
7. Kieny R, Batellier J, Kretz JG: Aortic reimplantation of the superior mesenteric artery for atherosclerotic lesions of the visceral arteries: sixty cases. *Ann Vasc Surg* 4:122–125, 1990.
8. Cormier JM, Fichelle JM, Vennin J, et al: Atherosclerotic occlusive disease of the superior mesenteric artery: late results of reconstructive surgery. *Ann Vasc Surg* 5:510–518, 1991.
9. Cunningham CG, Reilly LM, Rapp JH, et al: Chronic visceral ischemia: three decades of progress. *Ann Surg* 214:276–287, discussion 287–238, 1991.
10. McAfee MK, Cherry KJ, Jr, Naessens JM, et al: Influence of complete revascularization on chronic mesenteric ischemia. *Am J Surg* 164:220–224, 1992.
11. Calderon M, Reul GJ, Gregoric ID, et al: Long-term results of the surgical management of symptomatic chronic intestinal ischemia. *J Cardiovasc Surg (Torino)* 33:723–728, 1992.
12. Christensen MG, Lorentzen JE, Schroeder TV: Revascularisation of atherosclerotic mesenteric arteries: experience in 90 consecutive patients. *Eur J Vasc Surg* 8:297–302, 1994.
13. Gentile AT, Moneta GL, Taylor LM, Jr, et al: Isolated bypass to the superior mesenteric artery for intestinal ischemia. *Arch Surg* 129:926–931, discussion 931–932, 1994.
14. Johnston KW, Lindsay TF, Walker PM, Kalman PG: Mesenteric arterial bypass grafts: early and late results and suggested surgical approach for chronic and acute mesenteric ischemia. *Surgery* 118:1–7, 1995.
15. Moawad J, Gewertz BL: Chronic mesenteric ischemia: clinical presentation and diagnosis. *Surg Clin North Am* 77:357–369, 1997.
16. Mateo RB, O'Hara PJ, Hertzer NR, et al: Elective surgical treatment of symptomatic chronic mesenteric occlusive disease: early results and late outcomes. *J Vasc Surg* 29:821–831, discussion 832, 1999.
17. Sivamurthy N, Rhodes JM, Lee D, et al: Endovascular versus open mesenteric revascularization: immediate benefits do not equate with short-term functional outcomes. *J Am Coll Surg* 202:859–867, 2006.
18. Foley RN, Parfrey PS, Kent GM, et al: Serial change in echocardiographic parameters and cardiac failure in end-stage renal disease. *J Am Soc Nephrol* 11:912–916, 2000.
19. Jimenez JG, Huber TS, Ozaki CK, et al: Durability of antegrade synthetic aortomesenteric bypass for chronic mesenteric ischemia. *J Vasc Surg* 35:1078–1084, 2002.
20. Kihara TK, Blebea J, Anderson KM, et al: Risk factors and outcomes following revascularization for chronic mesenteric ischemia. *Ann Vasc Surg* 13:37–44, 1999.
21. Leke MA, Hood DB, Rowe VL, et al: Technical consideration in the management of chronic mesenteric ischemia. *Am Surg* 68:1088–1092, 2002.
22. Oderich GS, Bower TC, Sullivan TM, et al: Open versus endovascular revascularization for chronic mesenteric ischemia: risk-stratified outcomes. *J Vasc Surg* 49:1472–1479, e3, 2009.
23. Schermerhorn ML, Giles KA, Hamdan AD, et al: Mesenteric revascularization: management and outcomes in the United States, 1988-2006. *J Vasc Surg* 50:341–348, e1, 2009.
24. Park WM, Cherry KJ, Jr, Chua HK, et al: Current results of open revascularization for chronic mesenteric ischemia: a standard for comparison. *J Vasc Surg* 35:853–859, 2002.
25. Landis MS, Rajan DK, Simons ME, et al: Percutaneous management of chronic mesenteric ischemia: outcomes after intervention. *J Vasc Interv Radiol* 16:1319–1325, 2005.
26. Hallisey MJ, Deschaine J, Illescas FF, et al: Angioplasty for the treatment of visceral ischemia. *J Vasc Interv Radiol* 6:785–791, 1995.
27. Allen RC, Martin GH, Rees CR, et al: Mesenteric angioplasty in the treatment of chronic intestinal ischemia. *J Vasc Surg* 24:415–421, discussion 421–423, 1996.
28. Maspes F, Mazzetti di Pietralata G, Gandini R, et al: Percutaneous transluminal angioplasty in the treatment of chronic mesenteric ischemia: results and 3 years of follow-up in 23 patients. *Abdom Imaging* 23:358–363, 1998.
29. Nyman U, Ivancev K, Lindh M, Uher P: Endovascular treatment of chronic mesenteric ischemia: report of five cases. *Cardiovasc Intervent Radiol* 21:305–313, 1998.
30. Sheeran SR, Murphy TP, Khwaja A, et al: Stent placement for treatment of mesenteric artery stenoses or occlusions. *J Vasc Interv Radiol* 10:861–867, 1999.
31. Kasirajan K, O'Hara PJ, Gray BH, et al: Chronic mesenteric ischemia: open surgery versus percutaneous angioplasty and stenting. *J Vasc Surg* 33:63–71, 2001.
32. AbuRahma AF, Stone PA, Bates MC, Welch CA: Angioplasty/stenting of the superior mesenteric artery and celiac trunk: early and late outcomes. *J Endovasc Ther* 10:1046–1053, 2003.
33. Sharafuddin MJ, Olson CH, Sun S, et al: Endovascular treatment of celiac and mesenteric arteries stenoses: applications and results. *J Vasc Surg* 38:692–698, 2003.
34. Silva JA, White CJ, Collins TJ, et al: Endovascular therapy for chronic mesenteric ischemia. *J Am Coll Cardiol* 47:944–950, 2006.
35. Cognet F, Ben Salem D, Dranssart M, et al: Chronic mesenteric ischemia: imaging and percutaneous treatment. *Radiographics* 22:863–879, discussion 879–880, 2002.

36. Matsumoto AH, Angle JF, Spinosa DJ, et al: Percutaneous transluminal angioplasty and stenting in the treatment of chronic mesenteric ischemia: results and longterm followup. *J Am Coll Surg* 194:S22–S31, 2002.
37. Oderich GS, Tallarita T, Gloviczki P, et al: Mesenteric artery complications during angioplasty and stent placement for atherosclerotic chronic mesenteric ischemia. *J Vasc Surg* 55:1063–1071, 2012.
38. Oderich GS, Erdoes LS, Lesar C, et al: Comparison of covered stents versus bare metal stents for treatment of chronic atherosclerotic mesenteric arterial disease. *J Vasc Surg* 58:1316–1323, 2013.
39. van Petersen AS, Kolkman JJ, Beuk RJ, et al: Open or percutaneous revascularization for chronic splanchnic syndrome. *J Vasc Surg* 51:1309–1316, 2009.
40. Davies RSM, Wall ML, Silverman SH, et al: Surgical versus endovascular reconstruction for chronic mesenteric ischemia: a contemporary UK series. *Vasc Endovascular Surg* 43:157–164, 2009.
41. Atkins MD, Kwolek CJ, LaMuraglia GM, et al: Surgical revascularization versus endovascular therapy for chronic mesenteric ischemia: a comparative experience. *J Vasc Surg* 45:1162–1171, 2007.
42. Dias NV, Acosta S, Resch T, et al: Mid-term outcome of endovascular revascularization for chronic mesenteric ischaemia. *Br J Surg* 97:195–201, 2010.
43. Oderich GS, Malgor RD, Ricotta JJ, 2nd: Open and endovascular revascularization for chronic mesenteric ischemia: tabular review of the literature. *Ann Vasc Surg* 23:700–712, 2009.

Renal Artery Stenosis

42

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KEY POINTS

- Renal artery stenosis (RAS) is caused by a heterogeneous group of diseases with various causes, clinical manifestations, courses, treatments, and outcomes. Atherosclerotic renal artery sclerosis and fibromuscular dysplasia are the most common causes of renal artery sclerosis.
- Patients in whom atherosclerosis is progressive may have signs and symptoms of chronic ischemic renal disease, resulting in renovascular hypertension and renal dysfunction. However, the causal relationship between RAS, hypertension, and renal dysfunction is difficult to prove.
- Duplex Doppler ultrasonography, when performed noninvasively in a high-volume, experienced vascular laboratory, is an excellent diagnostic tool and ideal for surveillance. The specificity and sensitivity of ultrasound is competitive with computed tomography angiography and magnetic resonance angiography, but ultrasound has a lower cost.
- Renal arteriography remains the gold standard for the diagnosis of atherosclerotic renal artery sclerosis, allowing full definition of the perirenal abdominal aorta and assessment of the diameter and contour of the renal artery and its branch vessels. However, angiographic evaluation of the severity of atherosclerosis (i.e., percent diameter stenosis) alone may be inadequate in establishing the cause and effect between atherosclerotic renal artery sclerosis and hypertension or renal dysfunction.
- The CORAL study demonstrated that renal artery stenting does not confer a significant benefit for the prevention of clinical events when added to comprehensive, multifactorial medical therapy in people with RAS and hypertension or kidney disease.
- Accepted consensus indications for renal artery revascularization include severe, refractory hypertension; recurrent pulmonary edema; and progressive renal insufficiency despite optimal medical therapy. However, these recommendations are based on limited supporting clinical trial evidence.
- Percutaneous revascularization with bare-metal stents represents the current endovascular standard of care for atherosclerotic patients with appropriate clinical indications. The clinical effectiveness and safety of adjunctive renal endovascular technologies (i.e., distal protection devices) and medications (i.e., glycoprotein IIb/IIIa inhibitors) have not been established in robust clinical trials.
- Percutaneous radiofrequency renal sympathetic denervation is safe, but its efficacy has not been demonstrated in a randomized, blinded, sham-controlled study.

Atherosclerotic renal artery stenosis (ARAS) is associated with chronic renal ischemia and increased cardiovascular morbidity and mortality. The primary aim of renal revascularization therapies is to improve blood pressure control, salvage renal function, and reduce cardiovascular risk. Although technical advances in the endovascular treatment of ARAS have improved dramatically in the past decade, allowing patients with more extensive ARAS to be considered for revascularization, the indications for treating these patients remain controversial and highlight the major divergence in practice among physicians regarding the appropriate treatment for patients with ARAS.[1] Small and large prospective, randomized clinical trials from Europe have failed to demonstrate the clinical benefit of renal revascularization in reducing cardiovascular events or poor renal outcomes compared with medical therapy alone.[2-4] Determining the essential role of renal revascularization and appropriate patient selection has become the central issue among physicians. Consensus regarding the technical aspects of renal stent revascularization has reached a general level of acceptance among interventionalists.

The emergence of percutaneous renal sympathetic denervation as a safe and effective technology in the treatment of drug-resistant hypertensive patients has highlighted the important role of the sympathetic nervous system in hypertension.[5] Ongoing large clinical trials in the treatment of hypertension and renal insufficiency in these patient populations, with and without ARAS, will ensure that renal interventional therapies for hypertension control will remain an exciting area of clinical research.

EPIDEMIOLOGY AND NATURAL HISTORY

ARAS is the most common secondary cause of hypertension. Left untreated, it may progress to renal dysfunction. The prevalence of end-stage renal disease in the United States is 372,407 patients per year, with approximately 100,000 new cases diagnosed each year[6]; 2.1% of these new cases are attributed to ARAS.[7] ARAS is reported in 0.5% to 5%[8] of all hypertensive patients and 45% of patients with severe or malignant hypertension.[9]

The prevalence of ARAS increases with age, especially in patients with diabetes, hypertension, coronary artery disease (CAD), or aortoiliac occlusive disease.[10] A population-based study reported a prevalence of renal artery stenosis (RAS) (>60% stenosis) to be 6.8% among patients older than age 65.[11]

In a Mayo Clinic series, more than 19% of patients with CAD and hypertension were found to have greater than 50% stenosis of the renal arteries.[12] The risk factors for the development of ARAS are similar to those of CAD. Similarly, stroke and peripheral arterial disease (PAD) are highly prevalent among patients with end-stage renal disease on hemodialysis. ARAS is progressive in 36% to 71% of patients with this condition, and 39% of patients with greater than 75% ARAS progress to complete occlusion within the 3-year follow-up.[13] In a prospective study of 84 patients with at least one abnormal renal artery, progression of RAS occurred at a rate of approximately 20% per year.[14] Unfortunately, it is difficult to identify the subset of patients who will progress to renal failure.

Although 90% of renal artery lesions are atherosclerotic, the remaining 10% result from other causes. Fibromuscular dysplasia (FMD), the second most common cause of RAS, results in fibrous thickening of the intima, media, or adventitia of the arterial wall. FMD is more common among women between the ages of 15 and 50 years and is recognized by its beaded appearance on angiography.[15] Less common causes include trauma, dissection, external compression by a tumor or mass, thromboemboli, renal artery aneurysms, neurofibromatosis, vasculitis, retroperitoneal fibrosis, and radiation-induced stenosis.[16]

PATHOPHYSIOLOGY OF RENOVASCULAR HYPERTENSION AND ISCHEMIC NEPHROPATHY

The renal vasculature is richly innervated by sympathetic afferent and efferent nerve fibers that control renovascular resistance and the resultant increase in renin release.[17] Efferent renal nerve activity is controlled by several inputs, such as aortic and carotid baroreflexes[18] and cardiac stretch receptors.[19] Renal nerves often receive greater sympathetic activation than others, especially in the setting of essential hypertension.[20] This disproportionate increase in renal sympathetic activity results in increased renovascular resistance and increased plasma renin activity, and it promotes the retention of sodium and water.[21] The afferent renal nerves contribute to the pathogenesis of renovascular hypertension by increasing activation of the sympathetic nervous system.[17]

In unilateral ARAS, decreased blood flow through the affected kidney results in increased production of renin, which cleaves angiotensin to produce angiotensin I, which is converted to angiotensin II. Angiotensin II is a direct vasoconstrictor that stimulates aldosterone secretion and results in sodium reabsorption. The retained salt and water is then excreted by the unaffected kidney, producing a renin-dependent hypertensive state. In bilateral ARAS or ARAS in a solitary functioning kidney without the ability to sense an elevated blood pressure, pressure natriuresis does not occur, resulting in volume expansion and suppression of renin activity. These patients become highly dependent on angiotensin II for glomerular filtration. Angiotensin II maintains the efferent arteriolar tone of the glomeruli. When angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are administered, the efferent arteriolar tone is no longer maintained, and glomerular filtration is decreased, resulting in renal insufficiency. Sodium restriction and diuresis convert bilateral RAS to a renin-mediated form of hypertension.[22]

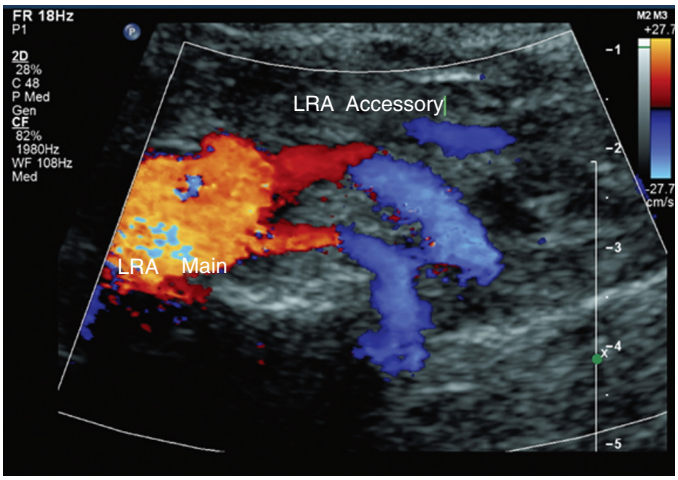

FIGURE 42-1 Main and accessory left renal arteries (LRA) as defined on duplex ultrasound.

DIAGNOSTIC TESTS AND IMAGING

Duplex ultrasound, computed tomography angiography (CTA), and magnetic resonance angiography (MRA) are contemporary noninvasive imaging modalities used to diagnose RAS. Other tests can be used to assess the potential physiologic effect of RAS.

Ultrasonography

Duplex ultrasonography is a useful noninvasive test to screen for RAS, with sensitivity between 75% and 98% and specificity between 87% and 100%.[23] Its sensitivity in identifying accessory renal arteries is 67% (Fig. 42-1). Duplex ultrasonography can produce images of the renal arteries, assess blood flow velocity and pressure waveforms, and measure kidney size without contrast or radiation exposure (Figs. 42-2 and 42-3). Estimation of renal artery percent diameter stenosis is based on the renal artery velocity and the ratio of renal artery to aortic velocity (Table 42-1), and antihypertensive medications do not interfere with duplex imagining. It can also provide information regarding renal parenchymal disease, tumors, and calculi. It is less expensive than CTA or MRA, can be used for renal artery stenting surveillance, and can be easily performed at the patient's bedside. Unfortunately, early studies of this technology reported a 10% to 20% rate of failure due to operator inexperience, patient obesity, or bowel gas.[23] The test may be time consuming when done by inexperienced technologists.

The renal resistive index (RI) is a commonly used measure of resistance to arterial flow within the renal vascular bed. It is calculated during duplex ultrasonography (see Fig. 42-3).

Peak Systolic Renal Parenchymal Velocity

An elevated RI is considered to be an indicator of nephrosclerosis and intrinsic kidney disease. Radermacher and colleagues used an RI greater than 0.8 as the sole screening tool to identify a patient subset

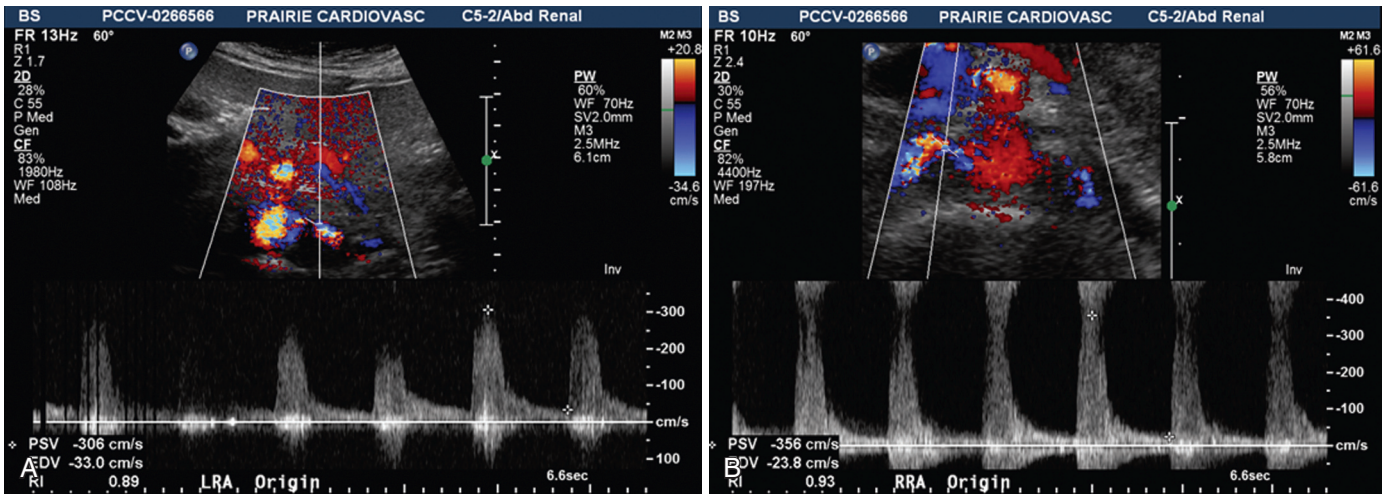

FIGURE 42-2 **A** and **B,** Bilateral renal artery stenosis of 60% to 99% on duplex ultrasonography in a 69-year-old woman.

that may have a less than optimal response of blood pressure control and improved renal function with renal artery stent revascularization.[24] However, these findings were refuted by other studies suggesting improved renal function and blood pressure control after successful renal artery stenting.[25,26] RI should not be considered the sole parameter in deciding whether a patient will have a clinically favorable response to percutaneous renal revascularization.

Magnetic Resonance Angiography and Computed Tomography Angiography

MRA and CTA, both excellent noninvasive techniques to evaluate patients for possible renal pathology, are widely available. If duplex ultrasonography is nondiagnostic, these modalities can be used to confirm the findings of duplex ultrasound and used for patients whose anatomy is unfavorable for invasive angiography. However, CTA does require the use of iodinated contrast. Both CTA and MRI can provide additional visualization of the aorta, accessory renal arteries, and renal parenchymal anatomy.

MRA requires no contrast but cannot be used in patients with ferromagnetic devices or those who are claustrophobic. Stented vessels cannot be adequately evaluated by MRA. Grobner and Marckmann and colleagues postulated that the gadolinium used in MRA was causative in the development of nephrogenic fibrosing dermopathy.[27,28] Since then, the use of MRA has been restricted to patients with a serum creatinine level less than 1.5 to 2.0 mg/dL. The sensitivity and specificity of MRA are 62% and 84%, respectively.[29] The drawbacks of CTA include large contrast load and nephrotoxicity, along with the radiation exposure. The sensitivity and specificity of CTA are 64% and 92%, respectively.[29] CTA can also be used for stent surveillance if duplex ultrasonography is nondiagnostic (Fig. 42-4).

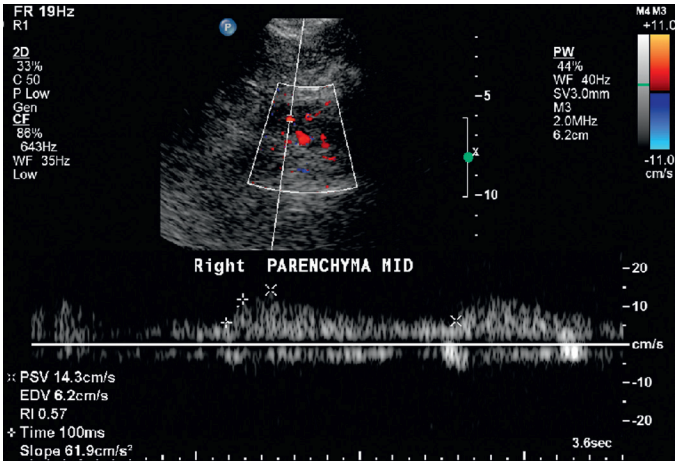

FIGURE 42-3 Resistive index (RI) and prolonged acceleration time (≥100 msec) in a patient with 60% to 99% renal artery stenosis.

TABLE 42-1 American College of Cardiology/American Heart Association Peripheral Arterial Guidelines for the Management of Renal Artery Stenosis

Degree of Stenosis (%)	Duplex Criteria
0-59	RAR < 3.5 and renal artery PSV < 200 cm/sec
60-99	RAR ≥ 3.5 or renal artery PSV > 200 cm/sec (and flow turbulence)
Occluded	Absence of arterial flow and low-amplitude signal

PSV, Peak systolic velocity; *RAR,* renal-aortic ratio.

FUNCTIONAL ASSESSMENT OF RENAL ARTERY STENOSIS

Brain natriuretic peptide (BNP) is secreted by ventricular myocytes in response to increased myofibril stretch. Its production is also stimulated by angiotensin II, which is elevated in patients with RAS, and by hypertension. BNP antagonizes plasma renin activity and promotes diuresis and sodium excretion. Silva and colleagues studied the role of BNP levels in patients with RAS and hypertension.[30] In this small study, baseline BNP was elevated in patients with severe ARAS. A significant blood pressure response to renal stenting was seen in patients with elevated baseline BNP levels. The test may be useful in identifying patients with renovascular hypertension who would be likely to respond to stent revascularization; however, larger confirmatory studies are required to prove this.

Radionuclide imaging has been historically used to diagnose unilateral RAS. With this technique, a detector gamma camera is used to assess baseline renal flow by injecting a radionuclide tracer (^{99m}Tc diethylene triamine pentaacetic acid [DTPA]). Repeat scans are performed after administering the ACEI captopril, which decreases renal function on the ipsilateral side of RAS, whereas the uptake of the unaffected side is normal or increased. The reported sensitivity and specificity are 90% and 93%, respectively.[31,32] The wide availability of duplex ultrasound, CTA, and MRA has resulted in the near elimination of this test to diagnose RAS. It is occasionally used for cortical functional assessment of the ipsilateral and contralateral kidney in the setting of renal atrophy and RAS or for cortical functional assessment of a horseshoe kidney with RAS.

Plasma renin activity or plasma renin assay (PRA) has also been used as a screening test for renovascular hypertension. Plasma renin levels have a low specificity in the diagnosis of RAS, but the concomitant use of an ACEI improves the specificity of PRA levels. PRA is measured at baseline and 1 hour after oral administration of 50 mg of captopril. Unfortunately, the sensitivity ranges widely, between 34% and 100%, and the specificity varies from 80% to 90%.[33,34] In patients with bilateral or unilateral RAS in a solitary kidney, the sensitivity and specificity is this assay is much lower because the resultant volume overload suppresses PRA levels.

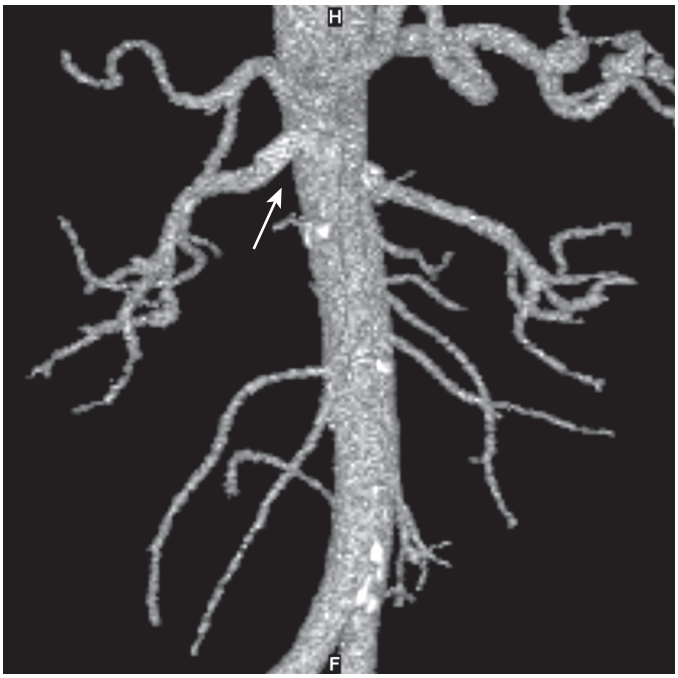

FIGURE 42-4 Computed tomography angiography images after right renal artery stenting demonstrates patency *(arrow)*.

Assessment of renal vein renin level is another test for diagnosing renovascular hypertension. It is performed using a catheter to compare the renin levels of both kidneys. Although it may identify blood pressure responders to endovascular intervention or surgery, it has fallen out of favor because of the invasive nature of the test. Measurement of plasma renin and renal vein renin activity is seldom needed in contemporary diagnosis and management of RAS because of the availability of noninvasive imaging modalities.

Identification of At-Risk Patients and Indications for Renal Artery Revascularization

ARAS should be suspected in patients with resistant hypertension or progressive renal insufficiency who have CAD or PAD. Specific clinical clues are listed in Table 42-2. Preprocedural identification of the patient with poorly controlled hypertension who is likely to benefit from renal stent revascularization is challenging. The recommendations of the American College of Cardiology/American Heart Association (ACC/AHA) for the management of PAD, including revascularization in RAS, are as listed in Table 42-3.[35] Appropriate indications for renal revascularization include unilateral RAS, bilateral RAS, or RAS involving a solitary functioning kidney in patients in whom blood pressure cannot be adequately controlled with maximal tolerable doses of at least three antihypertensive medications of different classes or if side effects of the antihypertensive medication prohibit sufficient control.[36]

In patients with unilateral RAS with normal renal function and well-controlled hypertension, revascularization may not be required. Instead, close follow-up for potential loss of pharmacologic control and accelerating hypertension or a potential decline in renal function may suffice. In these instances, a renal duplex ultrasound should be considered.

Patients who have undergone successful stent revascularization are often prescribed antiplatelet and statin therapies. The routine use of clopidogrel (Plavix) in combination with aspirin after successful stent revascularization has not been adequately evaluated, but most investigators use this combination in light of other indications (i.e., drug-eluting coronary stent implantation). Statins (HMG-CoA reductase inhibitors) are frequently given to patients with ARAS; these agents may slow the progression of renal atherosclerosis after renal revascularization and in some instances induce plaque regression.[37] Cheung and coworkers found a reduction of ARAS progression from 30% to 6% in patients without and with statins, respectively.[37] They also found 12 of 79 patients exhibited signs of disease regression.[37] Statins should therefore be considered for all patients with established dyslipidemia and ARAS.

TABLE 42-2 Clinical Clues Suggesting Renal Artery Stenosis

Hypertension beginning before age 30 or after age 55
Acute elevation of plasma creatinine levels or azotemia after initiation of ACEI or ARB
Patients with hypertension and asymmetric kidney size
Moderate to severe hypertension in patients with diffuse atherosclerosis
Recurrent congestive heart failure or flash pulmonary edema in a patient with hypertension
Malignant hypertension
Resistant hypertension
Epigastric bruit

ACEI, Angiotensin-converting enzyme inhibitor; *ARB,* angiotensin-receptor blocker.

TABLE 42-3 Duplex Ultrasound Criteria for a Diagnosis of Renal Artery Stenosis

Indication	Classification of Recommendation	Level of Evidence
Asymptomatic bilateral or unilateral RAS in a solitary kidney	IIb	C
Accelerated hypertension	IIa	B
Resistant hypertension	IIa	B
Hypertension and unexplained unilateral small kidney	IIa	B
Hypertension with intolerance to antihypertensive medications	IIa	B
Progressive kidney disease and bilateral RAS or RAS in a solitary kidney	IIa	B
Chronic renal insufficiency and unilateral RAS	IIb	C
Recurrent, unexplained CHF or sudden and unexplained pulmonary edema	I	B

CHF, Congestive heart failure; *RAS,* renal artery stenosis.

The CORAL Study

The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study was a open-label, randomized, international, multicenter, controlled clinical trial, sponsored by the National Heart, Lung, and Blood Institute (NHBLI) of the National Institutes of Health (NIH).[38] The study compared medical therapy alone with medical therapy plus renal artery stenting in patients with atherosclerotic RAS and elevated blood pressure or chronic kidney disease, or both. Patients with severe ARAS (>60% angiographic stenosis) with a systolic blood pressure of 155 mm Hg or higher although on two or more antihypertensive medications were eligible for enrollment in the trial. Although 5322 patients were screened, only 947 were randomized.

The primary end point was death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal insufficiency, or need for kidney replacement. Although the stent group had a modest but statistically significant lowering of systolic blood pressure (2.3 mm Hg, $P = .03$), this did not translate into a lowering of clinical events. Over a median follow-up time of 43 months, there was not a significant difference between the two treatment groups in the occurrence of the primary end point or any of its individual components or all-cause mortality. The study concluded that renal artery stenting did not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in people with RAS and hypertension or kidney disease.

There have been criticisms of the study. Patients with RAS of 60% or more could be enrolled in the study, and the mean degree of stenosis in the trial was 68%. There is debate about the severity of stenosis necessary to justify intervention. It is possible that patients with hemodynamically insignificant lesions were enrolled in the study. The study authors reported that in patients with more than 80% stenosis, as measured by the investigators, no clear benefit was seen. The trial took almost 5 years to complete enrollment. Some patients who were eligible were not enrolled because of the preference of their physicians, who might have been convinced of the clinical benefit of the RAS.

Despite the negative results of the study, there are still situations in which patients can benefit from renal artery stenting. Patients with severe RAS and refractory hypertension or declining renal function despite intensive medical therapy may benefit from renal artery stenting. Renal artery stenting should be considered for patients with severe RAS and recurrent acute pulmonary edema without an alternative cause.

Clinical Follow-Up

Patients must be monitored closely after renal artery intervention for recurrent or worsening hypertension or renal dysfunction. Although no medical society has offered guidelines, surveillance duplex ultrasonography should be considered every 6 months after the placement of a renal artery stent (Figs. 42-5 and 42-6). Four duplex ultrasound

criteria have been reported for the diagnosis of in-stent restenosis (ISR) (Table 42-4). If ISR is identified in a patient with stable renal function and well-controlled hypertension, the original indication for renal artery intervention should be reviewed, and close clinical monitoring should continue.

RENAL ENDOVASCULAR INTERVENTIONS

Invasive Assessment of Renal Ischemia

The first renal artery balloon angioplasty was reported by Andreas Grüntizig in Zurich, Switzerland, in 1977.[42] The initial endovascular strategies consisted of balloon angioplasty alone and were associated with relatively poor acute procedural success and poor patency rates. These outcomes were the direct result of heavy renal aorto-ostial plaque burden and calcification with resultant vessel recoil and/or dissections. However, with the introduction of balloon-expandable metal stents, many of the mechanical limitations of primary balloon angioplasty were overcome, with resultant acute procedural success rates as high as 98% and 9-month duplex Doppler binary restenosis rates of approximately 20% to 25%.[43]

Over the subsequent decade, the tools used for percutaneous renal artery intervention evolved rapidly, from hand-crimped stents on 5- or 6-Fr balloons designed on 0.035-inch wire systems to low-profile, 6-Fr, guiding catheter–compatible, premounted stent-balloon combinations on 0.014- to 0.018-inch wire systems designed specifically for renal interventions. Despite technical improvements, the enthusiasm for percutaneous renal artery stent revascularization has waxed and waned, in part because of the lack of clinical evidence supporting the effectiveness of renal stenting in ARAS patients to improve blood pressure and renal function.[2,4,44-46]

Although the limitations of the trials (i.e., visual estimate of ARAS degree of stenosis, significant crossover to the intervention therapy, lack of standardized methods of blood pressure and microcirculation assessment, and the definition of clinical success) have been well enumerated, patients in these studies were all selected on the basis of angiographic lesion severity. Use of this inclusion criterion reflects the commonly held belief that angiographic lesion severity is proportional to renal ischemia and that stent revascularization will result in clinical benefit. However, this paradigm has been challenged by several investigators,[47,48] underscoring the fact that although quantitative angiography improves the accuracy of assessment compared with visual estimation, it does not improve the accuracy of diagnosing renal ischemia. ARAS angiographic severity may often be overestimated compared with other modalities that may reflect the presence of renal ischemia.[49]

Among the other invasive modalities that can be used to assess ischemia is renal fractional flow reserve (FFR).[50] A series of reports by Belgian investigators emphasized the importance of the invasive physiologic assessment of ARAS lesions in preparation for renal revascularization in a well-selected group of patients. De Bruyne and colleagues demonstrated that the magnitude of the renal artery occlusion was proportional to the activation of the renin-angiotensin system and required at least a 10% gradient (Fig. 42-7). Follow-up work by Mangiacapra and coworkers suggested that similar invasive translesional

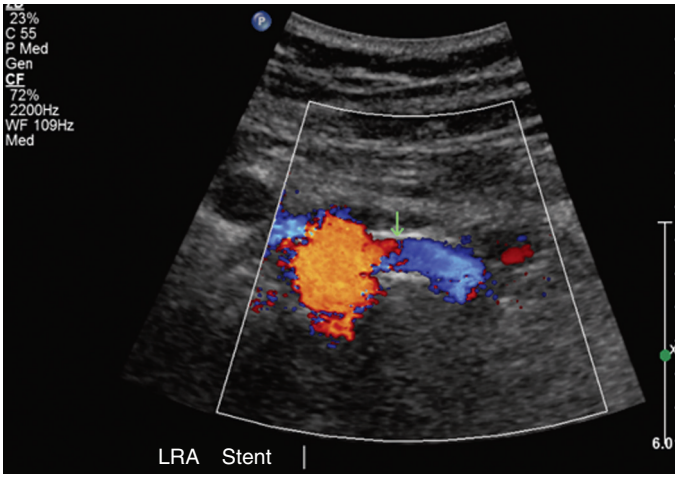

FIGURE 42-5 Follow-up renal artery duplex ultrasonography demonstrates a patent stent *(arrow)*.

TABLE 42-4 Ultrasound Criteria for the Diagnosis of In-Stent Restenosis

Percent In-Stent Restenosis (%)	Criteria
>60	PSV > 200 cm/sec or RAR > 3.5[38]
>60	PSV > 225 cm/sec or RAR > 3.5[39]
>70	PSV > 395 cm/sec or RAR > 5.1[40]
>60	PSV > 280 cm/sec or RAR > 4.5[41] (PTRAS after fenestrated and branched endovascular repair)

PSV, Peak systolic velocity; *PTRAS,* percutaneous transluminal renal artery stenting; *RAR,* renal-aortic ratio.

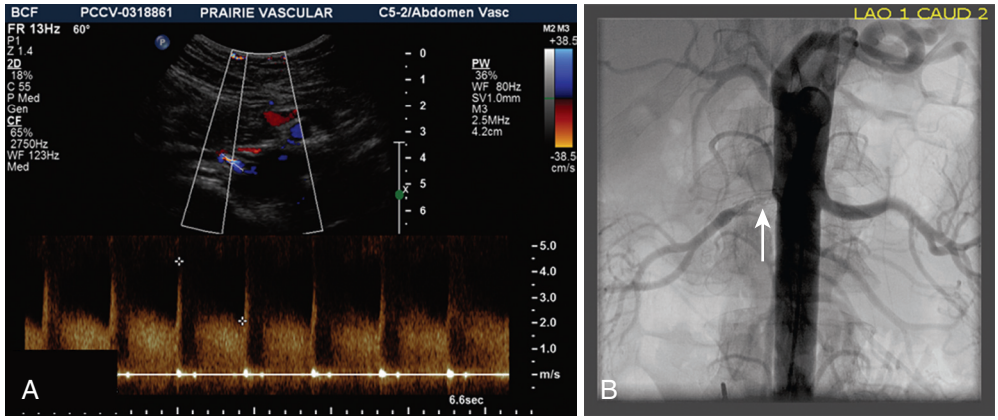

FIGURE 42-6 **A,** In-stent restenosis is demonstrated by duplex ultrasound with very high peak systolic (440 cm/sec) and end-diastolic (206 cm/sec) velocities. **B,** Right renal artery in-stent restenosis *(arrow)* is confirmed by contrast angiography.

pressure gradient assessment after a bolus administration of intraarterial dopamine might further improve the patient selection for renal stenting. In this small study ($N = 53$), a dopamine-induced mean pressure gradient of 20 mm Hg or more before revascularization was the sole independent predictor of blood pressure improvement at the 3-month follow-up. However, the investigators described an 18% nonresponder rate despite a dopamine-induced gradient of 20 mm Hg or more, underscoring the heterogeneity of the potential pathophysiologic mechanisms responsible for hypertension in this patient cohort.[1]

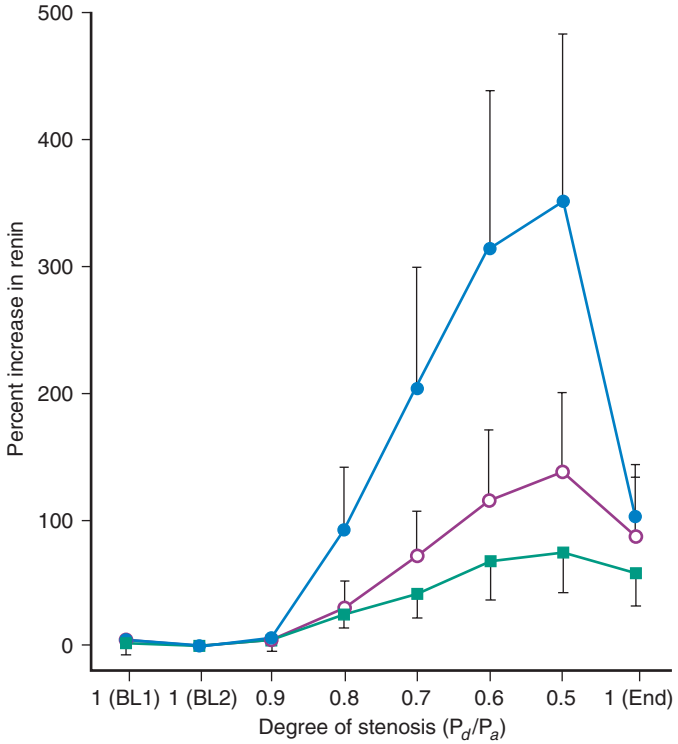

FIGURE 42-7 Effects of a balloon-induced, unilateral, controlled, graded stenosis, expressed as the ratio of distal pressure (P_d) corrected for aortic pressure (P_a). (Modified from De Bruyne B, Manoharan G, Pijls M, et al: Assessment of renal artery stenosis severity by pressure gradient measurements. *J Am Coll Cardiol* 48:1851-1855, 2006.)

Renal Contrast Angiography

Abdominal aortography should be performed before renal stenting. It assists in identifying the renal ostia, extent of ostial disease, accessory renal arteries, degree of perirenal aortic calcification, angulation of the renal artery takeoff from the aorta, and degree of aneurysmal enlargement of the abdominal aorta. If indicated, subsequent selective renal angiography can be performed with a series of 4-, 5-, or 6-Fr diagnostic catheters. Typical catheter configurations include internal mammary, renal double curve, Sos, and Cobra catheters. Left anterior oblique–angled views often assist in the identification of the right and left renal ostia.[51]

Renal Artery Stenting

All patients should be pretreated with aspirin therapy; the efficacy of adjunctive use of clopidogrel, although widely practiced, has not been adequately studied in renal stent patients. After sheath insertion, the patient should be fully anticoagulated with unfractionated heparin to obtain an activated coagulation time of at least 250 seconds. In most cases, arterial access is acquired in a retrograde approach from either common femoral artery. However, in patients with severe bilateral aortoiliac disease or tortuosity or a sharply downward-angulated renal artery, an antegrade radial or brachial approach may be considered.

In most cases, renal artery revascularization is performed using a 6-Fr guiding catheter. The guiding catheter should reflect the angle at which the renal artery arises off the aorta, location of the stenosis, anatomy of the perirenal aorta, and operator preference. The most commonly used guides are the internal mammary artery, renal standard curve, renal double curve, or hockey stick. The multipurpose guide is well suited for a brachial or radial approach. For the common femoral arterial approach, a sheath 35-cm long is preferable because it minimizes guide catheter manipulation in a potentially heavily diseased perirenal aorta and can facilitate guiding catheter exchanges over smaller diagnostic catheters if required.

The goal of renal artery intervention is to achieve an optimal angiographic and hemodynamic result with minimal manipulation of the renal artery and to minimize potential atheroembolization and dissection of the renal artery or aortic wall. The no-touch technique can be used in an attempt to minimize distal atheroembolization (Fig. 42-8). To use this technique, a 35-cm sheath is placed below the renal artery and a hand injection of contrast is performed to locate the renal ostium (see Fig. 42-8, *A*). A 0.035-inch, J-tip guidewire is advanced in the abdominal aorta superior to the renal arteries. Over this wire, the guide catheter is advanced in proximity to the renal artery. The 0.035-inch

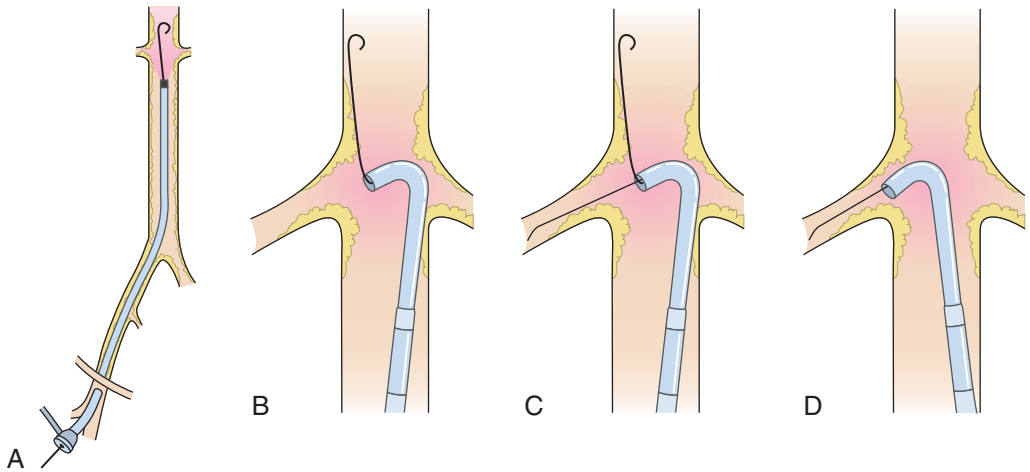

FIGURE 42-8 The no-touch technique: guiding the catheter. **A,** 35-cm sheath inserted over 0.035-inch guidewire. **B,** Guide catheter is positioned near renal artery ostium with soft portion of 0.035-inch wire out to protect the ostium. **C,** 0.014-inch wire is advanced into the renal artery. **D,** 0.035-inch guidewire is removed.

wire is then retracted to the soft portion of the wire so that the guide catheter begins to assume its shape and approach the ostium of the renal artery. The J-shaped portion of the wire is left outside to guide against the aortic wall (see Fig. 42-8, *B*).

The ostium of the guiding catheter is gently rotated and aligned with the renal ostium, with the J wire preventing guiding catheter intubation into the renal artery. From this position, a 0.014-inch wire is directed through the guide and into the distal renal artery (see Fig. 42-8, *C*). The 0.035-inch J wire is then removed, and the guide catheter is allowed to gently engage the ostium of the renal artery (see Fig. 42-8, *D*).

Another method for safely engaging the renal ostium is the exchange technique (Fig. 42-9). A 35-cm sheath is placed below the renal artery, and a hand injection of contrast is used to locate the renal ostium. A 4-Fr, soft-tipped diagnostic catheter is used to gently locate and engage the renal ostium (see Fig. 42-9, *B*). Use of a small, soft catheter minimizes the possibility of atheroembolization or dissection, which could be caused by a larger, stiffer guide. Once engaged, a 0.014- or 0.018-inch guidewire is passed through the diagnostic catheter and into the main renal artery (see Fig. 42-9, *C*). The diagnostic catheter is then removed (see Fig. 42-9, *D*), leaving the guidewire in place. A 6- or 7-Fr guide is placed over the guidewire, maintaining the 35-cm sheath below the renal artery and facilitating placement the guide (see Fig. 42-9, *E*). The renal predilation balloon can then be safely passed into the renal artery (see Fig. 42-9, *F*).

Another commonly used method for engaging the renal artery involves a dilator/guide system (Veripath Peripheral Guiding Catheter, Abbott Vascular Devices, Mountain View, CA). With this technique, the renal artery is wired with a 0.014-inch wire through the softer selective diagnostic catheter. With the 0.014-inch wire in the renal artery, the diagnostic catheter is removed, and the renal dilator/guide system is back-loaded onto the 0.014-inch wire. The dilator provides a smooth transition across the lesion and is gently withdrawn, allowing the guiding catheter to advance to the renal ostium; however, dottering of the renal lesion occurs with this technique, and the possibility of atheroembolization is a concern. The average diameter of a normal renal artery is approximately 5.0 to 6.0 mm, which depends on the presence of accessory renal arteries and poststenotic dilation.

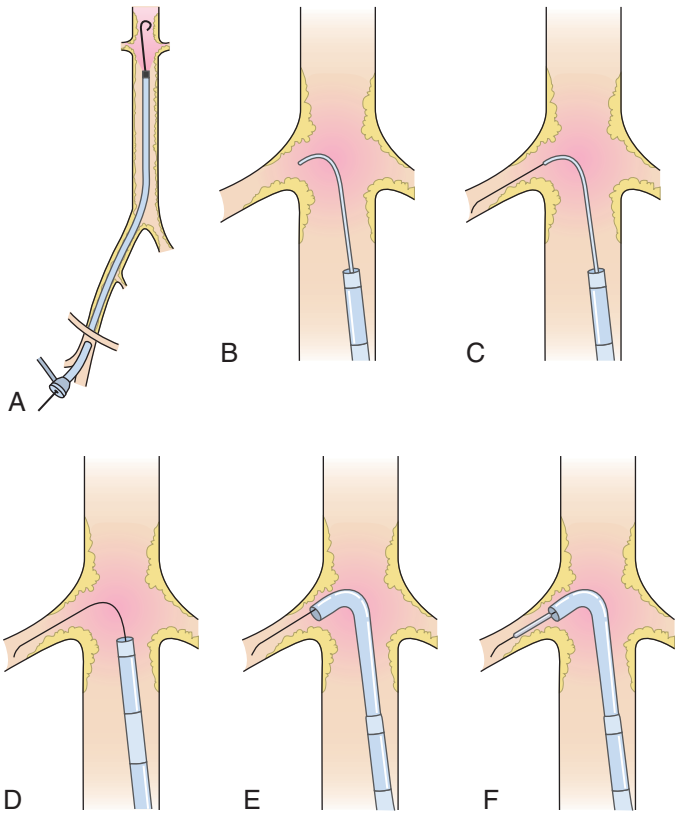

FIGURE 42-9 The exchange technique. **A,** 35-cm sheath inserted over 0.035-inch guidewire. **B,** Renal artery engaged with a 5-Fr diagnostic catheter. **C,** 0.014-inch wire inserted into the renal artery through the diagnostic catheter. **D,** Diagnostic catheter removed. **E,** Guide inserted over the 0.014-inch guidewire. **F,** Interventional equipment can be inserted.

Predilation of the renal lesion is highly recommended and should be performed with a balloon diameter slightly smaller than that of the renal reference vessel. Inflation is performed to full expansion of the balloon. Flank pain should be closely monitored because it indicates stretching of the adventitia. If detected, higher-pressure inflations should be avoided because further dilation could result in perforation. Most atherosclerotic renal artery lesions demonstrate significant recoil after balloon angioplasty and therefore require stent placement. Balloon-expandable stents should be positioned such that 1 to 2 mm of the stent protrudes into the aorta to ensure proper coverage of the arterial ostium. It is often necessary to place the stent in two views to ensure proper placement.

Use of the Ostial Pro Stent positioning system (Ostial Solutions, Kalamazoo, MI) can assist in proper stent placement and adequate coverage of the ostium of the renal artery (Fig. 42-10). It is a disposable device compatible with 6-, 7-, and 8-Fr systems. It has opaque gold-plated feet that are used to identify the ostium and assist in placement of the stent to confirm coverage of the ostium.

After correct placement, the stent should be deployed with the proper pressure to achieve a 1 : 1 ratio with the diameter of the reference vessel. After stent deployment to nominal balloon pressures, the deflated balloon is reduced to within the stent confines, with the proximal aspect of the balloon protruding into the aorta. The balloon is then taken to high pressures for the postdilation step. For this maneuver, as the balloon is being deflated, the guide can be advanced forward to reengage the renal artery. The deflating balloon is used as a dilator to less traumatically advance the guide back into proper position if necessary. A completion angiogram should be done to assess proper coverage of the renal ostium by the stent, the main renal artery, and its branches for signs of dissection or spasm and the renal parenchymal blush to exclude evidence of atheroembolization. Although there are no data to establish the routine use of aspirin and clopidogrel after stenting, most operators continue the use of these agents for at least 30 days.

Distal Protection Devices to Prevent Atheroembolization

Despite successful renal artery revascularization, renal function may deteriorate in 8% to 32% of patients.[51] Although this decline in renal function may reflect the continued effects of underlying disease processes (e.g., diabetes, hypertension) or reperfusion injury, atheroembolization may also be a potential cause. During a simulated renal stent procedure, Hiramoto and coworkers demonstrated that angioplasty and stenting of ex vivo aortorenal atheroma specimens can produce thousands of atheroemboli particles.[52] Intuitively, distal protection devices may provide beneficial results in selected patients by preventing distal atheroembolization, but limited clinical studies have proved inconclusive. Although several study authors[53-55] have suggested an improvement in renal function or its stabilization associated with the use of distal protection devices, they are designed primarily for use in carotid artery stent procedures and coronary artery bypass grafts. Which patient cohort may potentially benefit from the use of these devices has not been clearly established.

Insight into the potential mechanism of atheroembolic decline in renal function was provided by Cooper and colleagues.[56] This study randomized 100 patients in a 2×2 factorial design to distal protection (filter type) versus no distal protection and the glycoprotein IIb/IIIa platelet receptor inhibitor abciximab or placebo. Renal artery stenting with distal protection or abciximab alone was associated with a decline in estimated glomerular filtration rate (GFR) at 30 days. However, the combination of distal protection and abciximab use was not associated

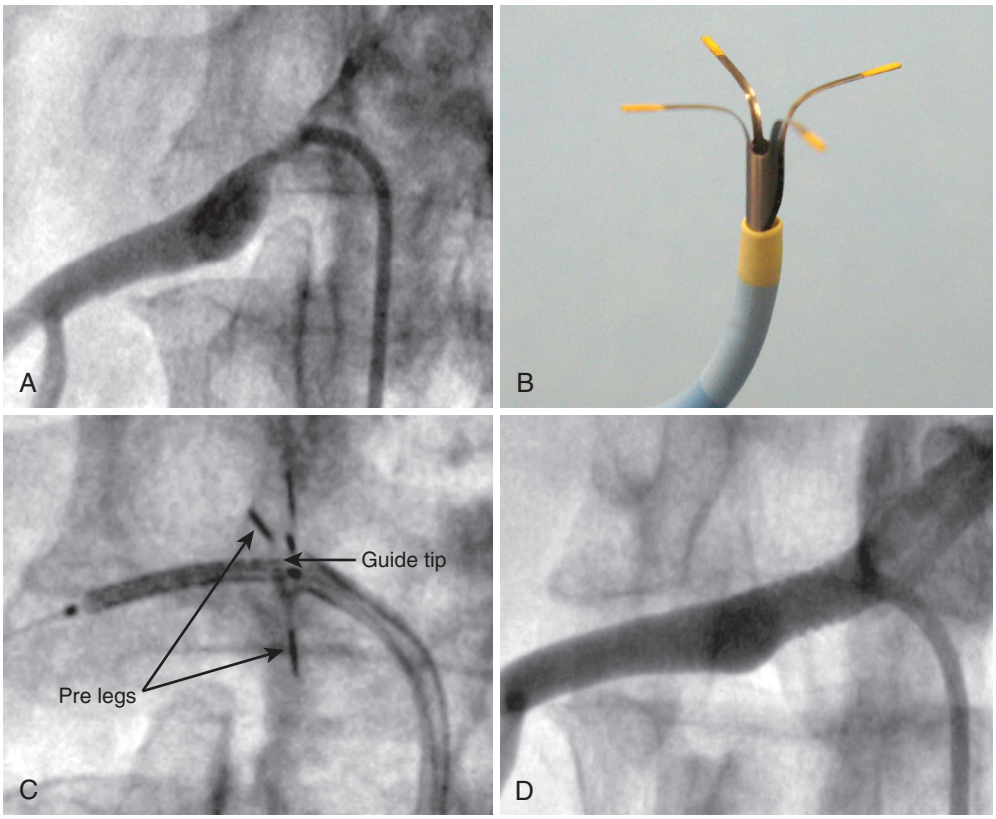

FIGURE 42-10 **A,** High-grade renal lesion is identified using a 5-Fr diagnostic catheter. **B,** Ostial Pro Stent (Ostial Solutions, Kalamazoo, MI) demonstrates four gold-plated feet in the deployed position through a 6-Fr guide catheter. **C,** The deployed radiopaque feet are deployed against the aortic wall. These markers are aligned with the proximal balloon marker before stent deployment. **D,** After stent placement, the angiogram demonstrates excellent renal stent deployment at the aortorenal ostium.

with a decline in GFR. Abciximab use also was associated with lower incidence of platelet-rich emboli in the filter device.

The use of distal protection in the renal arteries is not without risk; occlusive devices (e.g., PercuSurge) can predispose to renal ischemia, and filter devices not specifically designed for the renal vasculature may cause renal artery spasm. Moreover, the distal filter wire may cause dissection of the distal renal vessel. These filters are associated with various filter efficiencies and may not trap all of the atheromatous debris generated by the renal intervention. Use of the filters is limited to renal arteries with sufficient "landing zones," excluding their use in patients with early renal artery bifurcations. They are associated with a learning curve, and inexperience may prolong the procedure and increase contrast use. Filter retrieval also may be problematic because the recapture catheter can become entrapped within the newly deployed stent.

Management of In-Stent Restenosis

Duplex Doppler–defined restenosis rates after successful stenting depend on a variety of anatomic and patient-related factors. Smaller-diameter vessels (<4 mm) can have restenosis rates as high as 40%, whereas larger vessels (>6 cm) usually have restenosis rates of less than 10%.[56] A history of tobacco use, diabetes, and time to restenosis evaluation also appear to be associated with higher restenosis rates.[57]

Although the endovascular options for ISR treatment are many—including repeat balloon angioplasty, repeat stenting deployment (i.e., bare-metal or drug-eluting stent), or placement of a covered stent (iCAST, Atrium Medical, Hudson, NH)—there are few data to suggest the superiority of any one modality.[58] Because of the recoil in the vessel, balloon angioplasty for ISR usually does not provide a durable result. Placement of more metal into the vessel often results in recurrent restenosis.[59] Brachytherapy,[60] atherectomy, cryoplasty,[61] and laser debulking[62] techniques have been described.[60]

Although the efficacy of drug-eluting stents in the coronary vasculature is well established, their use in renal revascularization is less clear. The GREAT trial was a randomized evaluation of bare-metal stents versus drug-eluting stents in 105 patients with ARAS. At 6 months, no significant difference in stent patency between the two treatment arms was discerned (6.7% vs. 14.6%, $P = .30$). At 1 year, target lesion revascularization rates were 11.5% for bare-metal stents and 1.9% for drug-eluting stents (i.e., sirolimus-eluting balloon expandable stent versus bare-metal low-profile stent for renal artery treatment[63]). Although the rate of adverse events was lower in the treatment group, statistical significance was not demonstrated in this small patient cohort.

Drug-eluting stents also have been compared with brachytherapy for the treatment of renal ISR. At 3 years, there were lower rates of major adverse clinical events and target lesion revascularization with drug-eluting stents, but they did not reach statistical significance.[64]

One challenge for the use of drug-eluting stents in the renal arteries is sizing. Currently, the largest-diameter coronary artery drug-eluting stent is 4.0 mm, and overdilation of an undersized stent may reduce its radial strength. At this diameter, most small renal arteries can be safely treated, but recoil at the renal ostium may be problematic because the radial strength of these stents (designed for coronary arteries) is not comparable with that of bare-metal stents designed specifically for the renal artery.

Another option for treatment of ISR is placement of a balloon-expandable covered stent (iCast). In theory, this strategy could reduce the risk of neointimal proliferation through the stent struts. Use of this stent has been reported in the renal and iliac beds for treatment of

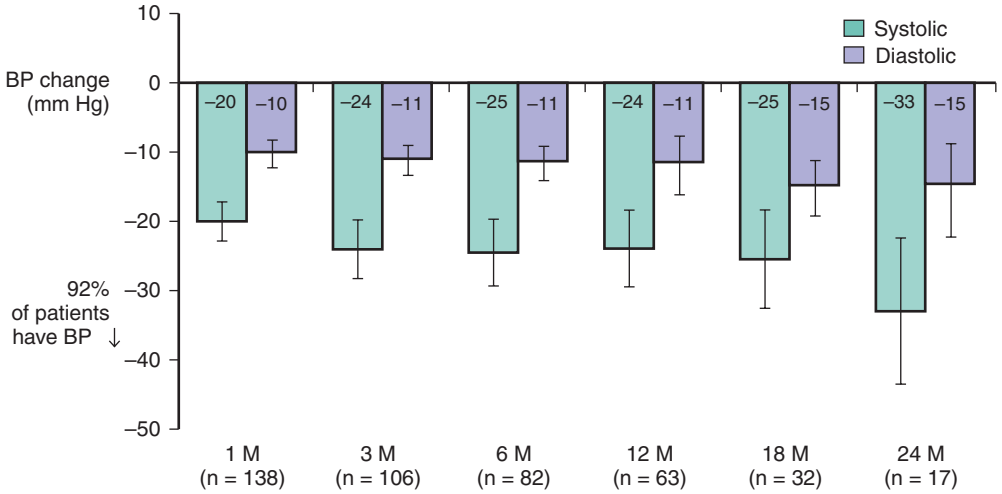

FIGURE 42-11 Sustained improvement in blood pressure (BP) response during a 2-year follow-up.

restenosis.[65] Drug-eluting balloons may eventually play a role in this space as well but are clearly an off-label indication at this point.

Complications

Most complications associated with percutaneous renal artery revascularization are related to arterial access. They include groin hematomas, retroperitoneal hemorrhage, pseudoaneurysm, arteriovenous fistula, and infection. These complications should be treated as usual and are discussed in other sections of this textbook. Serious complications may arise due to atheroembolization to the kidneys, bowel, or lower extremities, resulting in renal failure, ischemic bowel, or digital ischemia, respectively.

Renal artery dissection can usually be treated with stent placement. Distal wire perforation may resolve spontaneously with reversal of anticoagulation or may require coil embolization. Renal artery perforation may respond to prolonged balloon inflation with reversal of anticoagulation or may require the placement of a stent graft.

Percutaneous Renal Sympathetic Denervation to Treat Resistant Hypertension

The kidney plays an essential role in the regulation of blood pressure through sodium, volume, and renin modulation and renal sympathetic neuronal activation. Renal sympathetic drive, which contributes to the development and perpetuation of hypertension and sympathetic outflow to the kidney, is activated in patients with essential hypertension. Studies indicate that the renal nerves contribute to the development and maintenance of hypertension and all hypertensive processes. Efferent sympathetic outflow stimulates renin release, increases tubular sodium reabsorption, and reduces renal blood flow. Afferent signals from the kidney modulate central sympathetic outflow and directly contribute to neurogenic hypertension.

Early studies in nonselective surgical sympathectomy have demonstrated effective control of severe hypertension. Catheter-based technologies enable selective denervation of the human kidney with radiofrequency energy (Medtronic, Minneapolis, MN) delivered to the renal artery lumen, ablating the renal nerves located in the adventitia of the renal arteries. Krum and colleagues, in a first study of this approach in humans, demonstrated successful renal denervation with resultant reduction of sympathetic activity, renin release, and central sympathetic outflow.[5] This feasibility trial demonstrated that percutaneous sympathetic renal denervation was safe and effective in reducing blood pressure in patients with severe resistant hypertension.

A subsequent case report suggested that renal denervation was also associated with a decrease in norepinephrine level spill-over and in muscle sympathetic activity.[66] Two-year follow-up of this patient cohort demonstrated a substantial reduction in blood pressure, averaging 33 mm Hg, which persisted without significant adverse events[67] (Fig. 42-11). The SYMPLICITY HTN-2 trial extended these original observations.

The SYMPLICITY HTN-2 trial[68] was a multicenter, prospective, randomized, crossover trial of patients with baseline systolic hypertension of 160 mm Hg or higher despite taking three or more antihypertensive medications. The trial randomized 106 patients in a 1:1 ratio to undergo renal denervation or previous drug treatment alone with a primary end point of blood pressure control assessed at 6 months. Six-month office-based blood pressure assessment demonstrated a mean reduction of 31/12 mm Hg below the pretreatment baseline values in the renal denervation cohort. The blood pressure values in the control group were unchanged, whereas 84% of the patients who underwent renal denervation had a reduction of systolic blood pressure of at least 10 mm Hg. There were no serious procedure- or device-related complications or adverse events in the renal denervation group. The trials demonstrated that catheter-based renal denervation could be safely used to substantially reduce blood pressure in patients with resistant hypertension.

In an effort to gain approval from the .U.S. Food and Drug Administration, the SYMPLICITY HTN-3 trial was performed at 88 sites in the United States. This study was a prospective, single-blinded, randomized, sham-controlled study evaluating patients with refractory hypertension.[69] Patients with refractory hypertension were randomized in a 2:1 fashion to renal denervation or sham procedure. After almost 2 years, the study enrolled 535 patients. Of the 1441 patients assessed for inclusion in this trial, only 37.1% (535) were randomized. The primary end point was the change in office systolic blood pressure at 6 months. The mean reduction in office systolic blood pressure was 14.13 ± 23.93 mm Hg in the renal denervation group compared with 11.74 ± 25.94 mm Hg in the sham group. This resulted in an absolute difference of 2.39 mm Hg, which was importantly *not* statistically significant ($P = .26$) (Fig. 42-12). The difference was even less when ambulatory systolic blood pressures were compared. The renal denervation group had a lower ambulatory systolic blood pressure, but the difference was only 1.96 mm Hg. The prespecified superiority margin for systolic blood pressure reduction was determined to be 5 mm Hg.

These results did not meet this end point for superiority. The safety end point showed no concerns, and there was no change in GFRs for patients receiving renal denervation therapy. The results were in conflict with prior nonblinded, nonsham studies and took most observers by surprise. There were many differences between SYMPLICITY HTN-3 and prior studies. Most important, this was a sham-controlled

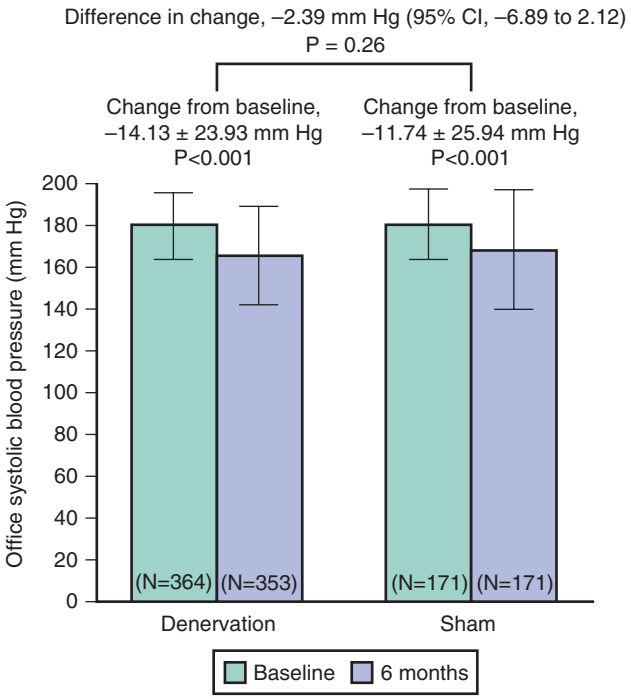

FIGURE 42-12 The primary end point from the SYMPLICITY HTN-3 study. At 6 months, office systolic blood pressure dropped in the sham and treatment groups. The difference between the denervation and the sham group did not meet significance. (Modified from Bhatt DL, Kandzari DE, D'Agostino R, et al: A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 370:1393-1401, 2014.)

trial. In this study, the sham group had almost a 12-mm Hg reduction in systolic blood pressure.

Similar impressive placebo effects have been seen in prior clinical trials with a sham arm. In the DIRECT study,[70] percutaneous myocardial laser revascularization was randomized to treatment or to sham arms and evaluated the effect on angina. Remarkably, significant improvement in angina as measured by Canadian Cardiovascular Society class was seen for all treatment groups at 6 months: 2.0 ± 1.2, 1.9 ± 1.3, and 2.2 ± 1.2, in high-dose, low-dose, and placebo groups, respectively ($P = .413$).

SYMPLICITY HTN-3 was the first blinded and sham-controlled study to evaluate renal denervation for the treatment of hypertension. Based on its results, any subsequent studies will likely be required to include a sham arm. The size of the study was also different from the preliminary studies. It was the largest randomized study of renal denervation, and the larger sample size in the study might have influenced results based on the theory of regression to the mean: the more data points obtained, the more accurate the result. Randomization also tends to eliminate selection bias. Both factors likely played a role in the neutral result obtained.

Results of the trial could also have been affected by the population studied. In the renal denervation arm, 25% of the patients treated were African American. This subgroup showed a decreased or no response to therapy compared with non–African Americans.

Efficacy of the denervation is difficult to assess objectively. There were many new, inexperienced operators performing these procedures in this trial. Many of the operators performed fewer than five procedures. The equipment used also was the newer-generation catheter and control unit. Despite the presence of error messages, the treatments were counted as completed. The efficacy of the procedure may be in question.

A combination of the described factors may have played a role in the negative results seen in SYMPLICITY HTN-3. Alternatively, the technology may not be clinically efficacious.

Various new technologies are being developed to achieve renal denervation. They include radiofrequency energy, ultrasound, and locally delivered drugs. The next renal denervation technology to be evaluated in the United States will likely be required to compare its results to that of a sham group. These new trials will ultimately determine the fate of this strategy for the treatment of hypertension and other medical conditions.

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REFERENCES

1. Textor S, Lerman L, McKusick M: The uncertain value of renal artery interventions. Where are we now? *J Am Coll Cardiol Intervent* 2:175–182, 2009.
2. Wheatley K, Ives N, Gray R, et al: Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med* 361:1953–1962, 2009.
3. Balk E, Raman G, Chung M, et al: Effectiveness of management strategies for renal artery stenosis: a systematic review. *Ann Intern Med* 145:901–912, 2006.
4. Bax L, Woittiez A, Kouwenberg H, et al: Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. *Ann Intern Med* 150:840–848, 2009.
5. Krum H, Schlaich M, Whitbourn R, et al: Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 373:1275–1281, 2009.
6. McCullough PA: Cardiorenal risk: an important clinical intersection. *Rev Cardiovasc Med* 3(2):71–76, 2002.
7. Fatica RA, Port FK, Young EW: Incidence trends and mortality in end-stage renal disease attributed to renovascular disease in the United States. *Am J Kidney Dis* 37(6):1184–1190, 2001.
8. Derkx FH, Schalekamp MA: Renal artery stenosis and hypertension. *Lancet* 344(8917):237–239, 1994.
9. Mann SJ, Pickering TG: Detection of renovascular hypertension. State of the art: 1992. *Ann Intern Med* 117(10):845–853, 1992.
10. Crowley JJ, Santos RM, Peter RH, et al: Progression of renal artery stenosis in patients undergoing cardiac catheterization. *Am Heart J* 136(5):913–918, 1998.
11. Hansen KJ, Edwards MS, Craven TE, et al: Prevalence of renovascular disease in the elderly: a population-based study. *J Vasc Surg* 36(3):443–451, 2002.
12. Rihal CS, Textor SC, Breen JF, et al: Incidental renal artery stenosis among a prospective cohort of hypertensive patients undergoing coronary angiography. *Mayo Clin Proc* 77(4):309–316, 2002.
13. Leertouwer TC, Gussenhoven EJ, Bosch JL, et al: Stent placement for renal arterial stenosis: where do we stand? A meta-analysis. *Radiology* 216(1):8–85, 2000.
14. Zierler RE, Bergelin RO, Davidson RC, et al: A prospective study of disease progression in patients with atherosclerotic renal artery stenosis. *Am J Hypertens* 9(11):1055–1061, 1996.
15. Olin JW, Pierce M: Contemporary management of fibromuscular dysplasia. *Curr Opin Cardiol* 23(6):527–536, 2008.
16. Kolluri R, Goldstein JA, Rocha-Singh K: Percutaneous vascular interventions in renal artery diseases. *Minerva Cardioangiol* 54(1):95–107, 2006.
17. Katholi RE, Rocha-Singh KJ: The role of renal sympathetic nerves in hypertension: has percutaneous renal denervation refocused attention on their clinical significance? *Prog Cardiovasc Dis* 52(3):243–248, 2009.
18. Schultz HD, Li YL, Ding Y: Arterial chemoreceptors and sympathetic nerve activity: implications for hypertension and heart failure. *Hypertension* 50(1):6–13, 2007.
19. Zucker IH: Novel mechanisms of sympathetic regulation in chronic heart failure. *Hypertension* 48(6):1005–1011, 2006.
20. DiBona GF: Sympathetic nervous system and the kidney in hypertension. *Curr Opin Nephrol Hypertens* 11(2):197–200, 2002.
21. Kirchheim H, Ehmke H, Persson P: Sympathetic modulation of renal hemodynamics, renin release and sodium excretion. *Klin Wochenschr* 67(17):858–864, 1989.
22. White CJ, Olin JW: Diagnosis and management of atherosclerotic renal artery stenosis: improving patient selection and outcomes. *Nat Clin Pract Cardiovasc Med* 6(3):176–190, 2009.
23. Olin JW, Piedmonte MR, Young JR, et al: The utility of duplex ultrasound scanning of the renal arteries for diagnosing significant renal artery stenosis. *Ann Intern Med* 122(11):833–838, 1995.
24. Radermacher J, Chavan A, Bleck J, et al: Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. *N Engl J Med* 344(6):410–417, 2001.
25. Zeller T, Frank U, Muller C, et al: Predictors of improved renal function after percutaneous stent-supported angioplasty of severe atherosclerotic ostial renal artery stenosis. *Circulation* 108(18):2244–2249, 2003.
26. Zeller T, Muller C, Frank U, et al: Stent angioplasty of severe atherosclerotic ostial renal artery stenosis in patients with diabetes mellitus and nephrosclerosis. *Catheter Cardiovasc Interv* 58(4):510–515, 2003.
27. Grobner T: Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 21(4):1104–1108, 2006.
28. Marckmann P, Skov L, Rossen K, et al: Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol* 17(9):2359–2362, 2006.
29. Vasbinder GB, Nelemans PJ, Kessels AG, et al: Accuracy of computed tomographic angiography and magnetic resonance angiography for diagnosing renal artery stenosis. *Ann Intern Med* 141(9):674–682, discussion 682, 2004.
30. Silva JA, Chan AW, White CJ, et al: Elevated brain natriuretic peptide predicts blood pressure response after stent revascularization in patients with renal artery stenosis. *Circulation* 111(3):328–333, 2005.
31. Mann SJ, Pickering TG, Sos TA, et al: Captopril renography in the diagnosis of renal artery stenosis: accuracy and limitations. *Am J Med* 90(1):30–40, 1991.

32. Nally JV, Jr, Black HR: State-of-the-art review: captopril renography—pathophysiological considerations and clinical observations. *Semin Nucl Med* 22(2):85–97, 1992.
33. Elliott WJ, Martin WB, Murphy MB: Comparison of two noninvasive screening tests for renovascular hypertension. *Arch Intern Med* 153(6):755–764, 1993.
34. Frederickson ED, Wilcox CS, Bucci M, et al: A prospective evaluation of a simplified captopril test for the detection of renovascular hypertension. *Arch Intern Med* 150(3):569–572, 1990.
35. Hirsch AT, Haskal ZJ, Hertzer NR: ACC/AHA guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic). *J Am Coll Cardiol* 47:1239–1312, 2006.
36. Rosenfield K, Jaff MR: An 82-year-old woman with worsening hypertension: review of renal artery stenosis. *JAMA* 300(17):2036–2044, 2008.
37. Cheung CM, Patel A, Shaheen N, et al: The effects of statins on the progression of atherosclerotic renovascular disease. *Nephron Clin Pract* 107(2):c35–c42, 2007.
38. Cooper CJ, Murphy TP, Cutlip DE, et al: Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med 370*(1):13–22, 2014.
39. Nolan BW, Schermerhorn ML, Powell RJ, et al: Restenosis in gold-coated renal artery stents. *J Vasc Surg* 42(1):40–46, 2005.
40. Rocha-Singh K, Jaff MR, Lynne Kelley E: Renal artery stenting with noninvasive duplex ultrasound follow-up: 3-year results from the RENAISSANCE renal stent trial. *Catheter Cardiovasc Interv* 72(6):853–862, 2008.
41. Chi YW, White CJ, Thornton S, et al: Ultrasound velocity criteria for renal in-stent restenosis. *J Vasc Surg* 50(1):119–123, 2009.
42. Mohabbat W, Greenberg RK, Mastracci TM, et al: Revised duplex criteria and outcomes for renal stents and stent grafts following endovascular repair of juxtarenal and thoracoabdominal aneurysms. *J Vasc Surg* 49(4):827–837, discussion 37, 2009.
43. Gruntzig A, Vetter W, Meier B, et al: Treatment of renovascular hypertension with percuataneous transluminal dilatation of a renal artery stenosis. *Lancet* 15:801–802, 1978.
44. Leertouwer TC, Gussenhoven EJ, Bosch JL, et al: Stent placement for renal arterial stenosis: where do we stand? A meta-analysis. *Radiology* 216:78–85, 2000.
45. Plouin PF, Chatellier G, Darne B, et al: Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis: a randomized trial, The EMMA Study Group. *Hypertension* 31:823–829, 1998.
46. Webster J, Marshall F, Abdalla M, et al: Randomized comparison of percutaneous angioplasty vs. continued medical therapy for hypertensive patients with atheromatous renal artery stenosis. *J Hum Hypertens* 12:329–335, 1998.
47. Van Jaarsveld BC, Krijnen P, Pieterman H, et al: For the Dutch Renal Artery Stenosis Intervention Cooperative Study Group. The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. *N Engl J Med* 342:1007–1014, 2000.
48. De Bruyne B, Manoharan G, Pijils M, et al: Assessment of renal artery stenosis severity by pressure gradient measurements. *J Am Coll Cardiol* 48(48):1851–1855, 2006.
49. Mangiacapra F, Trana C, Sarno G, et al: Translesional pressure gradients to predict blood pressure response after renal artery stenting in patients with renovascular hypertension. *Circ Cardiovasc Interv* 3(6):537–542, 2010.
50. Drieghe B, Madaric J, Sarno G, et al: Assessment of renal artery stenosis: side-by-side comparison of angiography and duplex ultrasound with pressure gradient measurements. *Eur Heart J* 29:517–524, 2008.
51. Submramanian R, White C, Rosenfield K, et al: Renal fractional flow reserve: a hemodynamic evaluation of moderate renal artery stenoses. *Catheter Cardiovasc Interv* 64:480–486, 2005.
52. Bates MC, Crotty B, Kavasmaneck C, et al: Renal artery angiography: "the right ipsilateral oblique" myth. *Catheter Cardiovasc Interv* 67(2):283–287, 2006.
53. Hiramoto J, Hansen KJ, Pan XM, et al: Atheroemboli during renal artery angioplasty: an ex-vivo study. *J Vasc Surg* 41:1026–1030, 2005.
54. Henry M, Klonaris C, Henry I, et al: Protected renal stenting with the PercuSurge GuardWire device: a pilot study. *J Endovasc Ther* 8:227–237, 2001.
55. Holden A, Hill A, Jaff MR, et al: Renal artery stenting revascularization with embolic protection in patients with ischemic nephropathy. *Kidney Int* 70:948–955, 2006.
56. Cooper CJ, Haller ST, Colyer W, et al: Embolic protection and platelet inhibition during renal artery stenting. *Circulation* 117: 2752–2760, 2008.
57. Gray BH: Intervention for renal artery stenosis: endovascular and surgical roles. *J Hypertens* 23(Suppl 3):S23–S29, 2005.
58. Shammas NW, Kapalis MJ, Dippel EJ, et al: Clinical and angiographic predictors of restenosis following renal artery stenting. *J Invas Cardiol* 16(1):10–13, 2004.
59. Bax L, Mali WP, Van De Ven PJ, et al: Repeated intervention for in-stent restenosis of the renal arteries. *J Vasc Intervent Radiol* 13(12):1219–1224, 2002.
60. Zeller T, Rastan A, Schwarzwälder U, et al: Treatment of in-stent restenosis following stent-supported renal artery angioplasty. *Catheter Cardiovasc Interv* 70(3):454–459, 2007.
61. Chrysant GS, Goldstein JA, Casserly IP, et al: Endovascular brachytherapy for treatment of bilateral renal artery in-stent restenosis. *Catheter Cardiovasc Interv* 59(2):251–254, 2003.
62. Jeffreies JL, Dougherty K, Krajcer Z: First use of cryoplasty to treat in-stent renal artery restenosis. *Texas Heart Inst J* 35(4):489–491, 2008.
63. Waheed A, Rajachandran M, Altin R, et al: An unusual case of renal artery stent restenosis: a case report. *Angiology* 58:249–254, 2007.
64. Zähringer M, Sapoval M, Pattynama P, et al: GREAT trial: angiographic follow-up after 6 months and clinical outcome up to 2 years. *Endovasc Ther* 14:460–468, 2007.
65. Holmes D, Teirstein P, Satler L, et al: 3-year follow-up of the SISR (Sirolimus-Eluting Stents Versus Vascular Brachytherapy for In-Stent Restenosis) trial. *JACC Cardiovasc Interv* 1(4):439–448, 2008.
66. Giles H, Lesar C, Erdoes L, et al: Balloon-expandable covered stent therapy of complex endovascular pathology. *Ann Vasc Surg* 22(6):762–768, 2008.
67. Symplicity HTN-1 Investigators: Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension* 57:911–917, 2011.
68. Symplicity HTN-2 Investigators: Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomized controlled trial. *Lancet* 376:1903–1909, 2010.
69. Bhatt DL, Kandzari DE, O'Neill WW, et al; for the SYMPLICITY HTN-3 Investigators: A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 370:1393–1401, 2014.
70. Leon MB, Kornowski R, Downey WE, et al: A blinded, randomized, placebo-controlled trial of percutaneous laser myocardial revascularization to improve angina symptoms in patients with severe coronary disease. *J Am Coll Cardiol* 46:1812–1819, 2005.

43 Device Therapy for Resistant Hypertension

MARVIN H. ENG | MARAT FUDIM | PAUL A. SOBOTKA

KEY POINTS

- Uncontrolled hypertension is a significant health care problem with far-reaching public health and economical consequences.
- Novel therapies target neurohumoral modulation and mechanical alteration of vascular compliance to treat hypertension.
- Reduction of the sympathetic nervous output from the renal nerves has some supporting clinical data but remains experimental.
- A variety of technologies can be used to modulate renal sympathetic tone through destruction of renal nerves, with the most common modality being radiofrequency ablation.

DEFINITION AND EPIDEMIOLOGY

Hypertension (HTN) is estimated to be present in 77.9 million adults in the United States, including 60% to 75% of those older than 60 years of age.[1] Globally, 51% of strokes and 45% of cases of ischemic heart disease are attributable to HTN.[2] HTN-related stroke, cardiac disease, and renal failure are preventable with adequate lowering of blood pressure (BP), which may be achieved by several means.[3,4]

Surveys suggest that almost 50% of U.S. patients with identified and treated hypertension have systolic blood pressure (SBP) values greater than 140 mm Hg, and 13% (26% of the uncontrolled cases) have SBPs greater than 160 mm Hg.[5] Despite the wide availability of effective drugs for BP control, as many as 51% of patients have low adherence, resulting in a 38% increased rate of cardiovascular morbidity relative to those compliant with medications.[6] Even in clinical trial settings, only 57% of patients elect to persist and adhere to medication recommendations after 2 years, signaling the futility of relying on patient compliance for management of chronic HTN.[7] Further, the BP values in a subset of patients who choose to be compliant with complex multidrug formulations remain above target pressures, and these patients are designated as having resistant hypertension. Despite compliance with medications, patients with BP values greater than clinical targets continue to have excess cardiovascular mortality, stroke, myocardial infarction, and onset of renal insufficiency.[4,8,9] Treatment strategies to complement pharmacotherapy in reducing BP would address a large unmet clinical need and potentially reduce the cardiovascular morbidity of uncontrolled HTN among patients who are either nonadherent or have HTN resistant to pharmacotherapy.

The pathophysiology of HTN is multifactorial, with neurohumoral activation making a significant contribution to its genesis (Fig. 43-1). Secondary pathologies such as arteriosclerosis and loss of vascular compliance further accelerate disease progression. A treatment approach addressing the separate components of the pathophysiology has resulted in the emergence of two separate and perhaps complementary device-driven strategies: sympathetic nervous modulation to decrease downstream maladaptive events in vascular tone and sodium balance and mechanical alteration of the systemic vascular resistance using an arterial-venous anastomosis to change vascular compliance.

NEUROMODIFICATION: TARGETING THE SYMPATHETIC NERVOUS SYSTEM AND HYPERTENSION

Renal Denervation: Science and Clinical Application

Maintenance of body fluid composition, volume, and vascular tone is a complex integrated process regulated by the autonomic nervous system that is heavily renal driven.[10] The sympathetic nervous system (SNS) acquires signals reflecting changes in renal hydrostatic pressure and chemistry, the information is processed in the central SNS, and efferent signals from the CNS adjust the renal contribution to vascular tone and volume homeostasis. Afferent nerve endings rise from the kidney vasculature and parenchyma to relay information via the ipsilateral cell bodies in the dorsal root ganglia to the posterior gray column; finally, the brainstem and midbrain integrate afferent signals from multiple end-organ sensors and baroreceptors (Fig. 43-2).[10] Efferent fibers rise from the CNS and extend to the sympathetic preganglionic neurons in the intermediolateral cell column. At approximately T10-12 and L1-2, splanchnic nerves connect via prevertebral ganglia (e.g., celiac, mesenteric) to postganglionic neurons and communicate to the kidneys bilaterally.[10] Additionally, the renal nervous system may reflexively autoregulate without CNS output.[11]

Afferent (from kidney to brain) and efferent (from brain to kidney) nerves function in a reflex loop: Afferent signals from the kidney to the CNS regulate the efferent sympathetic nerve output back to the kidney. Two main types of renal afferents are responsible for signaling information to the CNS—mechanosensitive and chemosensitive receptors. Mechanosensitive receptors transmit hydrostatic data from the renal arteries, veins, and pelvis. Renal ischemia, ionic composition, adenosine concentration, osmolar concentration, oxidative stress, and chemicals (i.e., bradykinin) activate renal chemoreceptors.[10]

The efferent arm of the reflex loop innervates the renal tubules, juxtaglomerular apparatus, and renal vasculature. Increased renal sympathetic efferent activity stimulates the β_1-adrenergic receptor of the juxtaglomerular apparatus to release renin.[12,13] α_{1B}-Adrenergic receptor stimulation increases sodium resorption.[13,14] α_{1A}-Adrenergic stimulation vasoconstricts renal arterioles, decreasing renal blood flow.[13,15] The graded responses of low- or high-frequency signals from the CNS modify renal activity. Coincidentally, the efferents are colocated with the afferents in the renal adventitia, providing the anatomic feasibility for percutaneous ablation technology (Fig. 43-3).[16]

Data Supporting Renal Denervation

Preclinical Research

Of the vast preclinical research on renal sympathetic innervation in HTN, a few studies merit mention. Electrical stimulation of feline and canine renal afferents increased vasoconstriction-mediated BP rises.[17] Interruption of afferent fibers via dorsal rhizotomy in a rodent nephrectomy model of chronic renal failure caused a decrease in norepinephrine turnover, attenuated HTN, and improved renal function, confirming the renal contribution to BP regulation.[18] Surgical renal artery denervation (RDN) in several HTN models consistently lowered BP[19,20] and improved natriuresis.[21]

Surgical Denervation for Hypertension Control

Before the development of antihypertensive pharmacotherapy, surgical thoracolumbar splanchnicectomy served as a therapeutic option for

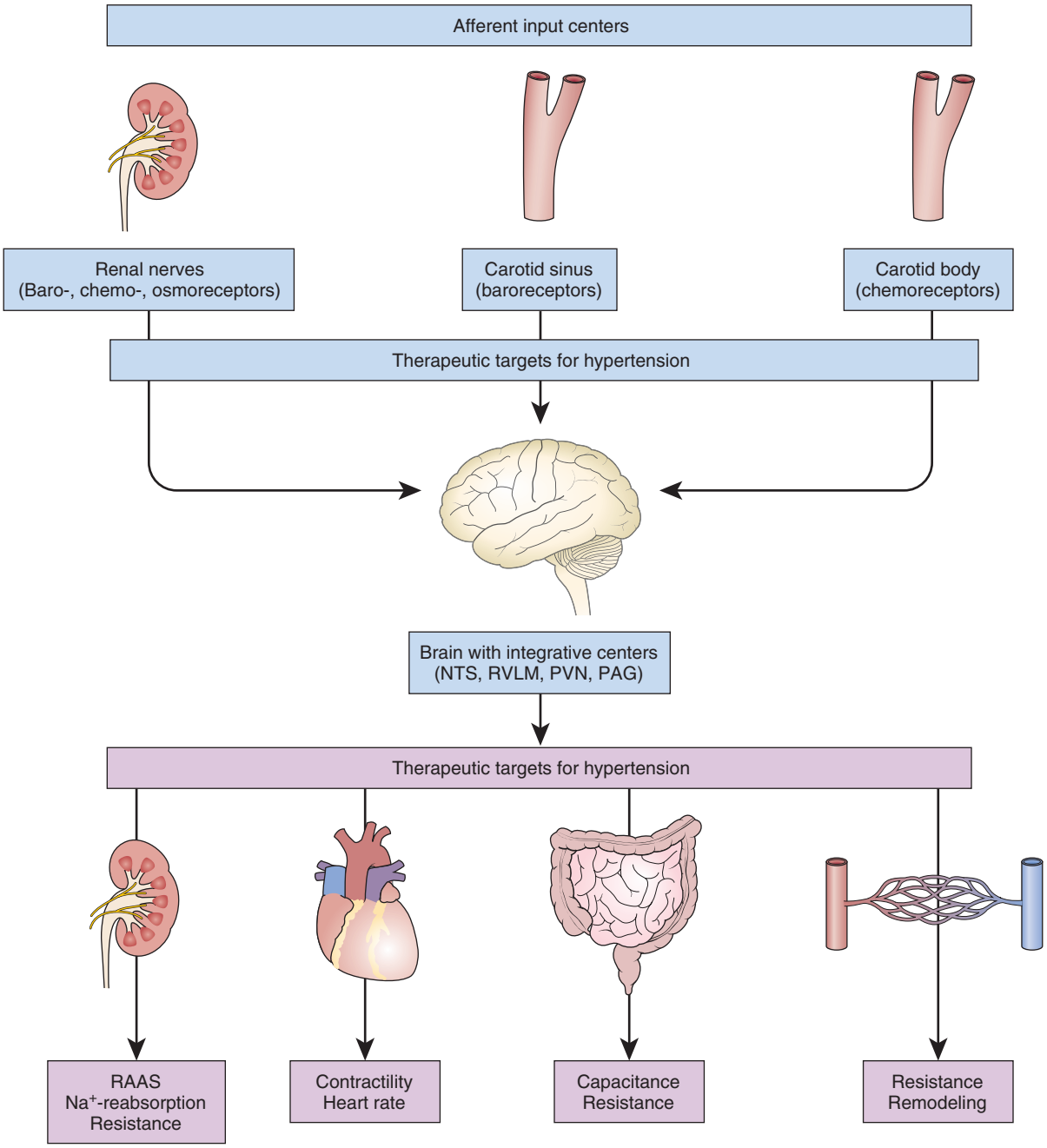


FIGURE 43-1 Key neurohumoral contributors to hypertension and the affected target organs. *NTS,* Solitary nucleus; *PAG,* periaqueductal gray; *PVN,* paraventricular nucleus of the hypothalamus; *RAAS,* renin-angiotensin-aldosterone system; *RVLM,* rostral ventrolateral medulla.

reducing BP.[22,23] In a large, prospective, observational study, 1266 patients underwent splanchnicectomy, and 467 received medical therapy; durable BP lowering in conjunction with improved 5-year survival was achieved by 81% in the surgical group versus 46% in the medical group.[24] Additionally, symptomatic relief of headaches and precordial pain, reduction in cardiac size, and renal function improvement were observed,[23,25,26] at the cost of significant operative mortality (5%).[24] Subsequent studies in nephrectomized patients observed postsurgical reductions in resting sympathetic tone corresponding to substantial lowering of BP, reinforcing the pathophysiologic evidence for modulation of renal sympathetic output as a treatment for HTN.[27,28]

RENAL ARTERY DENERVATION

Sympathetic modulation for treatment of HTN has been rediscovered, and various methodologies have been explored to ablate renal efferent and afferent sympathetics. The most developed technology is endovascular radiofrequency (RF) ablation. Initial devices provide unipolar or bipolar RF ablation in repeated spiral patterns, using energy levels that attempt to achieve sufficient depth to reach the adventitia and disrupt nerve traffic. Delivery of pharmacoablative agents and transmission of focused ultrasonic energy to ablate renal nerves are investigational (see later discussion).

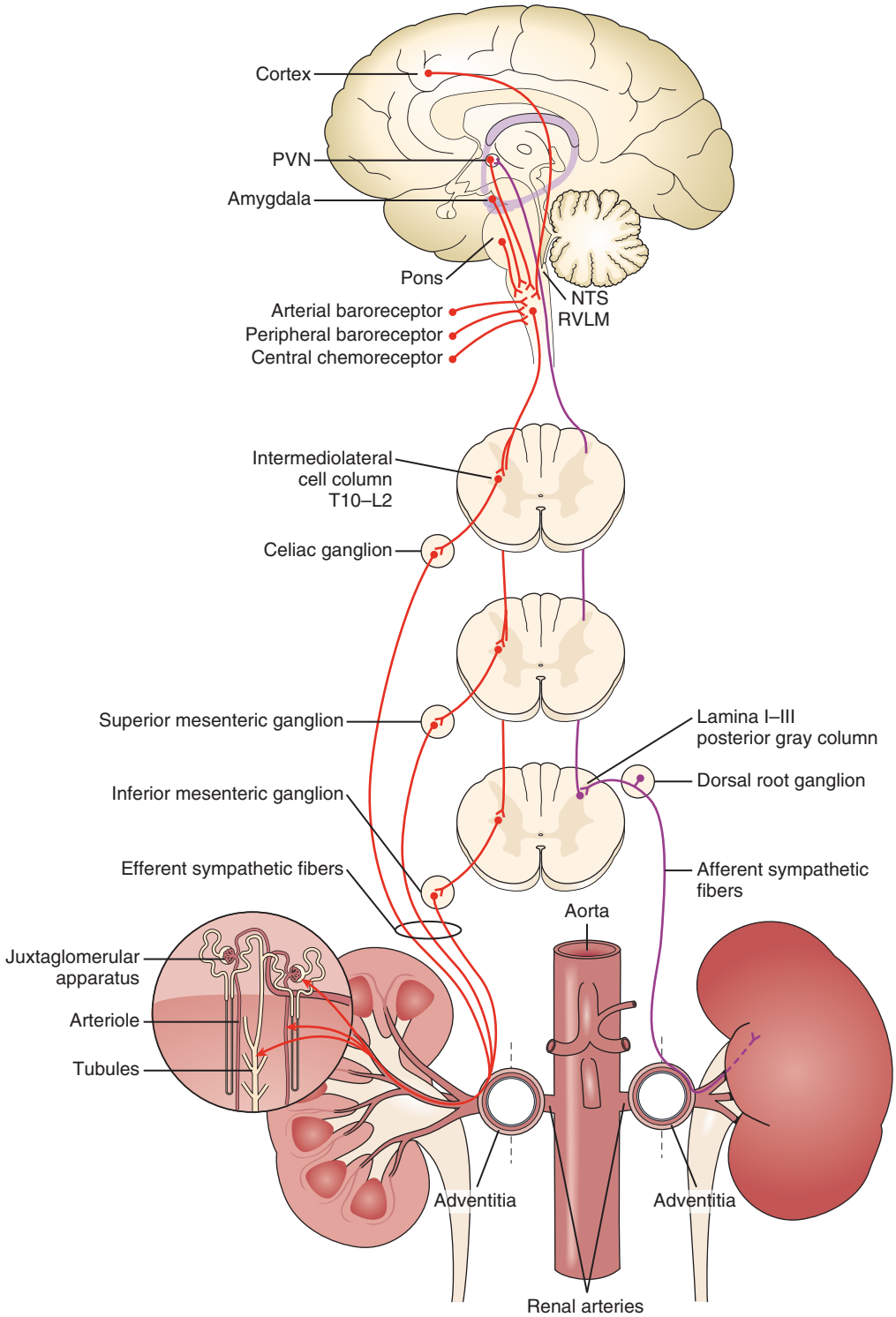


FIGURE 43-2 Anatomy of the sympathetic autonomic nervous system and renal innervation. *NTS,* Solitary nucleus; *PVN,* paraventricular nucleus of the hypothalamus; *RVLM,* rostral ventrolateral medulla. (From Bertog SC, Sobotka PA, Sievert H: Renal denervation for hypertension. *JACC Cardiovasc Interv* 5[3]:249-258, 2012.)

Radiofrequency Ablation: Symplicity Catheter System

Clinical Evidence

The Symplicity Catheter System (Medtronic, Minneapolis, MN) is a 6-Fr RF catheter that directs energy (8 watts) to the endoluminal surface to ablate renal nerves located in the adventitia. This single-electrode catheter requires a manual 360-degree rotation to accomplish a circumferential ablation. The SYMPLICITY HTN-I and -II studies were performed with multiple independent ablations using a unipolar RF system, and the catheter underwent iteration from a fixed arch to a physician-enabled bend for the SYMPLICITY HTN-3 study (FLEX catheter). This later catheter iteration enabled physicians

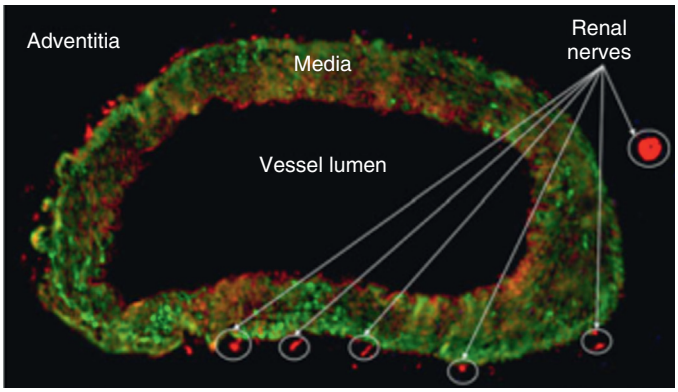


FIGURE 43-3 Cross-sectional histology reveals the adventitial location of renal nerves. (From Sobotka PA, Mahfoud F, Schlaich MP, et al: Sympatho-renal axis in chronic disease. *Clin Res Cardiol* 100[12]:1049-1057, 2011.)

to alter both the pressure of the ablation lead on the artery wall and the angle of attack of the lead—both of which appear to be determinates of depth of RF injury (Table 43-1).

Efficacy

SYMPLICITY HTN-1 was a proof-of-concept, first-in-man trial testing the safety and efficacy of RF ablation for HTN therapy. Forty-five patients with treatment-resistant HTN were followed prospectively after bilateral renal nerve RF ablation. Despite treatment with a mean of 4.7 antihypertensive drugs, there was a decrease from the mean baseline office BP (177/101 mm Hg) of 27/17 mm Hg at 12 months after ablation (Fig. 43-4). Noradrenaline turnover was assessed in 10 of the patients and was found to have decreased by 47% (95% CI, 28% to 65%), confirming a relationship between renal nerve ablation, reduction of sympathetic tone, and BP lowering.[29]

SYMPLICITY HTN-2 randomly assigned 106 patients with drug-resistant HTN to either medical therapy or RF ablation in conjunction with medical therapy. Mirroring SYMPLICITY HTN-1, the patients

TABLE 43-1 Devices Designed for Renal Nerve Ablation

Device	Attributes and Method of Ablation	Clinical Evidence and Development	6-Mo Results (Mean Office Blood Pressure)
Radiofrequency Ablation			
Symplicity (Medtronic, Minneapolis, MN)	Single unipolar electrode First iteration: ARCH (preformed, steerable, curved catheter) Second iteration: FLEX (physician-manipulated, flexible catheter) 6-Fr system	Symplicity HTN-1 Symplicity HTN-2 Symplicity HTN-3 Symplicity HTN Global Registry	–22/–11 mm Hg (n = 45) –32/–11 mm Hg (n = 52) –14/6.75 mm Hg (n = 364) –11.9 mm Hg SBP (n = 932)
Spyral (Medtronic, Minneapolis, MN)	4-Fr multielectrode 0.014-inch compatible	Symplicity HTN-Spyral	–16/–7 mm Hg (n = 29)
EnligHTN (St. Jude Medical, St. Paul, MN)	8-Fr system Basket shape with four unipolar electrodes	ARSENAL	–26/10 mm Hg (n = 46)
Vessix V2 (Boston Scientific, Natick, MA)	8-Fr system Over-the-wire balloon Four to eight bipolar electrodes	REDUCE-HTN	–25/–10 mm Hg (n = 139)
OneShot (Covidien, Mansfield, MA)	8-Fr system Irrigated unipolar lead Helical balloon-mounted	RHAS RAPID (not recruiting) This device is no longer being clinically developed.	–34/–18 mm Hg (n = 8)
Celsius Thermacool Catheter (Biosense Webster, Diamond Bar, CA)	7-Fr system External saline-irrigated catheter	SWAN-HTN RELIEF	–21/–11 mm Hg (n = 10)
Chilli II (Boston Scientific, Natick, MA)	8-Fr system Internal saline-irrigated catheter	SAVE	
Ultrasound			
PARADISE Ultrasonic Catheter (ReCor Medical, Menlo Park, CA)	Balloon-tipped, self-centering catheter containing an ultrasound emitter causing circumferential distribution of energy 6-Fr system	REALISE	–32/–16 (n = 20)
Therapeutic Intravascular Ultrasound System (TIVUS) (Cardiosonic Ltd., Tel-Aviv, Israel)	TIVUS I: unidirectional ultrasound ablation catheter TIVUS II: multidirectional ultrasound ablation catheter 0.014-inch compatible 6-Fr system	TIVUS II	
Surround Sound (Kona Medical, Bellevue, WA)	External platform that delivers focused, ablative, low-energy ultrasound waves	WAVE I WAVE II	–29/–12 mm Hg (n = 24) –19.4/16.5 mm Hg (n = 17)
Pharmacologic Tissue Delivery			
Peregrine (Ablative Solutions, Menlo Park, CA)	Self-centering catheter that delivers three needles for drug injection 7-Fr system	U.S. FDA 510(k) clearance for periadventitial drug delivery	
Bullfrog Microinfusion Catheter (Mercator Microsystems, San Leandro, CA)	Microneedle-equipped balloon for delivery of pharmacologic agents 0.014-inch compatible 6-Fr system	U.S. FDA 510(k) clearance for marketing	

FDA, Food and Drug Administration, *Fr,* French; *HTN,* hypertension; *SBP,* systolic blood pressure.

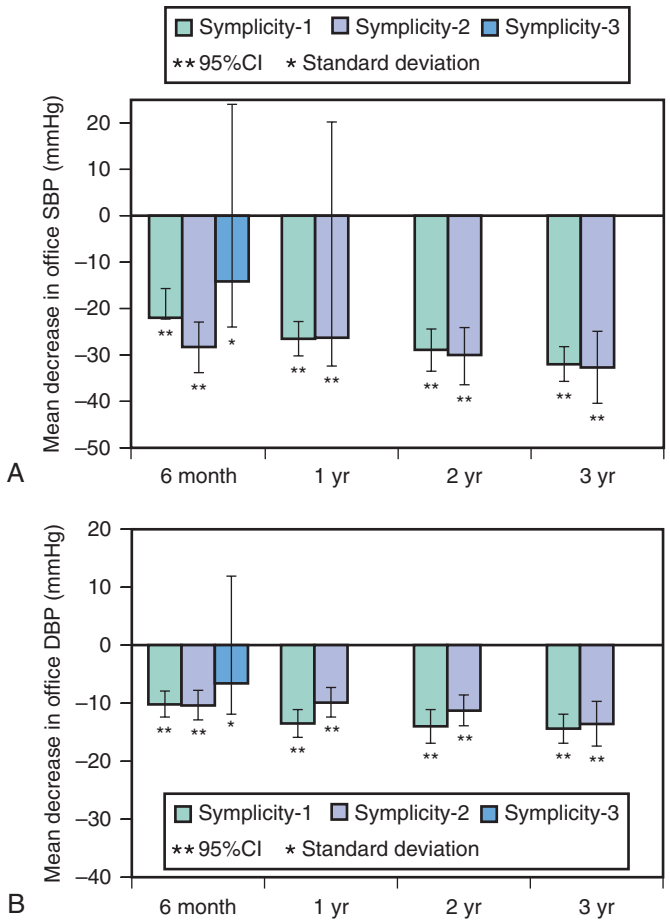


FIGURE 43-4 Blood pressure lowering among treatment groups across all three SYMPLICITY trials through long-term follow-up. **A,** Mean decrease in office systolic blood pressure (SBP) in SYMPLICITY HTN-1 and -2 through 3 years of follow-up and in SYMPLICITY HTN-3 through 6 months. . **B,** Mean decrease in office diastolic blood pressure (DBP) of SYMPLICITY HTN-1 and -2 through 3 years of follow-up and in SYMPLICITY HTN-3 through 6 months. *CI,* Confidence interval.

took an average of 5.2 to 5.3 medications, and the mean baseline office BP reading was 178/97-98 mm Hg for both RF and medical therapy cohorts. After RF ablation, office BP measurements decreased by a mean of 32/12 mm Hg at 6 months, whereas the medical therapy group saw no changes (+1/0 mm Hg; $P < .0001$).[30] Of the patients from the control group who crossed over to RDN therapy, SBP improved from 190.0 ± 19.6 mm Hg to 166 ± 24.7 mm Hg ($P < .001$) 12 months after denervation.[31]

On long-term follow-up at 3 years, there was a durable reduction of 32/14 mm Hg ($n = 88$) in patients from SYMPLICITY HTN-1 and 33/14 mm Hg ($n = 40$) in patients from SYMPLICITY HTN-2 (see Fig. 43-4).[32,33]

SYMPLICITY HTN-3, was a U.S.-based prospective, blinded, randomized, sham-controlled, pre–market approval trial for Medtronic's Symplicity FLEX ablation catheter.[34] Entry criteria included a stable medication regimen of three or more drugs prescribed at fully tolerated doses, including a diuretic, with an office SBP 160 mm Hg or higher. The trial randomized 530 patients to achieve 95% statistical power for detecting a mean difference of 15 ± 25 mm Hg in office SBP between treatment and control cohorts. Although the trial did confirm safety in the RDN cohort, no significant difference in BP between the treatment and control arms was seen (6-month office SBP, −14.13 ± 23.93 mm Hg in RDN group versus −11.74 ± 25.94 mm Hg in controls group; $P = .26$), resulting in a negative study.

The SYMPLICITY HTN-3 trial, although elegant in design, had unique trial elements that may have contributed to its negative findings. In the 6 weeks before enrollment, approximately 20% of patients had medication changes, as did 40% of patients after randomization. Thiazide diuretics and aldosterone antagonists require as long as 6 to 8 weeks to reach maximal BP-lowering effects, suggesting that the BP baselines may not have been stable for some patients enrolled.[35-37]

Previously, RDN had been tested predominantly on Caucasians of European descent, but 26% of those enrolled in SYMPLICITY HTN-3 were African American. Notably, medical therapy was more effective at lowering BP in African American patients (RDN group −15.5 mm Hg versus sham group −17.8 mm Hg, $P = .641$) compared with their non–African American counterparts (RDN group −15.2 mm Hg versus sham group −8.6 mm Hg, $P = .012$), suggesting that pharmacogenomic variances related to race may play a role in HTN management.[37]

Finally, procedural variability may have played a significant role in the lack of efficacy. Approximately 74% of patients received ablation of fewer than four quadrants of any renal artery, whereas approximately 6% of patients had ablation of all four quadrants of the renal artery circumference bilaterally. Those with ablation in fewer than four quadrants demonstrated decreases in office and ambulatory BP of 14.2 and 6.3 mm Hg, respectively, whereas those with four-quadrant bilateral RDN were had decreases of 24.3 and 10.3 mm Hg, respectively (Fig. 43-5).[37] Insufficient training at trial onset and use of a newer iteration of the ablation catheter (FLEX catheter) may have contributed to the differences in efficacy observed in SYMPLICITY HTN-2 compared with SYMPLICITY HTN-3. Currently, RDN remains experimental in the United States, and the proper selection of patients, optimal device design, and demonstration of technical success remain ill defined.

The Symplicity Global Registry plans to enroll 5000 patients and to assess both safety and efficacy of RDN. Six-month data for 913 patients showed a mean reduction of 11.9 mm Hg in office SBP, and those patients with the highest initial SBP (≥160 mm Hg) demonstrated the best response to RDN (mean decrease, 21.4 mm Hg).[38]

Complications and Management of Radiofrequency Ablation in Renal Denervation

The rate of serious complications documented with RDN is low. The most frequently reported complications are vasospasm, severe pain, renal artery dissection, renal artery stenosis, and vascular access complications. Vasospasm is mild and may be preempted with calcium channel blockers or nitrates.[39] Adventitial depth of ablation stimulates pain fibers that may trigger strong vagal reactions. Renal artery dissection resulting from catheter manipulation was reported in the SYMPLICITY HTN-1 trial, and those attempting ablation should be trained in renal artery stenting.[40] Endovascular complications and bleeding are the most frequently reported complication, and careful, fundamentally sound vascular access remains paramount.[30,40,41]

Alternative Radiofrequency Devices

Efforts to provide more consistent ablation, improve ease of use, and shorten procedure times have resulted in the development of alternative RF devices that improve on the single-lead, unipolar RF first-generation device. Later iterations apply multilead unipolar RF to deliver predictable circumferential denervation over a shorter duration and some use bipolar RF energy.

Multielectrode Radiofrequency Ablation

The EnligHTN Renal Denervation System (St. Jude Medical, St. Paul, MN) has a basket-like catheter design that causes contact with the endoluminal surface in a predictable pattern (Fig. 43-6; see Table 43-1). The Ablation-induced Renal Sympathetic Denervation Trial (ARSENAL) enrolled 44 patients, recapitulating the inclusion/exclusion criteria and primary efficacy end point (office BP) from SYMPLICITY

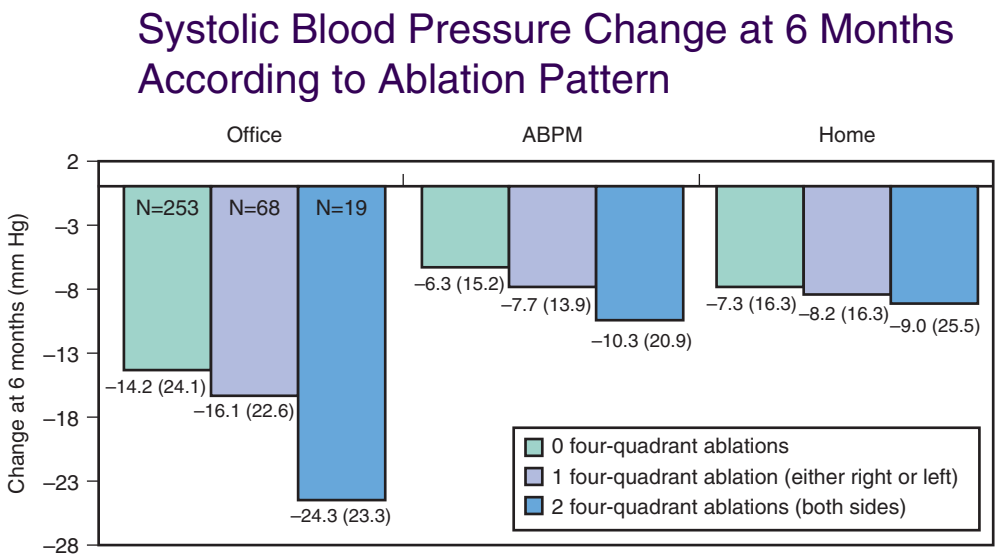


FIGURE 43-5 Mean systolic blood pressure changes according to completeness of ablation with respect to circumferential location in none, one, or both renal arteries. Results reported as mean decrease (mm Hg) and standard deviation. *ABPM,* Ambulatory blood pressure monitoring. (From Kandzari DE, Bhatt DL, Brar S, et al: Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. *Eur Heart J* 36:219-227, 2015.)

HTN-1. BP reduction was 26/10 mm Hg at 6 months, and this was sustained out to 18 months (24/10 mm Hg).[41,42]

Symplicity Spyral (Medtronic) is a multielectrode 4-Fr catheter delivered via a 0.014-inch guidewire in a rapid-exchange fashion (see Table 43-1 and Fig. 43-6). The first-in-man trial results in 29 patients were presented at the 2013 Transcatheter Cardiovascular Therapeutics (TCT) Scientific Symposium and showed a reduction of 16 ± 21 mm Hg systolic and 7 ± 12 mm Hg diastolic in office BP.[43]

The OneShot (Covidien, Mansfield, MA) device is a balloon-mounted, helical ablation electrode that was tested in a small group of patients and showed a BP reduction of 34/13 mm Hg at 6 months ($n = 8$) and 31/10 mm Hg at 12 months ($n = 6$) (see Table 43-1).[44] There are no further plans to develop this catheter.

The Vessix V2 catheter (Boston Scientific, Natick, MA) is another RF system that consists of an over-the-wire balloon catheter mounted with bipolar RF electrodes (see Table 43-1 and Fig. 43-6). Combined results from the REDUCE-HTN first-in-human and postmarketing studies of the Vessix RDN system showed a mean reduction in office BP of 25/10 mm Hg at 6 months ($n = 139$).[45]

Ultrasound Ablation

Ultrasound energy consists of high-frequency sound waves that can penetrate surrounding fluids and generate frictional heating in tissues, resulting in a rise in temperature that induces renal nerve injury.[46] This technology would permit ablation without contact with the endoluminal surface of the renal arteries.

The PARADISE Ultrasonic catheter (ReCor Medical, Menlo Park, CA) is a balloon catheter that causes renal artery ablation using ultrasound directed energy. Its first-in-man study of 20 patients with resistant HTN (REALISE trial) showed a reduction in BP of 32/16 mm Hg over 3 months, but no follow-up data have been released since 2012 (see Table 43-1 and Fig. 43-6).[47]

The Therapeutic Intravascular Ultrasound System (TIVUS) from Cardiosonic Ltd., Tel Aviv, Israel, completed enrolling its first-in-man trial in the winter of 2013.[48]

Using externally delivered ultrasound energy ablating renal nerves, Kona Medical (Bellevue, WA) reported 6-month BP reductions of 29/12 mm Hg ($n = 24$) and 19.4/6.5 mm Hg ($n = 17$) for the WAVE I and WAVE II studies, respectively.[49]

Tissue-Directed Pharmacologic Ablation

The failure of the RF approach in the SYMPLICITY HTN-3 trial raised the possibility that "point-by-point" ablation with a limited number of focal burns may result in ineffective RDN. Even under ideal conditions, with perfect "circumferential" energy delivery, RF (thermal) injury is likely to miss more than 50% of the renal sympathetic nerves due to a lack of sufficient depth of energy penetration.[50] Moreover, individual applications of RF energy may fail to successfully cause complete circumferential denervation or fail to successfully target key nerve trunks. It may be possible to achieve more complete denervation using a specialized drug delivery catheter to perform "chemical" RDN, with ethanol, a well characterized and predictable neurolytic agent.

A novel microneedle-based drug delivery catheter (Peregrine, Ablative Solutions, Menlo Park, CA) has obtained 510(k) clearance from the U.S. Food and Drug Administration (FDA) to cause predictable periarterial adventitial deep and circumferential renal sympathetic denervation with minimal injury to the normal structures (intima and media) of the renal arterial wall (Fig. 43-7). In preclinical testing, microdoses of ethanol were delivered locally to the adventitial and periadventitial space of the renal artery (PeriVascular Renal Denervation, or PVRD), with evidence of rapid and almost complete sympathetic denervation, as assessed by renal parenchymal norepinephrine and histopathologic evaluation.[51] This device, although cleared by the FDA to cause periarterial denervation on the basis of renal nerve studies, is not specifically approved for RDN; clinical trials for this specific indication are anticipated across multiple clinical applications, including HTN, heart failure, and sympathetically mediated tachyarrhythmias. Guanethidine is another agent considered for injection; it is already approved by the FDA for treatment of moderate to severe HTN.[48]

Beta-Irradiation of the Renal Artery

Prior research using radiation therapy in atrial fibrillation provided histologic evidence of nerve fibrosis.[52] Investigators postulated that vascular brachytherapy, a well-developed treatment for coronary restenosis, might have potential for inducing nerve damage in the renal vasculature as an alternative to RF ablation. Preclinical experiments in swine showed 50% nerve damage with doses of 50 Gray (Gy). No damage was seen to adjacent tissues.[53]

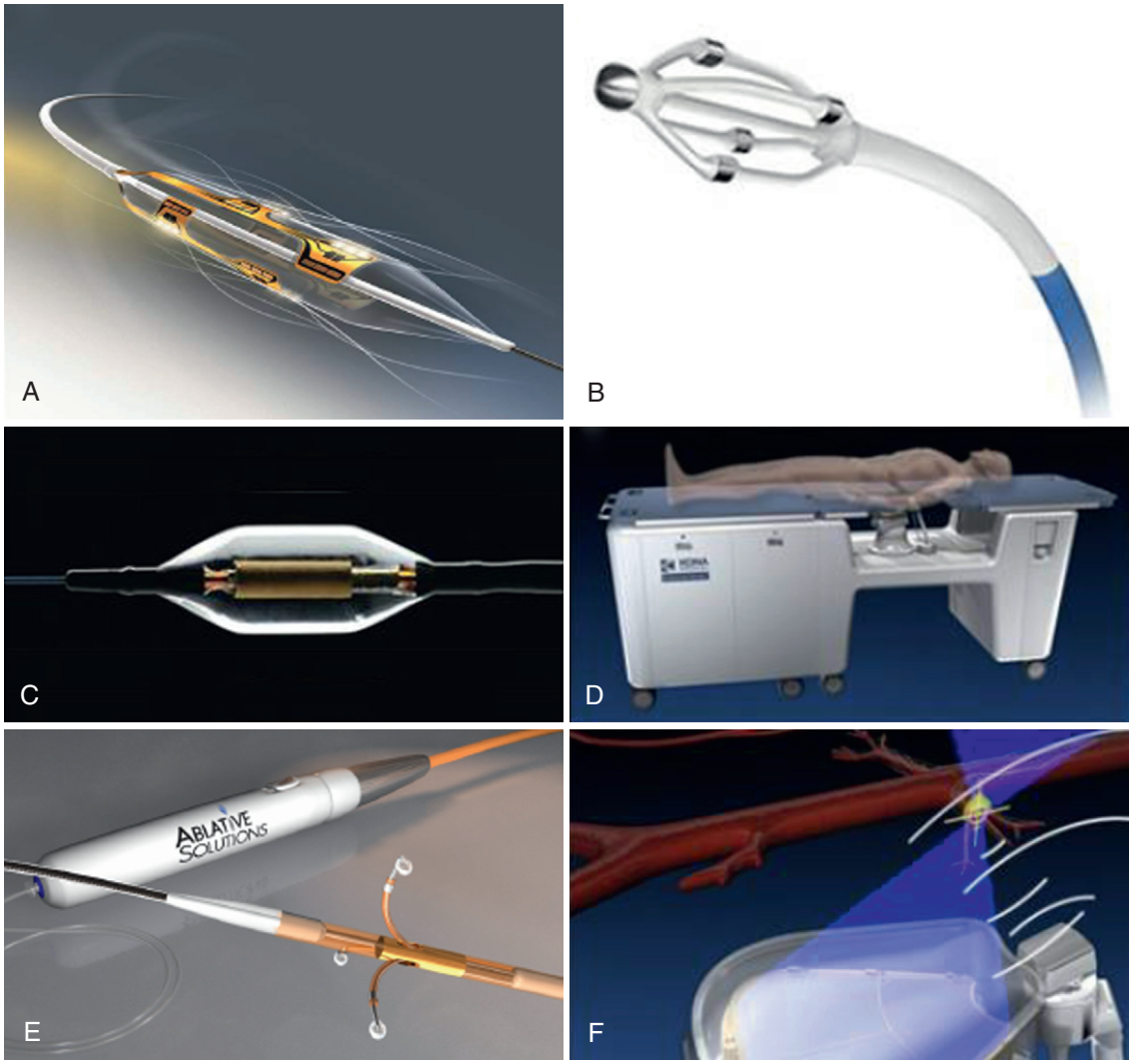


FIGURE 43-6 A nonexhaustive representation of ablation catheters and technologies currently applied for renal denervation. Various devices use radiofrequency energy: **A,** Vessix (Boston Scientific) and **B,** EnligHTN (St. Jude Medical). Others use ultrasound: **C,** intravascular device—ReCor Medical's Paradise catheter; **D** and **E,** extravascular denervation devices by Kona Medical. Perivascular chemical ablation is performed by Ablative Solutions' Peregrine catheter (**F**). (Images courtesy of the respective manufacturers.)

QUANTIFYING PROCEDURAL TECHNICAL SUCCESS, TITRATING ABLATIVE THERAPY, AND TARGETING IDEAL PATIENTS FOR RENAL DENERVATION

The failure of the SYMPLICITY HTN-3 trial to demonstrate a significant benefit associated with RDN may represent technical failure of the device or the physician to cause significant RDN, or it may reflect the selection of a population whose renal nerve contribution to HTN was negligible. Both possibilities suggest the importance of tools to assist in patient selection and verification of successful denervation. In the past, measurement of renal noradrenaline spillover or assessment of muscle sympathetic nerve activity (MSNA) quantified sympathetic activity and confirmed successful denervation during early experience with RDN.[29,54,55] However, not only is renal noradrenaline spillover technically challenging, but it gives no insight into renal afferent nerve activity. Likewise, few centers have the technical expertise to perform MSNA measurements, and it likely is not acceptable for patients to undergo repeated testing. Notably, a reduction in sympathetic tone is not automatically reflected by a reduction in BP.[56] This can probably be explained by the complexity of pathophysiology and the variable role that MSNA can play in it. Ineffective reduction in BP after RDN ranges from 10% to 50%.[29,57] Comparably, changes in left ventricular

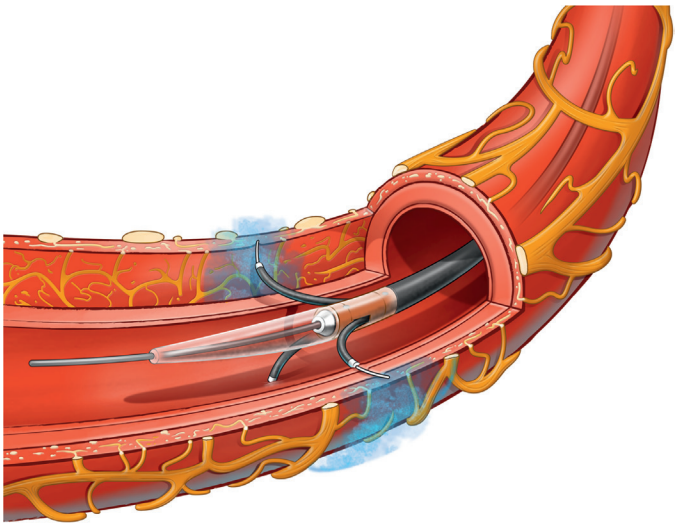


FIGURE 43-7 A three-needle delivery device (Peregrine) for injection of dehydrated ethanol into the adventitial and periadventitial space. (© Justin A. Klein, CMI, 2013. All Rights Reserved.)

hypertrophy after RDN were observed to be independent from BP improvement.[58] This indicates that BP may not necessarily be the best surrogate marker of technical success in RDN.

An appropriate tool to document the renal nerve contribution to elevated BP and the technical success of RDN may be available in the near future. Patents have been issued on a system that identifies changes in systemic BP and heart rate on stimulation of renal nerves. This diagnostic tool* could enable proper patient selection through screening for candidates whose BP is renal nerve activity dependent, and it could allow targeting of optimal ablation sites with documentation of technical success through the loss of systemic BP and heart rate changes after RDN.

The pathophysiology of multiple chronic diseases such as diabetes, arrhythmias, obstructive sleep apnea, heart failure, and chronic renal insufficiency is strongly attributed to the SNS, and modulation of sympathetic tone may have additional salutary effects beyond lowering BP.[59-62] A clinically meaningful and reproducible metric of the systemic sympathetic state ultimately may be required to select ideal candidates for RDN and to document technical success of intervention including alternative therapeutic targets such as diastolic heart failure or glucose intolerance.

ALTERNATIVE APPROACHES TO SYMPATHETIC MODULATION

The Carotid Body and Sinus

Given the role of excessive sympathetic tone in the pathogenesis of HTN and several chronic disease states, there is a long history of investigating sources of sympathetic tone, including the carotid body (CB) and carotid sinus. Located in at the bifurcation of the common carotid artery, the CB is a 1.5- to 7.0-mm, ovoid, bilateral organ innervated by the nerve fibers of the glossopharyngeal nerve, the vagal nerve, and the sympathetic nerve of the adjacent superior cervical ganglion. The CB is the body's primary peripheral chemoreceptor, sensing changes in oxygen saturation, carbon dioxide tension, acidosis, glycemia, and hypoperfusion.[63] CB stimulation signals to the solitary nucleus in the rostral ventrolateral medulla oblongata to elevate sympathetic tone, increasing BP and minute ventilation.[64] The carotid sinus is an outpouching of the internal carotid artery; it houses mechanoreceptors that detect BP changes and maintains arterial tone by modulating parasympathetic and sympathetic signaling. Chemoreflex and baroreflex control are intertwined: Heightened chemoreflex can cause sympathoactivation and inhibition of the baroreflex function.[65]

Preclinical research has shown that the CB chemoreceptor plays a significant role in HTN. Surgical CB denervation in both young and adult spontaneous hypertensive rats (SHR) prevented the onset of HTN and reduced systolic arterial pressures by approximately 20 mm Hg through the decrease of sympathetic vasomotor tone.[66] MSNA in men with untreated hypertension and nonhypertensive controls was measured at baseline and after inactivation of the chemoreceptor by administration of 100% oxygen.[67] After chemoreceptor inactivation, hypertensive patients demonstrated a significant decrease in MSNA, whereas control patients showed no changes in sympathetic activity, confirming that chemoreceptor sympathetic input contributes to HTN. Prior experience in surgical CB excision showed a decrease of approximately 20 mm Hg in SBP in 29 hypertensive asthmatic patients.[68] Given the potential benefits for treatment of chronic HTN, a trial of unilateral endovascular ablation of the CB for patients with resistant HTN is being conducted in Eastern Europe (Cibiem, Los Altos, CA; National Clinical Trial [NCT] 02099851).

Modulation of BP through manipulation of the carotid sinus is an old concept recently revived. Arterial baroreceptors rapidly reset in response to BP fluctuations and increase afferent baroreceptor firing when the BP is elevated. However, with chronically elevated BP, adjustment of baroreceptor response diminishes, and the threshold for activation changes. Therefore baroreceptors become less sensitive to change in the context of chronic HTN.[63] Experiments exploring the role of the carotid sinus have elucidated the effect of electrical impulse stimulation to chronically regulate BP.[69] Researchers in the past attempted to leverage this knowledge in the development of a device for anti-HTN therapy, but limitations in the technology of the 1960s led to failure to create an appropriate stimulator for patients. Technological limitations in conjunction with the emergence of pharmacotherapy caused baroreceptor stimulation to disappear from the therapeutic armamentarium. However, recognition of populations resistant to pharmacotherapy has stimulated renewed interest in baroreceptor pacing, culminating in the clinical development of mature pacing systems for HTN management.

The Rheos baroreceptor pacing system (CVRx, Minneapolis, MN) was tested in the randomized, double-blind, parallel-design Rheos pivotal trial in patients with resistant HTN.[70] All patients underwent implantation, but implementation of baroreceptor activation therapy (BAT) was randomized for the first 6 months. There was no difference in the primary end point of acute response (BAT 54% responders versus no-BAT 46% responders; $P = .97$), and the secondary end point of mean BP decrease just missed statistical significance (BAT 16 ± 29 mm Hg versus no-BAT 9 ± 29 mm Hg; $P = .08$).[70] The second-generation device, Barostim *neo*, was evaluated in a prospective, open-label fashion in 30 patients in Canada and Europe. Six months after implantation, BAT had reduced mean BP by 26 ± 4.4 mm Hg ($P \leq .001$).[71] With respect to safety, the Rheos pivotal trial showed 74.8% event-free procedural safety, which improved to 90% in the Barostim *neo* trial. A pivotal trial seeking FDA approval for the device is still underway (NCT 01679132).

In addition to baroreceptor stimulation, mechanoreceptor modulation as an anti-HTN therapy is being explored. Likely an extrapolation from hypotensive responses observed after carotid stenting, CALM-FIM (NCT 01831895) is a study investigating the BP-lowering effects of an implantable device in the carotid sinus that influences autonomic output via carotid sinus mechanoreceptors, the MobiusHD device (Vascular Dynamics, Mountain View, CA).

*Jie Wang: Mapping sympathetic nerve distribution for renal ablation and catheters for same. U.S. Patent 8702619, published on December 15, 2011, and issued on April 22, 2014.

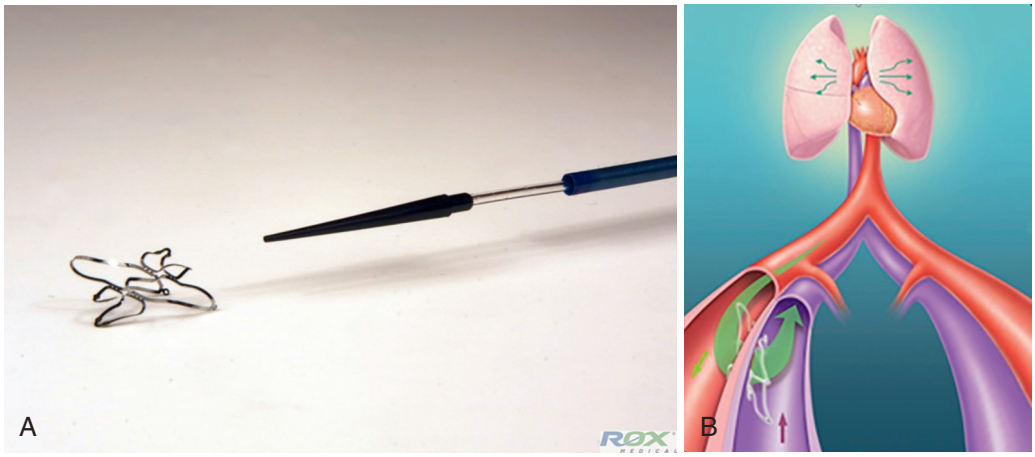


FIGURE 43-8 The ROX Coupler (**A**) is a 4-mm nitinol clip that is designed to cause a fistula between the iliac vein and artery (**B**). (Courtesy ROX Medical, San Clemente, CA.)

Mechanical Reduction of Vascular Resistance and Increase of Compliance for Hypertension Management

While investigating the implantation of a percutaneous arterial venous fistula (AVF) (ROX Medical Inc., San Clemente, CA) intended for treating dyspnea in patients with chronic obstructive pulmonary disease (COPD), researchers noticed an instantaneous significant lowering of BP in hypertensive patients.[72] This observation spurred interested in the use of a small central AVF to treat chronic HTN. Similar to observations in patients with chronic renal failure undergoing new fistula implantation, the mechanism is thought to be the addition of a fixed-volume, central arterial-venous anastomosis reduces BP by adding a low-resistance, high-compliance venous attachment to the central arterial tree.[73] With the addition of a low-capacitance circuit, total systemic vascular resistance and the effective arterial volume decrease.[72] Another possible salutary effect may be improvement of compliance of the arterial tree and reduction of the pulse wave. Multiple analyses have consistently demonstrated the association of reduced arterial compliance and increased pulse wave velocity with adverse cardiovascular outcomes.[74] HTN therapy with angiotensin-converting enzyme (ACE) inhibitors does improve arterial compliance, and perhaps a mechanical therapy to change vascular compliance may assist in BP lowering, but it remains to be seen whether changes in vascular compliance impact clinical outcomes.[75]

The ROX AV-Fistula device (ROX Medical) is a self-expanding, 4-mm nitinol clip that creates a fixed-diameter, common iliac arterial-venous fistula. To implant the ROX Coupler, the venous and arterial walls are punctured from the venous side, and a self-expanding nitinol clip is deployed (Fig. 43-8). Real-time invasive hemodynamic assessment allows immediate verification of technical success, and little pain is experienced during the creation of the anastomosis. Long-term patency of the device can easily be confirmed with bedside noninvasive techniques, and its effects may be reversed with application of a covered arterial stent. Complications seen in its use in COPD patients included episodes of right-sided heart failure, edema formation, venous stenosis, and the usual femoral access complications[76,77] Prospective investigation of the use of the ROX Coupler to treat HTN is underway, with results expected in late 2014 (NCT 01642498). This device has CE conformity marking, allowing sale within the European Economic Area, and reimbursement for the procedure is currently available throughout Europe; commercial release awaits publication of the trial results.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al: Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation* 127:e6–e245, 2013.
2. Organization WH: *Global health risks: mortality and burden of disease attributable to selected major risks*, Geneva, 2009, World Health Organization.
3. Lewington S, Clarke R, Qizilbash N, et al: Age-specific relevance of usual blood pressure to vascular mortality. *Lancet* 361:1391–1392, 2003.
4. Collaboration PS: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 360:1903–1913, 2002.
5. Egan BM, Zhao Y, Axon RN: US trends in prevalence, awareness, treatment and control of hypertension, 1988-2008. *JAMA* 303: 2043–2050, 2010.
6. Mazzaglia G, Ambrosioni E, Alacqua M, et al: Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. *Circulation* 120:1598–1605, 2009.
7. Naderi SH, Bestwick JP, Wald DS: Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. *Am J Med* 125:882–887.e1, 2012.
8. Kumbhani DJ, Steg PG, Cannon CP, et al: Resistant hypertension: a frequent and ominous finding among hypertensive patients with atherothrombosis. *Eur Heart J* 34:1204–1214, 2013.
9. Daugherty SL, Powers JD, Magid DJ, et al: Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation* 125:1635–1642, 2012.
10. DiBona GF, Kopp UC: Neural control of renal function. *Physiol Rev* 77:75–197, 1997.
11. Kopp UC, Smith LA, DiBona GF: Renorenal reflex: neural components of ipsilateral and contralateral renal response. *Am J Physiol* 249:F507–F517, 1985.
12. Handa RK, Johns EJ: Interaction of the renin-angiotensin system and renal nerves in the regulation of rat kidney function. *J Physiol* 369:311–321, 1985.
13. DiBona GF: Physiology in perspective: the wisdom of the body—neural control of the kidney. *Am J Physiol Regul Integr Comp Physiol* 289:R633–R641, 2005.
14. Johns EJ, Lewis BA, Singer B: The sodium-retaining effect of renal nerve activity in the cat: role of angiotensin formation. *Clin Sci Mol Med* 51:93–102, 1976.
15. Yoshimoto T, Sakagami T, Nagura S, Miki K: Relationship between renal sympathetic nerve activity and renal blood flow during natural behavior in rats. *Am J Physiol Regul Integr Comp Physiol* 286:R881–R887, 2004.
16. Sobotka PA, Mahfoud F, Schlaich MP, et al: Sympatho-renal axis in chronic disease. *Clin Res Cardiol* 100:1049–1057, 2011.
17. Kottke FJ, Kubicek WG, Visscher MB: The production of arterial hypertension by chronic renal artery-nerve stimulation. *Am J Physiol* 145:38–47, 1945.
18. Campese VM, Kogosov E, Koss M: Renal afferent denervation prevents the progression of renal disease in the renal ablation model of chronic renal failure in the rat. *Am J Kidney Dis* 26:861–865, 1995.
19. Ye S, Zhong H, Yanamadala S, Campese VM: Renal injury caused by intrarenal injection of phenol increases afferent and efferent renal sympathetic nerve activity. *Am J Hypertens* 2002:717–724, 2002.
20. Abramczyk P, Zwolinska A, Oficjalski P, Przybylski J: Kidney denervation combined with elimination of adrenal-renal portal circulation prevents the development of hypertension in spontaneously hypertensive rats. *Clin Exper Pharmacol Physiol* 26:32–34, 1999.
21. Villarreal D, Freeman RH, Johnson RA, Simmons JC: Effects of renal denervation on postprandial sodium excretion in experimental heart failure. *Am J Physiol* 266:R1599–R1604, 1994.
22. Grimson KS: Total thoracic and partial to total lumbar sympathectomy and celiac ganglionectomy in the treatment of hypertension. *Ann Surg* 114:753–775, 1941.
23. Peet M, Woods W, Braden S: The surgical treatment of hypertension: results in 350 consecutive cases treated by bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic gangliectomy.Clinical lecture at New York session. *JAMA* 115: 1875–1885, 1940.
24. Smithwick RH, Thompson JE: Splanchnicectomy for essential hypertension: results in 1,266 cases. *JAMA* 152:1501–1504, 1953.
25. Grimson KS, Orgain ES, Anderson B, et al: Results of treatment of patients with hypertension by total thoracic and partial to total lumbar sympathectomy, splanchnicectomy and celiac ganglionectomy. *Ann Surg* 129:850–871, 1949.
26. Smithwick RH: Surgery in hypertension. *Lancet* 2:65, 1948.
27. Converse RL, Jr, Jacobsen TN, Toto RD, et al: Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 327:1912–1918, 1992.

28. Hausberg M, Kosch M, Harmelink P, et al: Sympathetic nerve activity in end-stage renal disease. *Circulation* 106:1974–1979, 2002.
29. Krum H, Schlaich M, Whitbourn R, et al: Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 373:1275–1281, 2009.
30. Symplicity HTN-2 Investigators, Esler MD, Krum H, et al: Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomised controlled trial. *Lancet* 376:1903–1909, 2010.
31. Esler MD, Krum H, Schlaich M, et al: Renal sympathetic denervation for treatment of drug-resistant hypertension: one-year results from the Symplicity HTN-2 randomized, controlled trial. *Circulation* 126:2976–2982, 2012.
32. Krum H, Schlaich MP, Sobotka PA, et al: Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet* 383:622–629, 2014.
33. Palmer S, Stokes M, Judkins C, et al: TCT 209 Durable Reduction In Blood Pressure In the First Cohort of Patients Treated With Renal Sympathetic Denervation Therapy For Resistant Hypertension. *J Am Coll Cardiol* 60:B61, 2012.
34. Kandzari DE, Bhatt DL, Sobotka P, et al: Catheter-based renal denervation for resistant hypertension: rationale and design of the Symplicity HTN-3 trial. *Clin Cardiol* 35:528–535, 2012.
35. Oxlund CS, Henriksen JE, Tarnow L, et al: Low dose spironolactone reduces blood pressure in patients with resistant hypertension and type 2 diabetes mellitus: a double blind randomized clinical trial. *J Hypertens* 31:2094–2102, 2013.
36. Giles AHB, Morgan TO: A double-blind comparison of the effects of gydrochlorothiazide and tienylic acid (a diuretic with uricosuric properties) in hypertension. *Br J Clin Pharmacol* 6:357–362, 1978.
37. Kandzari DE, Bhatt DL, Brar S, et al: Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. *Eur Heart J* 36:219–227, 2015.
38. Mahfoud F, Mancia G, Schlaich MP, et al: TCT-60 Clinical and Procedural Outcomes of Renal Artery Denervation In Real World Patients with Hypertension: An Update From the Global SYMPLICITY Registry. *J Am Coll Cardiol* 62:B19–B20, 2013.
39. Scheurig-Muenkler C, Weiss W, Foert E, et al: Renal denervation for refractory hypertension: technical aspects, complications and radiation exposure. *Rofo* 185:550–557, 2013.
40. Krum H, Schlaich M, Whitbourn R, et al: Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 373:1275–1281, 2009.
41. Worthley SG, Tsioufis CP, Worthley MI, et al: Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: the EnligHTN I trial. *Eur Heart J* 34:2132–2140, 2013.
42. Worthley S, Worthley M, Chew DP, et al: TCT-59 Longer term safety and efficacy of sympathetic renal artery denervation using a multi-electrode renal artery denervation catheter in patients with drug-resistant hypertension: Eighteen month results of a first-in-human, multicenter study. *J Am Coll Cardiol* 62:B19, 2013.
43. Whitbourn R, Harding SM, Rothman MT, Walton T: Renal artery denervation with a new simultaneous multielectrode catheter for treatment of resistant hypertension: results from the Symplicity Spyral(™) first-in-man study. *J Am Coll Cardiol* 62: B150, 2013.
44. Ormiston JA, Watson T, van Pelt N, et al: Renal denervation for resistant hypertension using an irrigated radiofrequency balloon: 12-month results from the Renal Hypertension Ablation System (RHAS) trial. *EuroIntervention* 9:70–74, 2013.
45. Sievert H, et al: *REDUCE-HTN: 6-month results from a prospective registry study of renal denervation using a novel percutaneous bipolar radiofrequency balloon catheter in patients with resistant hypertension*, Presented at the Transcatheter Cardiovascular Therapeutics (TCT) Scientific Symposium, San Francisco, CA, 2013.
46. Barbash IM, Waksman R: Sympathetic renal denervation: hypertension beyond Symplicity. *Cardiovasc Revasc Med* 14:229–235, 2013.
47. Bonan R: *PARADISE: first in man results of a novel circumferential catheter-based ultrasound technology for renal denervation*, Abstract presented at the Annual Scientific Sessions of the European Association for Percutaneous Cardiovascular Interventions, Paris, May 16, 2012.
48. Bunte MC, Infante de Oliveira E, Shishehbor MH: Endovascular treatment of resistant and uncontrolled hypertension: therapies on the horizon. *JACC Cardiov Interv* 6:1–9, 2013.
49. Wang Q, Guo R, Rong S, et al: Noninvasive renal sympathetic denervation by extracorporeal high-intensity focused ultrasound in a pre-clinical canine model. *J Am Coll Cardiol* 61:2185–2192, 2013.
50. Henegar JR, Zhang Y, Rama RD, et al: Catheter-based radiorefrequency renal denervation lowers blood pressure in obese hypertensive dogs. *Am J Hypertens* 27:1285–1291, 2014.
51. Fischell TA, Vega F, Raju N, et al: Ethanol-mediated perivascular renal sympathetic denervation: preclinical validation of safety and efficacy in a porcine model. *EuroIntervention* 9:140–147, 2013.
52. Franceschi F, Bonan R, Khairy P, et al: Histopathological effects and evolution of transvenous beta-radiation applications in right and left atria: an animal study. *Europace* 14:745–751, 2012.
53. Waksman R, Barbash IM, Chan R, et al: Beta radiation for renal nerve denervation: initial feasibility and safety. *EuroIntervention* 9:738–744, 2013.
54. Esler M: The 2009 Carl Ludwig Lecture: pathophysiology of the human sympathetic nervous system in cardiovascular diseases—the transition from mechanisms to medical management. *J Appl Physiol* 108:227–237, 2010.
55. Schlaich MP, Sobotka PA, Krum H, et al: Renal sympathetic-nerve ablation for uncontrolled hypertension. *N Engl J Med* 361: 932–934, 2009.
56. Morlin C, Wallin BG, Eriksson BM: Muscle sympathetic activity and plasma noradrenaline in normotensive and hypertensive man. *Acta Physiol Scand* 119:117–121, 1983.
57. Hart EC, McBryde FD, Burchell AE, et al: Translational examination of changes in baroreflex function after renal denervation in hypertensive rats and humans. *Hypertension* 62:533–541, 2013.
58. Schirmer SH, Sayed MM, Reil JC, et al: Improvements of left-ventricular hypertrophy and diastolic function following renal denervation: effects beyond blood pressure and heart rate reduction. *J Am Coll Cardiol* 63:1916–1923, 2013.
59. Mahfoud F, Schlaich M, Kindermann I, et al: Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulation* 123:1940–1946, 2011.
60. Linz D, Mahfoud F, Schotten U, et al: Renal sympathetic denervation suppresses postapneic blood pressure rises and atrial fibrillation in a model for sleep apnea. *Hypertension* 60:172–178, 2012.
61. Brandt MC, Mahfoud F, Reda S, et al: Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. *J Am Coll Cardiol* 59:901–909, 2012.
62. Hering D, Mahfoud F, Walton AS, et al: Renal denervation in moderate to severe CKD. *J Am Soc Nephrol* 23:1250–1257, 2012.
63. Krum H, Sobotka P, Mahfoud F, et al: Device-based antihypertensive therapy: therapeutic modulation of the autonomic nervous system. *Circulation* 123:209–215, 2011.
64. Marshall J: Peripheral chemoreceptors and cardiovascular regulation. *Physiol Rev* 74:543–594, 1994.
65. Despas F, Lambert E, Vaccaro A, et al: Peripheral chemoreflex activation contributes to sympathetic baroreflex impairment in chronic heart failure. *J Hypertens* 30:753–760, 2012.
66. Abdala AP, McBryde FD, Marina N, et al: Hypertension is critically dependent on the carotid body input in the spontaneously hypertensive rat. *J Physiol* 590:4269–4277, 2012.
67. Sinski M, Lewandowski J, Przybylski J, et al: Tonic activity of carotid body chemoreceptors contributes to the increased sympathetic drive in essential hypertension. *Hypertens Res* 35:487–491, 2012.
68. Nakayama K: Surgical removal of the carotid body for bronchial asthma. *Dis Chest* 40:595–604, 1961.
69. Warner HR: The frequency-dependent nature of blood pressure regulation by the carotid sinus studied with an electric analog. *Circ Res* 6:35–40, 1958.
70. Bisognano JD, Bakris G, Nadim MK, et al: Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled rheos pivotal trial. *J Am Coll Cardiol* 58:765–773, 2011.
71. Hoppe UC, Brandt MC, Wachter R, et al: Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: results from the Barostim neo trial. *J Am Soc Hypertens* 6:270–276, 2012.
72. Burchell AE, Lobo MD, Sulke N, et al: Arteriovenous anastomosis: is this the way to control hypertension? *Hypertension* 64:6–12, 2014.
73. Korsheed S, Eldehni MT, John SG, et al: Effects of arteriovenous fistula formation on arterial stiffness and cardiovascular performance and function. *Nephrol dial transplantation* 26:3296–3302, 2011.
74. Zieman SJ, Melenovsky V, Kass DA: Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol* 25:932–943, 2005.
75. Manolis AJ, Iraklianou S, Pittaras A, et al: Arterial compliance changes in diabetic normotensive patients after angiotensin-converting enzyme inhibition therapy. *Am J Hypertens* 18:18–22, 2005.
76. Bertog SC, Kolmer C, Kleschnew S, et al: Percutaneous femoral arteriovenous shunt creation for advanced chronic obstructive pulmonary disease: a single-center safety and efficacy study. *Circ Cardiovasc Interv* 5:118–126, 2012.
77. Faul JL, Galindo J, Posadas-Valay R, et al: An arteriovenous fistula increases exercise capacity in patients with COPD. *Chest* 138:52–58, 2010.

44 Thoracic and Abdominal Aortic Vascular Interventions

CHRISTOPH A. NIENABER | IBRAHIM AKIN

KEY POINTS

- Acute aortic dissection is an uncommon but potentially catastrophic illness that occurs with an incidence of approximately 3.5 per 1 million person-years, with at least 8000 cases occurring annually in the United States.
- Aortic stent grafts are primarily used to reconstruct the compressed true lumen cranial to major aortic branches and to increase distal aortic flow. Proximal communications are sealed to direct flow into the true lumen, depressurize the false lumen, and induce thrombosis in the false lumen, with fibrotic transformation and subsequent remodeling of the aortic wall.
- Percutaneous stent graft placement in the dissected aorta is safer and produces better results than surgery for type B dissections.
- Use of endovascular stent grafts for repair of thoracic aortic aneurysms is a promising and less invasive therapeutic alternative to conventional surgical treatment. Most devices use a metal skeleton made of stainless steel, nitinol, or Elgiloy.
- Evaluation for repair of a thoracic aortic aneurysm considers the patient's overall risk profile, evidence of rapid enlargement of the aneurysm, diameter equal to or greater than 5.5 cm, and symptoms. Suitability for endovascular repair is based on clinical and anatomic considerations.
- Endoleaks are the most prevalent complications after stent graft treatment of thoracic aortic aneurysms. Treatment options include transcatheter coil or glue embolization, balloon angioplasty, placement of endovascular graft extensions, and open repair.
- Procedural success and long-term outcome of endovascular repair of abdominal aortic aneurysms depend on proximal and distal fixation and sealing.

AORTIC DISSECTION

Acute aortic dissection is an uncommon but potentially catastrophic illness. It occurs with an incidence of approximately 3.5 per 100,000 person-years, and at least 8000 cases occur each year in the United States.[1,2] About 0.5% of patients with chest or back pain have an aortic dissection.[3] Two thirds of patients are male, with an average age at presentation of approximately 65 years. A history of systemic hypertension, found in up to 72% of patients, is by far the most common risk factor.[1,2]

Acute aortic dissection is diagnosed within 2 weeks of onset of symptoms, which is the high-mortality period. Patients surviving 2 weeks are considered to have subacute disease, and chronic aortic dissection is diagnosed after 8 weeks. Aortic dissections are further classified according to their anatomic location using the Stanford and DeBakey classifications. The fundamental distinction is whether the dissection is proximal (i.e., involving the aortic root or ascending aorta) or distal (i.e., beyond the left subclavian artery) (Fig. 44-1).

Important precursors of typical aortic dissection include intramural hematoma, penetrating aortic ulcers, and localized intimal tears that are variants of a wall-dissecting process. Chronic hypertension affects arterial wall composition, causing intimal thickening, fibrosis, and calcification and extracellular fatty acid deposition. The extracellular matrix also undergoes accelerated degradation, apoptosis, and elastolysis with hyalinization of collagen. Both mechanisms may eventually lead to intimal disruption. Adventitial fibrosis may obstruct nutrient vessels feeding the arterial wall and the small intramural vasa vasorum. Both result in necrosis of smooth muscle cells and fibrosis of elastic structures, rendering the vessel wall vulnerable to pulsatile forces and creating a substrate for aneurysms and dissections.[1,2]

In addition to chronic hypertension, smoking, dyslipidemia, and use of crack cocaine are risk factors. Rarely, inflammatory diseases destroy the media layers and cause weakening, expansion, and dissection of the aortic wall. Iatrogenic aortic dissection may be associated with invasive retrograde catheter interventions or occur during or after valve or aortic surgery.[1,2]

Men are affected twice as often as women by acute aortic dissection, with 60% of cases classified as proximal (type A) and 40% as distal (type B) according to the Stanford classification.[1,2] Historical data for untreated aortic dissection of the ascending aorta show a mortality rate of 1% to 2% per hour within the first 24 hours, resulting in a mortality rate of up to 50% to 74% during the acute phase.[1,2] Uncomplicated acute type B dissection is less frequently lethal, with survival rates for medically treated patients of 89% at 1 month, 84% at 1 year, and up to 80% within 5 years.[1,2] Survival may be significantly improved by the timely institution of appropriate therapy. Prompt clinical recognition and definitive diagnostic testing are essential in the management of aortic dissection.

Conventional treatment of Stanford type A (De Bakey types I and II) dissection (see Fig. 44-1) consists of surgical reconstruction of the ascending aorta with complete or partial resection of the dissected aortic segment. In type A dissections, interventional endovascular strategies have no clinical application except to relieve critical malperfusion before surgery of the ascending aorta. This is done by distal endovascular interventions in cases of thoracoabdominal extension of a proximal dissection (De Bakey type I) with distal ischemic complications. In Stanford type B dissections, stent graft placement aims to remodel the thoracic descending aorta, typically by sealing one or multiple proximal entry tears with a Dacron-covered stent, initiating thrombosis of the false lumen.[4-7]

Reconstruction of a collapsed true lumen may reestablish side branch flow (Fig. 44-2). Various scenarios of malperfusion syndrome are amenable to endovascular management, including static or dynamic collapse (i.e., intima invagination) of the aortic true lumen (i.e., pseudocoarctation) (Fig. 44-3), static or dynamic occlusion of one or more vital side branches, and an enlarging false aneurysm due to a patent proximal entry tear. Although peripheral pulse deficits often can be reversed with surgical repair of the dissected thoracic aorta, patients with signs of mesenteric or renal ischemia do not fare well. Mortality rates for patients with renal ischemia are between 50% and 70% and may be as high as 87% in cases with mesenteric ischemia.[8-10]

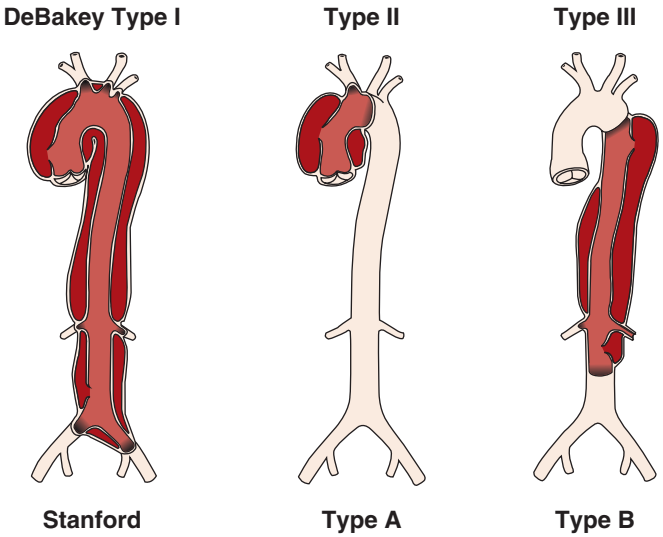
Surgical mortality rates for patients with acute peripheral vascular ischemic complications are similar to those for patients with mesenteric ischemia, and the in-hospital mortality rate may reach 89%.[11-14] Operative mortality rates for surgical fenestration are between 21% and 61%, which has encouraged percutaneous interventional management by endovascular balloon fenestration of a dissecting aortic membrane to treat mesenteric ischemia, a concept often discussed as a niche indication in complicated cases of malperfusion.[13-15]

Management of Stanford type B (De Bakey type III) dissection with the use of endovascular stent grafts has evolved slowly in anticipation of an unknown risk of paraplegia from spinal artery occlusion, as seen in up to 18% of cases after open surgery.[14,15] After technical improvements, a large series of patients has been successfully treated in various specialized centers by endovascular stent grafts placed to cover entry tears in the descending aorta and in the aortic arch. Studies have demonstrated that closure of proximal entry tears is essential to reconstruct the aortic wall and reduce the total aortic diameter. Entry tear closure promotes depressurization of the false lumen, thrombus formation in the false lumen (Fig. 44-4), and remodeling of the entire aorta.[5,6,15] In the near future, combined surgical and interventional procedures are likely to be developed for proximal dissections.[16-18]

Indications for Endovascular Aortic Interventions

Significant perioperative morbidity and mortality in cases of acute, complicated type B dissection have prompted alternative therapeutic concepts. Thoracic endovascular aortic repair (TEVAR), even though it is an off-label indication for dissection, has been approved by the U.S. Food and Drug Administration (FDA) for aneurysmal disease of the aorta. The natural course of aortic dissection is determined by two elements: early complications and late events. In the acute phase, TEVAR has abrogated impending rupture and relieved static and dynamic malperfusion. A later benefit appears to be false lumen thrombosis, mitigating the risk of aneurysmal dilation and subsequent rupture.

The role of interventional management of static or dynamic obstruction of aortic branch arteries in complicated and complex distal dissection was settled in 2010, when static obstruction of a branch was overcome by placing endovascular stents in the ostium of a compromised side branch. Dynamic obstruction may benefit from stents in the aortic true lumen, sometimes combined with side branch stenting



DeBakey

Type I	Originates in the ascending aorta, propagates at least to the aortic arch and often beyond it distally
Type II	Originates in and is confined to the ascending aorta
Type III	Originates in the descending aorta and extends distally down the aorta or, rarely, retrograde into the aortic arch and ascending aorta

Stanford

Type A	All dissections involving the ascending aorta, regardless of the site of origin
Type B	All dissections not involving the ascending aorta

FIGURE 44-1 Common classifications of thoracic aortic dissection.

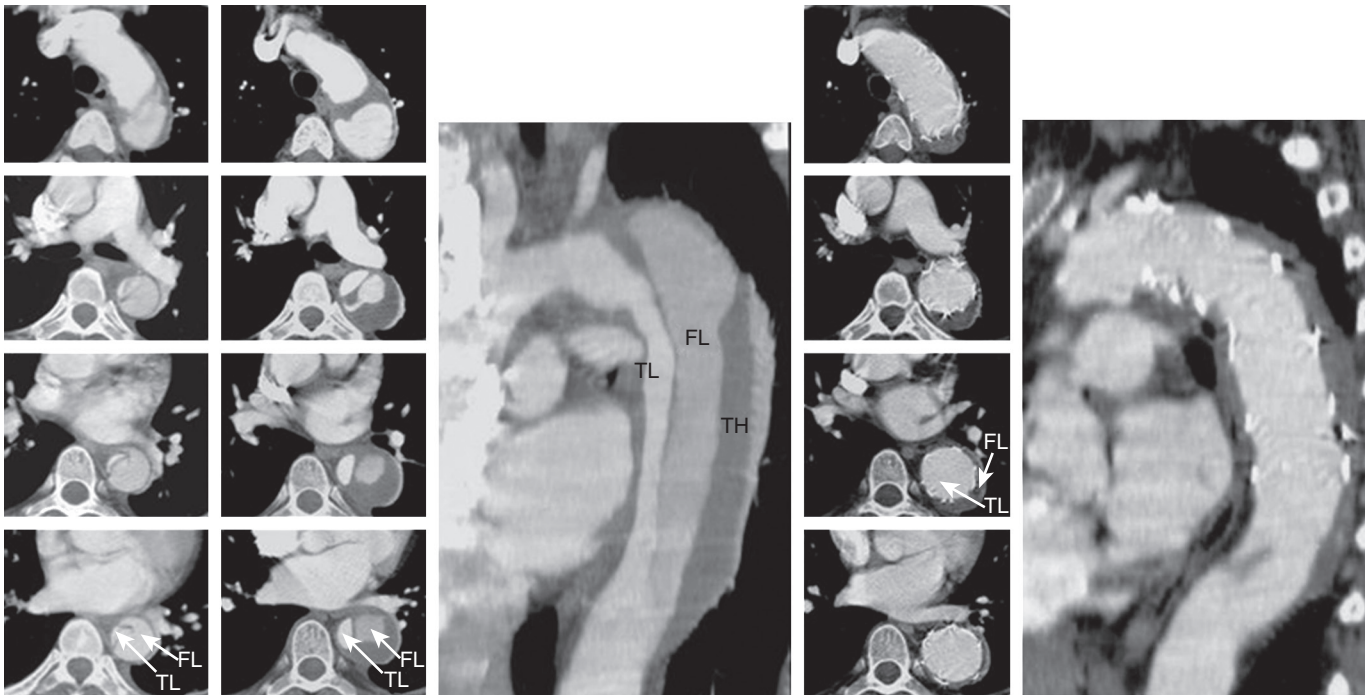


FIGURE 44-2 Type B aortic dissection in a 48-year-old man. Notice the dynamic obstruction of the true lumen (TL) in the acute phase. After stent graft placement across the proximal thoracic entry, the entire true lumen of the thoracic aorta is reconstructed over time, with complete healing of the dissected aortic wall and shrinking of the completely thrombosed (TH) false lumen (FL).

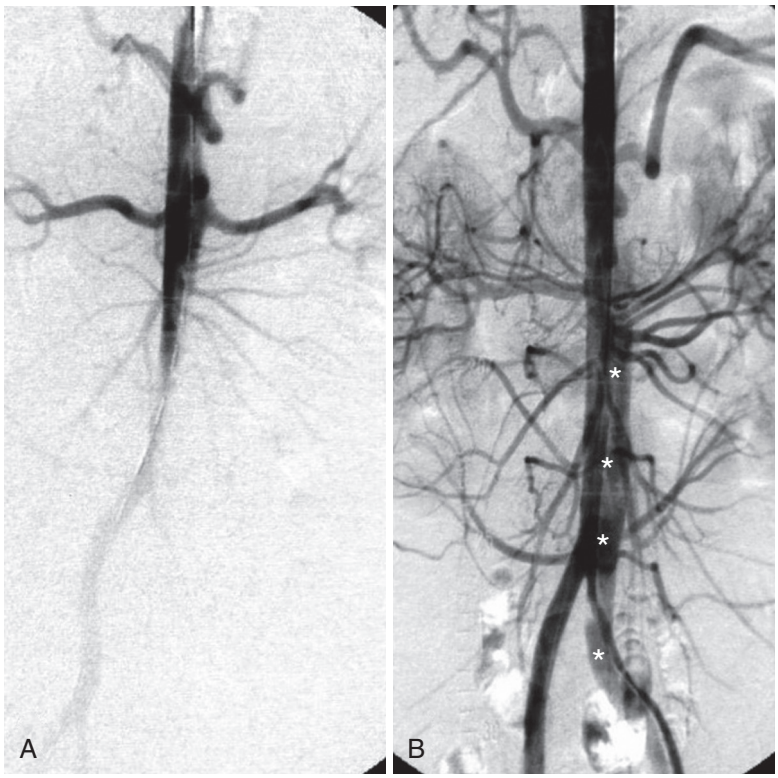


FIGURE 44-3 Digital subtraction angiography of a thoracoabdominal type B dissection. **A,** Dynamic obstruction of the true lumen distal to the renal arteries causes malperfusion of the mesentery and both lower extremities. **B,** At follow-up 3 months after stent graft placement in the proximal descending aorta, the true lumen has widened as a consequence of aortic remodeling, and the patient is asymptomatic. However, the false lumen *(stars)* in the abdominal aorta is not completely thrombosed.

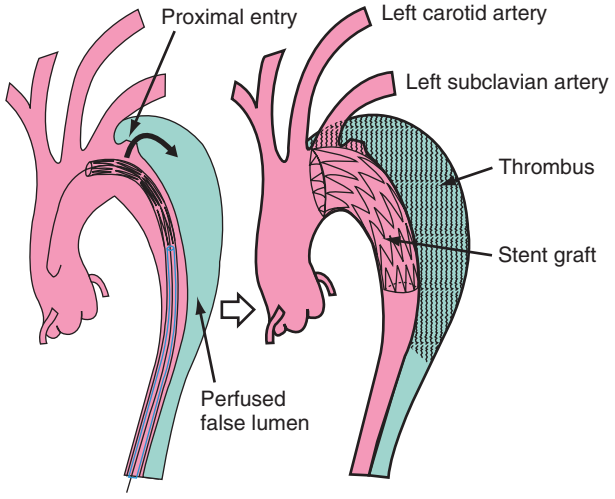


FIGURE 44-4 Interventional reconstruction of the dissected aorta with sealing of the proximal entries, depressurization of the false lumen, and initiation of the false lumen thrombosis.

and preferentially without additional balloon fenestration because fenestration does not improve stress and tension on the thin aortic wall.[19]

Sometimes, bare-metal stents deployed from the true lumen into side branches can buttress the flap in a stable position.[20] In rare cases, fenestration helps to create a reentry tear for the dead-end false lumen back into the true lumen, with the aim of preventing thrombosis of the false lumen and compromise of branches fed exclusively from the false lumen; however, this concept lacks clinical proof of benefit. Conversely, fenestration increases the long-term risk of aortic rupture because a large reentry tear promotes flow in the false lumen, which promotes aneurysmal expansion. There is also a risk of peripheral embolism from a patent but partly thrombosed false lumen.[20,21]

The most effective method to avoid an enlarging false lumen is sealing of proximal entry tears with a customized stent graft (Fig. 44-5). Absence of a distal reentry tear is desirable for optimal results but is not a prerequisite. Compression of the true aortic lumen cranial to the main abdominal branches with distal malperfusion (i.e., pseudocoarctation) is usually corrected by stent grafts that expand the compressed true lumen and improve distal aortic blood flow.[5,6,13,15] Depressurization and shrinking of the false lumen is the most beneficial result to be gained, ideally followed by complete thrombosis of the false lumen and remodeling of the entire dissected aorta (see Fig. 44-2).[17]

Like previously accepted indications for open surgical repair in complicated type B dissections, factors such as intractable pain with descending dissection, rapidly expanding false lumen diameter, extraaortic blood collection as a sign of imminent rupture, and distal malperfusion syndrome are accepted indications for emergent stent graft placement.[17,18,20-22] Even late-onset complications such as malperfusion of vital aortic side branches are likely to justify endovascular stent grafting of an occlusive lamella to improve distal true lumen flow as a first option. Surgery is employed only after an unsuccessful attempt because surgical repair has failed to prove superior to interventional treatment even in uncomplicated cases. In complicated cases, endoluminal treatment has replaced open surgery in advanced aortic centers.[4-6,20-23] Even in some cases of retrogradely extended type A dissections, TEVAR is feasible as a primary approach to seal the entry or as a secondary step after open repair of the ascending aorta.[17] Open surgery may include an "elephant trunk" or transposition of arch vessels to provide optimal landing zones for endovascular completion in a hybrid approach.[24,25] Treatment options are summarized in Table 44-1.

Stable Acute Type B Aortic Dissection

Patients with suspected acute aortic dissection should be admitted to intensive care and subjected to immediate diagnostic evaluation. Reduction of systolic blood pressure to 100 to 120 mm Hg with an eye on renal function and pain relief is an initial priority and is usually

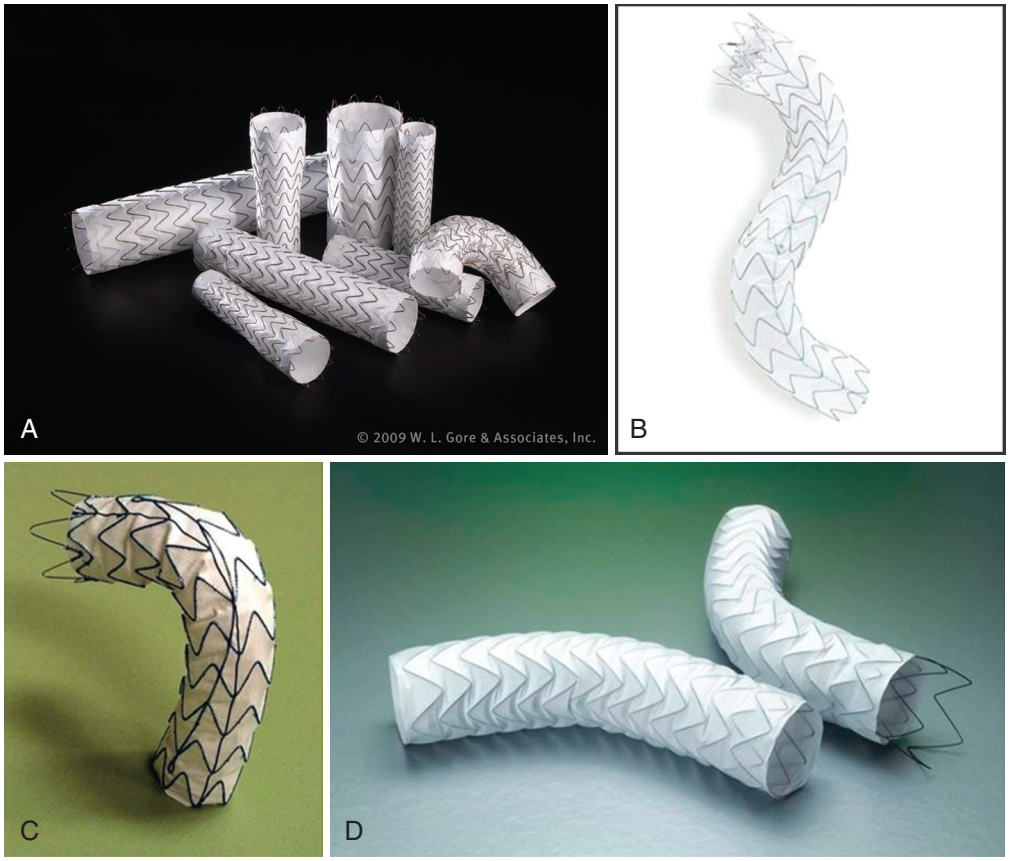


FIGURE 44-5 A selection of thoracic stent grafts from American manufacturers that are available in Europe: **A,** TAG (Gore, Flagstaff, AZ). **B,** Valiant (Medtronic AVE, Santa Rosa, CA). **C,** Relay stent-graft (Bolton Medical, Sunrise, FL). **D,** EndoFit (Duke Vascular, Inc., Santa Cruz, CA).

TABLE 44-1 Therapeutic Strategies for Aortic Dissection

Surgery
Type A aortic dissection
Acute type B dissection complicated by the following:
Retrograde extension into the ascending aorta
Dissection in fibrilinopathies (e.g., Marfan syndrome, Ehlers-Danlos syndrome)
Rupture or impending rupture (historically classic indication)
Progression with compromise of vital organs
Medical Therapy
Uncomplicated type B dissection
Stable, isolated arch dissection
Uncomplicated chronic type B dissection
Interventional Therapy
Unstable acute or chronic type B dissection
Malperfusion
Rapid expansion (>1 cm/yr)
Critical diameter (≥5.5 cm)
Refractory pain
Type B dissection with retrograde extension into the ascending aorta
Hybrid procedure for extended type A aortic dissection

achieved by morphine sulfate and intravenous beta-blocking agents with or without vasodilating drugs such as sodium nitroprusside at a dose of 0.3 µg/kg per minute or angiotensin-converting enzyme inhibitors (Table 44-2).

The heart rate should be kept low; a heart rate below 60 beats per minute significantly decreases secondary adverse events (e.g., aortic expansion, recurrent aortic dissection, aortic rupture, need for aortic surgery) in type B aortic dissections compared with a conventional rate of more than 60 beats per minute.[26] After stable blood pressure and symptom relief are obtained, a patient with an uncomplicated type B aortic dissection can be discharged (usually within 14 days) on oral drugs. Clinical and imaging follow-up are advised at 3 and 6 months and annually thereafter.

Of 384 patients with type B dissections from the International Registry of Aortic Dissection (IRAD), 73% were managed medically with an in-hospital mortality rate of 10%.[1,27] Short-term survival rates were 91% at 1 month and 89% at 1 year. The reported long-term survival rate with medical therapy varies between 60% and 80% at 4 to 5 years and is about 40% to 45% at 10 years.[1,27] Potential beneficial effects of early stenting are being studied in the ongoing Acute Uncomplicated Aortic Dissection Type B: Evaluation of Stent Graft Placement or Best Medical Treatment Alone (ADSORB) trial.[28]

Unstable Acute Type B Aortic Dissection

About 30% to 42% of acute type B aortic dissections are complicated, as evidenced by hemodynamic instability or peripheral vascular ischemia, and they have an unpredictable outcome.[27] Acute lower limb and visceral ischemia has been reported in 30% to 50%, and malperfusion syndrome occurs frequently with extended dissections, with mortality between 50% and 85% if untreated.[29] However, operative mortality rates for patients with acute aortic dissection complicated by renal ischemia are about 50% and can be as high as 88% for those with mesenteric malperfusion.[30] Of 571 patients with acute type B aortic dissection in the IRAD, 390 were treated medically. In the 125 complicated cases, 59 patients underwent standard open surgery, and 66 were subjected to TEVAR. The in-hospital mortality rate was significantly lower with TEVAR than after open surgery (10.2% vs. 33.9%, $P = .002$) (Fig. 44-6).[31]

TABLE 44-2 Initial Medical Treatment for Aortic Dissection

Drug	Mechanism	Dose	Cautions and Contraindications
Esmolol	Cardioselective β_1-blocker	Load: 500 μg/kg IV Drip: 50 μg kg^{-1} min^{-1} IV Increase by increments of 50 μg/min	Asthma or bronchospasm Bradycardia Second- or third-degree AV block Cocaine or methamphetamine abuse
Labetalol	Nonselective $\beta_{1,2}$-blocker Selective α_1-blocker	Load: 20 mg IV Drip: 2 mg/min IV	Asthma or bronchospasm Bradycardia Second- or third-degree AV block Cocaine or methamphetamine abuse
Enalaprilat	ACE inhibitor	0.625-1.25 mg IV q6h Maximum dose: 5 mg q6h	Angioedema Pregnancy Renal artery stenosis Severe renal insufficiency
Nitroprusside	Direct arterial vasodilator	Begin at 0.3 μg•kg^{-1}•min^{-1} IV Maximum dose: 10 μg•kg^{-1}•min^{-1}	May cause reflex tachycardia Cyanide/thiocyanate toxicity, especially in renal or hepatic insufficiency
Nitroglycerin	Vascular smooth muscle relaxation	5 to 200 μg/min IV	Decreases preload; contraindicated in tamponade or other preload-dependent states Concomitant use of sildenafil or similar agents

ACE, Angiotensin-converting enzyme; *AV,* atrioventricular.

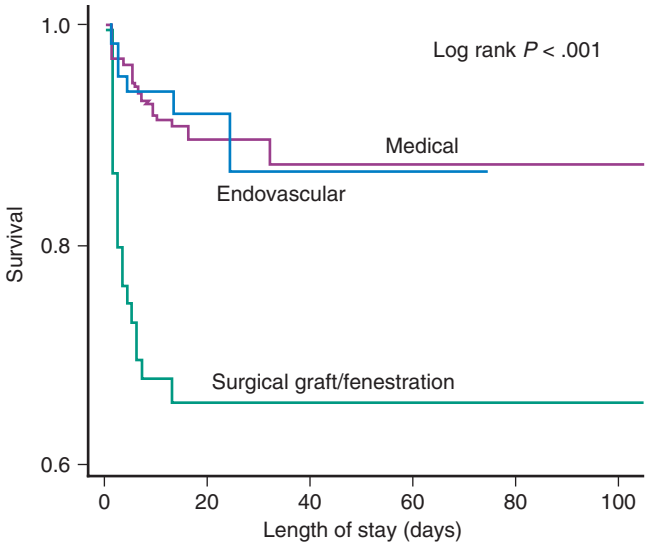


FIGURE 44-6 Comparison of medical, surgical, and endovascular treatment of complicated type B aortic dissection. (From Fattori R, Tsai TT, Myrmel T, et al: Complicated acute type B dissection: is surgery still the best option? A report from the International Registry of Acute Aortic Dissection. *JACC Cardiovasc Interv* 1(4):395-402, 2008.)

The provisional extension to induce complete attachment (PETTICOAT) technique pushes the idea of endothoracic reconstruction further by extending the stent graft scaffold distally with open-cell bare-metal stents until distal malperfusion is corrected.[32] Using this technique, aortic fenestration maneuvers and branch vessel revascularization with side branch stents usually are not needed and have almost become obsolete.

A meta-analysis of outcomes for 942 patients from 29 studies found an in-hospital mortality rate of 9% and reintervention rate of 10.4%.[33] Emergency surgical conversion or periprocedural stroke was rare (0.6% and 3.1%, respectively), and the survival rate was 88% at mean follow-up of 20 months. A second meta-analysis of outcomes for 1304 patients subjected to TEVAR for complicated acute type B aortic dissection found a technical success rate of 99% and a 30-day mortality rate of 2.6%.[34] At late follow-up, false lumen thrombosis was documented in 92.9% of patients, and surgical conversion was required in 0.8%, with endovascular reintervention performed in 1.6%. Retrograde extension into the ascending aorta and neurologic complications were reported for 0.4% and 0.6%, respectively.[34] Further results are listed in Table 44-3 and elsewhere.[35-52]

In patients deemed unsuitable candidates for conventional open surgical repair, 1- and 5-year survival rates were 74% and 31% with TEVAR compared with 93% and 78% ($P < .001$) survival rates for patients considered candidates for conventional open repair.[35] A comparison between endovascular treatment of complicated type B aortic dissection and medical therapy of uncomplicated type B dissection in 56 patients with a follow-up of 18.1 ± 16.9 months found similar outcomes in both groups but a better midterm fate of the descending thoracic aorta in the stent graft group and no associated paraplegia. There were no differences in the 5-year survival rates (86.3% for both groups).[36]

Chronic Type B Aortic Dissection

Evolution of an acute dissection to a chronic dissection involves progressive thickening of the intimal flap due to fibrosis. More intimal tears are reported in chronic type B aortic dissection than acute dissection. The growth rate of the chronically dissected distal aorta is estimated to be between 0.10 and 0.74 cm in diameter per year, depending on the initial aortic diameter and state of hypertension.[1,25]

Unfortunately, the long-term outcome after medical therapy alone is suboptimal, with a reported 50% mortality rate at 5 years and delayed expansion of the false lumen in 20% to 50% of patients at 4 years.[1,25] Expansion of the false lumen, for which an initial diameter beyond 4 cm and persistent perfusion of the false lumen are predictors, predisposes patients to aortic rupture or retrograde migration of the dissection toward the ascending aorta.[1,25] TEVAR should be considered when the aortic diameter exceeds 5.5 mm or when there is persistent thoracic pain or uncontrolled hypertension and rapid growth of the dissecting aneurysm (>1 cm/year).

Our group prospectively evaluated elective TEVAR in 12 patients with chronic type B dissection and compared the results with 12 matched surgical controls. Proximal entry closure and complete thrombosis of the false lumen at 3 months were achieved in all patients. Stent graft treatment resulted in no morbidity or mortality, whereas surgical treatment resulted in four deaths (33%, $P = .04$) and five adverse events (42%, $P = .04$)[5]. These results were confirmed by similar observations (see Table 44-3).

Whether prophylactic use of TEVAR in patients with chronic type B aortic dissections is superior to medical treatment alone was evaluated in the prospective, randomized, controlled Investigation of Stent

TABLE 44-3 Results of Endovascular Stent Graft Implantation in Various Clinical Conditions

Study	Year	N	Technical Success (%)	Paraplegia (%)	Mortality (%)	Follow-Up (mo)
Acute Complicated Type B Dissection						
Bortone et al[23]	2004	43	100	0	7	21
Xu et al[40]	2006	63	95	0	10.6	48
Verhoye et al[41]	2008	16	100	0	27	36
Fattori et al[31]	2008	66	100	3.4	10.6	1
Szeto et al[42]	2008	35	97.1	2.8	2.8	18
Khoynezhad et al[113]	2009	28	90	NA	18 (1 yr) 22 (5 yr)	36
Alves et al[114]	2009	106	99	1.8	18 (acute AD) 7 (chronic AD)	35.9
Parsa et al[115]	2010	55	100	2	37 (overall) 6 (aorta related)	14.4
Shu et al[43]	2011	45	100	NA	4.4 (1 yr)	13
Ehrlich et al[44]	2013	29	100	10	21 (1 yr) 39 (5 yr)	53
Wiedemann et al[45]	2014	110	100	4.5	15 (1 yr) 27 (5 yr)	60
Massmann et al[46]	2014	14	93	0	0	30
Chronic Type B Dissection						
Nienaber et al[5]	1999	12	100	0	0	12
Kato et al[47]	2001	15	100	0	0	24
Eggebrecht et al[47]	2005	28	100	0	13.6	12
Jing et al[61]	2008	35	100	0	7.6	48
Nienaber et al[53]	2009	72	95.7	2.8	11.1 (overall) 5.6 (aorta related)	24
Kang et al[50]	2011	76	100	0	15.7	34
Nienaber[51]	2013	72	100	2.8	11.3 (overall) 6.9 (aorta)	60
Andersen[52]	2014	75	100	0	14 (1 yr) 35 (5 yr)	34

AD, Aortic dissection; *NA,* not applicable.

Grafts in Aortic Dissection (INSTEAD) trial.[53] A total of 140 patients in stable clinical condition at least 2 weeks after the index dissection were randomly subjected to elective stent graft placement in addition to optimal medical therapy ($n = 72$) or to optimal medical therapy alone ($n = 68$). There was no difference in the all-cause death rate and a 2-year cumulative survival rate of 95.5% ± 2.5% with optimal medical therapy versus 88.9% ± 3.7% with TEVAR ($P = .15$) (Fig. 44-7). Moreover, the aorta-related death rate was not different (2.9% vs. 5.6%, $P = .68$), and the risk for the combined end point of aorta-related death and progression was similar ($P = .65$). Aortic remodeling (with true lumen recovery and thoracic false lumen thrombosis) occurred in 91.3% of patients with TEVAR and in 19.4% of those who received medical treatment ($P < .001$), which suggests ongoing aortic remodeling.

The 5-year follow up, which was evaluated in the INSTEAD-XL trial, revealed an all-cause mortality rate of 11.1% for TEVAR versus 19.3% for medical therapy ($P = .13$), whereas the aorta-specific mortality rate was 6.9% versus 19.3 ($P = .04$), with a progression rate of 27.0% versus 46.1% ($P = .04$). Landmark analysis suggested a benefit of TEVAR for all-cause mortality (0% vs. 16.9%, $P = .0003$), aorta-specific mortality (0% vs. 16.9%, $P = .0005$), and progression (4.1% vs. 28.1%; $P = .004$) between 2 and 5 years.[54]

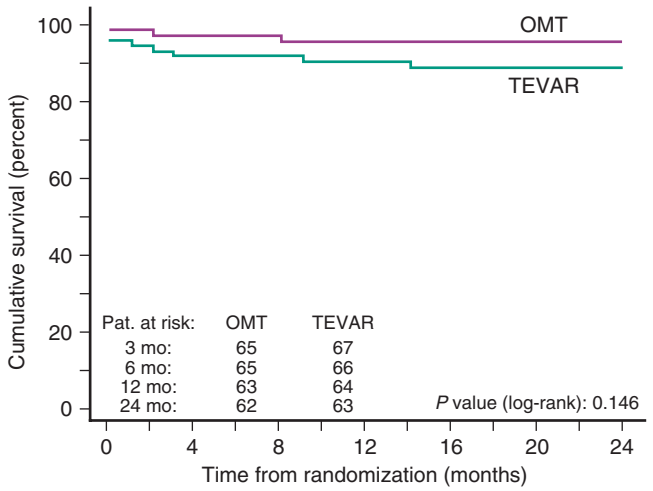


FIGURE 44-7 Cumulative survival of patients with chronic type B aortic dissection within 24 months after randomization. *OMT,* Optimal medical therapy; *TEVAR,* thoracic endovascular aortic repair. (From Nienaber CA, Rousseau H, Eggebrecht H, et al: Randomized comparison of strategies for type B aortic dissection: the Investigation of STEnt grafts in Aortic Dissection (INSTEAD) trial. *Circulation* 120:2519-2528, 2009.)

Aortic Stent Graft Placement

Aortic stent grafts are primarily used to reconstruct the compressed true lumen cranial to major aortic branches and to increase distal

aortic flow. Proximal communications are sealed to direct flow into the true lumen, depressurize the false lumen, and induce thrombosis in the false lumen, with fibrotic transformation and subsequent remodeling of the aortic wall. Stent graft placement across the origin of the celiac, superior mesenteric, and renal arteries may lead to fatal organ failure.

Important descriptive features of the thoracic aorta are derived from multislice computed tomography (CT), including the shape and size of the aortic pathology (i.e., diameter, length, and shape) and the condition of the aortic wall (e.g., atheroma, calcification, thrombus), and data are used for three-dimensional reconstruction. Although there is no standard convention for the measurement of vessel diameters, many operators measure the inner wall of the vessel (i.e., endothelial trailing edge) because it can ensure some degree of oversizing that is considered desirable for endograft placement. Contrast angiography does not provide reliable measurements.

In addition to the initial obligatory diagnostic CT angiography or magnetic resonance angiography (MRA), transesophageal echocardiography (TEE) and intravascular ultrasound may be performed to obtain additional valuable information. For instance, flow-sensitive MR sequences or contrast-enhanced TEE views show the communication sites between true and false lumens and provide insights into the dynamic flow pattern in the false lumen before stent graft placement. Access vessels must also be evaluated for size and tortuosity because the stent graft delivery systems are quite large (up to 24 Fr) and can cause significant trauma to the femoral access site and iliac arteries.

Features that are unfavorable for thoracic stent graft use include severe aortic angulation or tortuosity, friable atheroma or thrombus lining the aortic wall, and aortic pathology involving the ascending aorta. The vicinity of relevant side branches, usually the left subclavian artery (LSA) or left common carotid artery, is critical when planning to place a stent graft for type B dissection. Appropriate periinterventional image reconstruction of the aortic arch pathology enhances the result in individual cases.

The procedure is best performed in the catheterization and imaging laboratory using digital angiography and general anesthesia. The femoral artery is the most popular access site and can usually accommodate a 24-Fr stent graft system. In the Seldinger technique, a 260-cm stiff wire is placed over a pigtail catheter that is navigated with a soft wire in the true lumen under both fluoroscopic and transesophageal ultrasound guidance. In complex cases with multiple reentries in the abdominal aorta, the embracement technique, which uses two pigtail catheters, is useful (Fig. 44-8).

A pigtail catheter that has been installed in the true aortic lumen through the left brachial artery picks up the femoral pigtail catheter in the true lumen of the abdominal aorta and pulls it up into the aortic arch. This procedure ensures definite positioning of the stiff guidewire in the true lumen, which is essential for correct deployment of the stent graft. The stent is carefully advanced over the stiff wire, and the launching of the stent graft is performed with systolic blood pressure lowered to 50 to 60 mm Hg by infusion of sodium nitroprusside or by rapid right ventricular pacing to prevent dislodgement.[55,56] After deployment, short inflation of a latex balloon can improve apposition of the stent struts to the aortic wall, although only if proximal sealing of thoracic communications is incomplete.

Paraplegia may occur after the use of multiple stent grafts, but this appears to be a rare phenomenon, especially when the stented segment does not exceed 16 cm long. Both Doppler ultrasound and contrast fluoroscopy are instrumental for documenting the immediate result or initiating adjunctive maneuvers. The navigation of wires and instruments is easier for thoracic aortic aneurysms (TAAs) or ulcers, but dual imaging using ultrasound and fluoroscopy simultaneously is equally important.

A frequent anatomic consideration is the short distance between the origin of the LSA and the primary tear in type B dissections. Coverage of the ostium to the LSA must sometimes be accepted to perform endovascular aortic repair in the aortic pathology adjacent to the artery. According to observational evidence, prophylactic surgical maneuvers are not imperative or always required for safety reasons but may be relegated to an elective measure after an endovascular aortic intervention if intolerable signs or symptoms of ischemia occur.[57] However, before intentional LSA occlusion, careful attention must be paid to potential supraaortic variants (e.g., aberrant subclavian artery, nonintact vertebrobasilar system, dominant left vertebral artery) that originate directly from the aortic arch and other pathologies recognized during preinterventional vascular staging.

Retrograde Type A Thoracic Aortic Dissection

TEVAR is associated with complications. New and unexpected complications such as endoleak, graft migration, device separation, and retrograde type A thoracic aortic dissection (rATAD) have emerged. A European multicenter registry of 4750 procedures estimated the incidence of rATAD at 1.33%, with 25% being asymptomatic cases.[58] One single center reported a 2.5% rate of rATAD ($n = 11$); three of the patients had Marfan syndrome.[59] Of interest, rATAD developed intraoperatively in two patients, occurring 2 hours after the procedure in one patient, at 1 week in one patient, and in seven patients a month after TEVAR; eight of these cases were converted to open surgery, and two received medical treatment.[59]

Open surgery is the treatment of choice for potentially fatal complications, but the procedure-related mortality rate after rATAD surgery is between 20% and 57%.[58,59] The mechanisms of rATAD after TEVAR are unclear, but observations suggest that rATAD may have

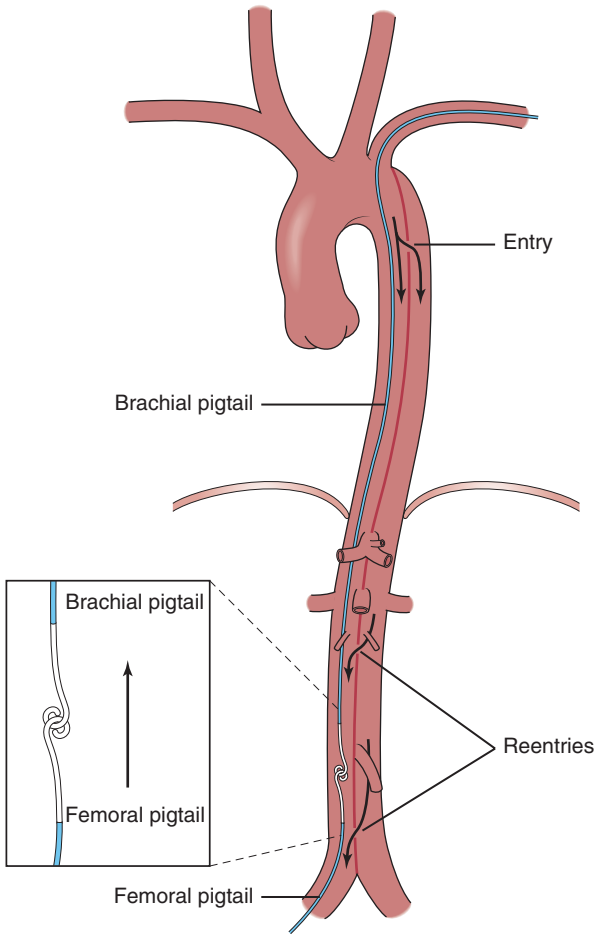


FIGURE 44-8 In complex cases with multiple reentries in the abdominal aorta, the embracement technique using two pigtail catheters ensures navigation of the guidewire in the true lumen before stent graft placement.

several causes, such as oversize ballooning, procedure- or device-related factors, unfavorable aortic dissection anatomy, and natural progression of initial aortic dissection. Among possible TEVAR-related factors, injury from proximal bare spring with outward pointing radial force was suspected. Lack of conformability of stent grafts when passively bent at the aortic arch may cause traumatic strain to the wall and create a tear. Balloon dilation after TEVAR can cause injury to the inner layers and retrograde extension. Additional balloon dilation was performed in 11 cases (23%) of rATAD in one series.[58] Oversizing of the stent graft by more than 20% in relation to the landing zone diameter was considered a risk factor for rATAD.

Genuine fragility of the aortic wall may predispose to rATAD and be a sign of natural disease progression. Newly developed type A dissections were observed in 4 of 180 and in 5 of 66 patients under medical treatment for acute type B dissection.[48,60]

Timing and Application of Endovascular Repair

The optimal timing for endovascular intervention in type B dissections remains controversial. Bortone and colleagues favor an early intervention within 2 weeks of the initial diagnosis; stent graft placement was successful in all patients referred for intervention within the first 2 weeks.[23] A high rate of reverse remodeling is likely when the patient is treated early after development of the dissection flap. With the passage of time, the dissection flap becomes more fibrosed, thickened, and matured, and it is less amenable to TEVAR.

Shimono and coworkers reported that complete obliteration and resolution of the false lumen after endovascular stent graft treatment was more frequently achieved in cases of acute aortic dissection than those of chronic aortic dissection (70% vs. 38.5%).[49] Conversely, others have observed higher mortality rates for patients with acute type B aortic dissection.[47,61] Morphologic change of the initially fragile dissecting membrane to a more fibrotic and seemingly stable membrane in the chronic phase are critical for endovascular repair, suggesting that TEVAR is safer after a minimum of 4 weeks after the onset of aortic dissection but before the chronic stage.[62] The more stable clinical status of patients in the chronic phase of aortic dissection may be an important determinant of better survival after TEVAR.

Because of the lack of prospective, randomized data comparing immediate and delayed intervention in various clinical and anatomic conditions, no general recommendation has been issued about the timing of endovascular treatment. However, observational evidence may favor an early intervention during the window of aortic plasticity when justified by a low complication rate.

Endovascular stent grafting has emerged as an alternative therapy to the open surgical repair of aortic dissection. Although patients at high surgical risk can benefit from the endovascular technology, the exact role of stent grafting awaits definition as long-term data and experience continue to accumulate and as devices and techniques evolve. Instead of replacing conventional surgical treatment completely, endovascular repair will likely play a complementary role and offer a less invasive option. The limitations of both approaches are distinct. What is considered high risk for surgery is defined by clinical parameters in terms of comorbidities, but contraindications to endovascular stent grafting are defined by anatomic constraints. Both strategies will continue to coexist and may merge to generate hybrid procedures.

DESCENDING THORACIC AORTIC ANEURYSM

Endovascular Repair by Stent Grafts

TAAs, which were classified by Crawford and Safi (Fig. 44-9), occur predominantly in the elderly and have been increasing in incidence as the population ages and diagnostic capabilities advance.[63] With an incidence of 6 to 10 per 100,000 person-years, TAAs are less common than abdominal aortic aneurysms (AAAs) but remain life-threatening.[63-65] In several series, the ascending aorta was involved in 51%, the aortic arch in 11%, and the descending thoracic aorta in 38% of TAA cases. One fourth of the patients had concomitant infrarenal aneurysmal aortic disease, and up to 13% had multiple aneurysms, whereas the risk of having a TAA when AAA was diagnosed was between 3.5% and 12%.[65]

The pathogenesis of aortic aneurysms has not been fully established, but it is thought to be multifactorial and include atherosclerosis, increased tissue protease activity, antiprotease deficiency, and genetic collagen defects such as Marfan syndrome and Ehlers-Danlos syndrome. Up to 20% of patients with an aneurysm have a first-degree relative with the same disorder.[66]

Weakening of the aortic wall can also be induced by inflammation resulting from microbiologic diseases or multisystem inflammation disorders. Aortitis induced by syphilis and *Staphylococcus aureus* infection is well known. Kawasaki syndrome is characterized by more circumscriptive wall thickening and aneurysm formation, whereas syphilis can induce diffuse wall thickening and aneurysm formation of the ascending aorta. Behçet disease, like other forms of vasculitis, may lead to local aneurysm formation and perforation rather than

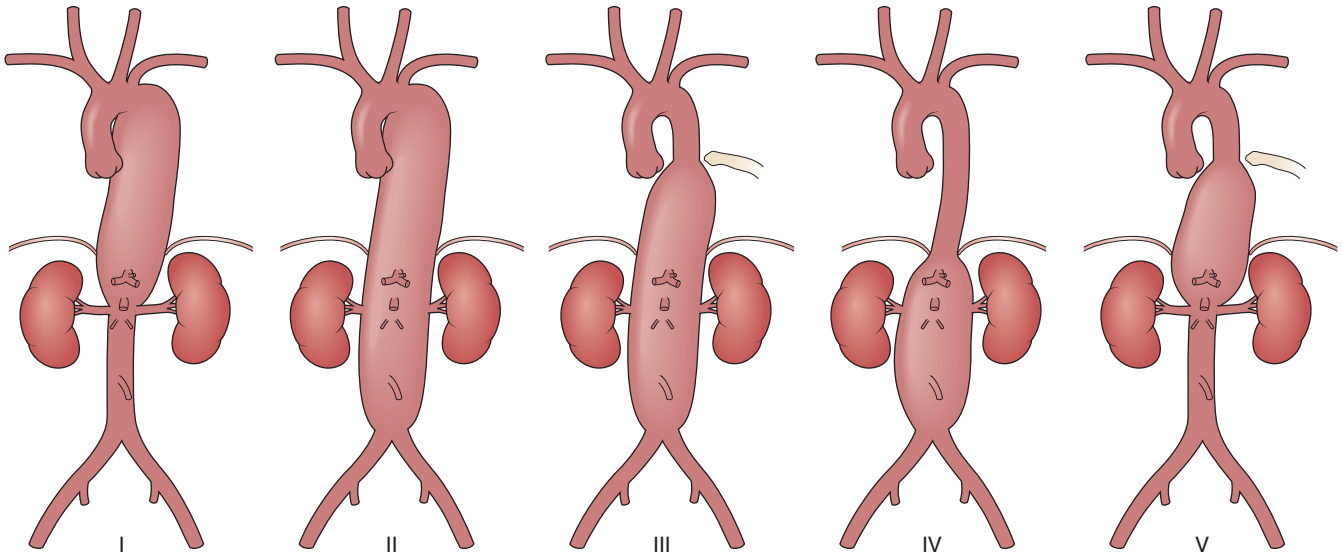


FIGURE 44-9 Classification of thoracoabdominal aortic aneurysms.

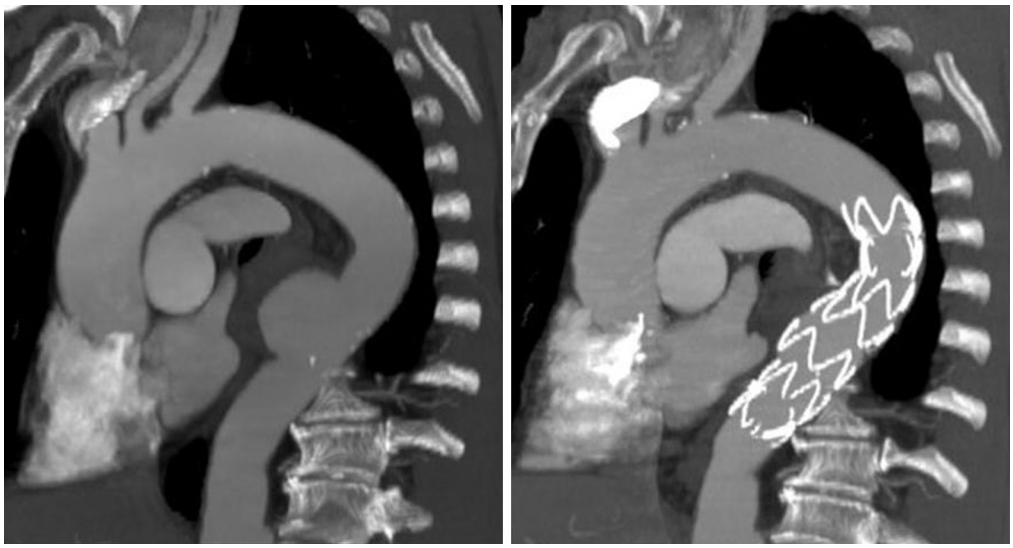


FIGURE 44-10 Computed tomography angiography shows a circumscribed aneurysm of the descending thoracic aorta in a middle-aged man selected for endografting *(left)*. One-year follow-up after successful endovascular exclusion of the aneurysm by stent graft placement demonstrates marked shrinkage of the periprosthetic aneurysm and optimal wall apposition of the stent graft *(right)*.

dissection. Thoracic and abdominal aneurysm may develop in giant cell arteritis.

The use of cocaine and amphetamines can lead to aortic wall thinning and aneurysm formation. In aortic stenosis, poststenotic aneurysm formation can occur, which may be enhanced after aortic valve prosthesis implantation. An important cause of aneurysm formation is related to trauma, particularly high-speed deceleration trauma involving the aortic isthmus in 95%. About 15% to 20% of deaths are related to aortic trauma in these patients.

The natural history of TAAs is one of progressive expansion and weakening of the aortic wall, leading to eventual rupture.[67-69] Initial aneurysmal size can also be an important predictor of aneurysm growth. A study of 721 patients found that TAA size had a profound impact on the risk of rupture, with an annual rate of 2% for aneurysms less than 5 cm, 3% for aneurysms 5 to 5.9 cm, and 7% for aneurysms larger than 6 cm in diameter. The risk appears to rise abruptly as thoracic aneurysms reach a size of 6 cm.[70] Nondimensional variables with an impact on the expansion rate and risk of rupture should also be evaluated. In a multivariate regression analysis, the Mount Sinai group identified older age, pain (even uncharacteristic pain), and a history of chronic obstructive pulmonary disease as independent risk factors for TAA rupture.[71]

With an associated mortality rate of 94%, TAA rupture is usually a fatal event.[64,72] Olsson and colleagues found that 22% of the patients in their survey with ruptured aortic aneurysms and dissection did not reach the hospital alive and that the diagnosis was made at autopsy.[73] The 5-year survival rate of unoperated TAA patients approximates 13%, whereas 70% to 79% of those who undergo elective surgical intervention are alive at 5 years.[74-76]

A novel predictor for TAA rupture, the aortic size index, may be useful for predicting increasing rates of rupture, dissection, or death. Individual body surface area is used for the aortic size index (aortic diameter/m^2), enabling improved selection of individual patients for surgical repair. An aortic size index of 2.75 cm/m^2 or less represents a low risk of rupture (≈4%/year), 2.75 to 4.24 cm/m^2 correlates with a moderate risk (≈8%/year), and greater than 4.25 cm/m^2 indicates a high risk (≈20%/year), underlining the importance of aortic size for predicting complications.[77] The risk of rupture should be assessed for all patients who are suitable candidates for surgical treatment.

The use of endovascular stent grafts for the repair of TAAs is emerging as a promising, less invasive therapeutic alternative to conventional surgical treatment. Endovascular treatment of aortic aneurysms is achieved by transluminal placement of one or more stent graft devices across the longitudinal extent of the lesion. The prosthesis bridges the aneurysmal sac to exclude it from high-pressure aortic blood flow, allowing sac thrombosis around the endograft and possible remodeling of the aortic wall (Fig. 44-10).

Endovascular aortic repair techniques were initially applied in cases of AAA, and efforts to adapt this technology for TAAs are ongoing. As is the case for AAAs, a less invasive approach to TAA repair is highly desirable because the patient population tends to be elderly and harbors multiple comorbidities.[69,76,78] Continued development of endovascular therapy for thoracic aneurysms is likely to provide greater benefits in terms of patient outcomes than those observed with AAAs. Conventional surgical treatment of TAA is physiologically more demanding and carries a greater operative risk. It mandates open thoracotomy, aortic cross-clamping, resection of the aneurysm, and replacement with a prosthetic graft; this often requires cardiopulmonary bypass.[79] For the aortic arch, surgical intervention is most likely the best method, and it is frequently combined with stent graft implantation to seal the distal aortic arch to the descending aorta.

Special systems have been designed so that implantation can be performed using an antegrade strategy.[76-79] For thoracic descending or thoracic-abdominal aortic aneurysms, the surgical strategy has been developed over the last 15 years to prevent ischemic complications. The operation requires permissive hypothermia (32 to 34° C nasopharyngeal value), moderate heparinization (1 mg/kg), renal artery perfusion with 4° C crystalloid solution, aggressive reattachment of segmental arteries (especially between T8 and L1), sequential aortic clamping and cerebrospinal fluid drainage, left heart bypass during proximal anastomosis, and selective perfusion of celiac and superior mesenteric arteries during intercostal, visceral and renal anastomosis.[76-79]

Despite advances in operative technique, intraoperative monitoring, and postoperative care, the mortality and morbidity rates for surgery remain substantial and less favorable than outcomes for open AAA repair. The mortality rate for TAA surgical repair ranges from 5% to 20% in elective cases and up to 50% in emergent situations.[76,80-84]

Major complications associated with surgical TAA treatment include renal and pulmonary failure, visceral and cardiac ischemia, stroke, and paraplegia. Paraplegia is a particularly devastating complication that is almost unique to the surgical treatment of TAAs, occurring in 5% to 25% of cases, compared with less than 1% for AAAs.[74,76,83-86]

For these reasons, significant numbers of TAA patients are not candidates for open repair and have been without a treatment option until recently.

Endovascular aneurysm repair of the thoracic aorta currently focuses on the descending portion. This aortic segment provides a substrate more amenable for endovascular stent graft repair due to avoidance of the great vessels proximally and major visceral branches and aortic bifurcation distally. Despite these anatomic advantages and the ability to draw from early experiences with endovascular AAA repair, the development of stent grafting in the thoracic aorta has progressed more slowly than that involving its infrarenal counterpart.

The thoracic aorta poses several challenges that have impeded simple adaptation of the endovascular devices and techniques developed for the abdominal aorta.[87] First, the hemodynamic forces of the thoracic aorta are significantly more aggressive and place greater mechanical demands on thoracic endografts. The potential for device migration, kinking, and late structural failure are important concerns. Second, greater flexibility is required of thoracic devices to conform to the natural curvature of the proximal descending aorta and to lesions with tortuous morphology. Third, because larger devices are necessary to accommodate the diameter of the thoracic aorta, arterial access is more problematic. More TAA patients than AAA patients are women, and access vessels tend to be smaller in women. Fourth, as with conventional open TAA repair, paraplegia remains a potential complication of the endovascular approach despite the absence of aortic cross-clamping.[88,89] Fifth, TAAs often extend beyond the boundaries of the descending thoracic aorta and involve more proximal or distal aorta than desired. Management of the LSA in particular has gained considerable attention.[90-92] With these challenges in mind, significant progress has been achieved since the first stent graft was deployed for TAA exclusion in 1992.[57,88,93]

Technical Aspects of Endovascular Repair

Early clinical experience with stent grafting of the thoracic aorta was based on the use of first-generation, homemade devices that were rigid and required large delivery systems (24 to 27 Fr).[93,94] Since then, several commercial manufacturers of abdominal endografts have created derivatives for the thoracic aorta with dramatic improvements over homemade devices. The endoprostheses are composed of a stent (nitinol or stainless steel) covered with fabric (i.e., polyester or polytetrafluoroethylene [PTFE]).

Evaluation for repair of a TAA considers the patient's overall risk profile, evidence of rapid enlargement of the aneurysm, a diameter of 5.5 cm or greater, and symptoms. The suitability of the patient for endovascular repair is based on clinical and anatomic considerations. Preprocedural imaging with spiral CT or magnetic resonance imaging (MRI) is essential to characterize the lesion and access route. Measurements from imaging data are used to select the appropriate diameter and length of a device. The aneurysm's location is determined in relation to the LSA and celiac axis.

Successful TAA exclusion requires normal segments of native aorta at both ends of the lesion (i.e., landing zone or neck) of at least 15 to 25 mm to ensure adequate contact between the endoprosthesis and the aortic wall and formation of a tight circumferential seal. Landing zones that are markedly angled or conical or that contain thrombus can result in poor fixation. Devices are oversized by 10% in diameter to provide sufficient radial force for adequate fixation. The vascular access route for device introduction and delivery to the pathologic target must be of sufficient size and suitable morphology. The preferred and most common site (41% to 58%) of vascular access is the common femoral artery. Less frequently, access to the iliac artery (9% to 44%) through an extraperitoneal approach is required.[94,95] Severe stenosis and tortuosity of the abdominal and thoracic aorta distal to the target are also contraindications for endovascular repair.

Despite these criteria, treatment failures can occur. However, the specific contributing factors and frequencies are unknown, particularly over the long term. Follow-up surveillance with serial CT scans at 1, 6, and 12 months and annually thereafter is recommended to monitor changes in aneurysm morphology, identify device failures, and detect endoleaks.

Hybrid Procedures for Aortic Arch Pathologies

The aortic arch morphology is challenging because of angulation and the proximity of the supraaortic branches that need to be preserved. Traditionally, open arch reconstruction using hypothermic cardiac arrest, extracorporeal circulation, and selective cerebral perfusion has been demonstrated to effectively manage aortic arch pathologies. However, this standard procedure for any arch pathology carries a significant mortality rate (2% to 9%) and risk of paraplegia and cerebral stroke in 4% to 13% of cases.[96,97] Open repair is therefore often reserved for low-risk patients.

Hybrid arch procedures are a combination of debranching bypass (i.e., supraaortic vessel transposition) to establish cerebral perfusion and subsequent thoracic endografting to provide patient-centered solutions for complex aortic arch lesions. Hybrid arch procedures are performed without hypothermic circulatory arrest and extracorporeal circulation. These procedures could expand the treatment group to older patients with severe comorbidities and to those requiring repeat surgery who are currently ineligible for open surgical intervention. The key to success is the quality of the unimpaired suitable ascending aorta as a donor site for the debranching bypass and proximal landing zone for the endografts (Fig. 44-11).

Clinical Experience

The literature on thoracic stent grafting consists mostly of small to medium-sized case series with short- to medium-term follow-up (Table 44-4). Nevertheless, these studies illustrate a consensual pattern of outcomes when viewed in the aggregate. Overall, successful device deployment is achieved in 85% to 100% of cases, and the periprocedural mortality rate ranges from 0% to 14%, falling within or below elective surgery mortality rates of 5% to 20%.[87,94-112] Outcomes have improved over time with accumulated technical expertise, the use of commercially manufactured devices, and improved patient selection criteria.

The published collective experiences of the European Collaborators on Stent-Graft Techniques for Abdominal Aortic Aneurysm Repair (EUROSTAR) and United Kingdom Thoracic Endograft registries ($N = 249$) demonstrate successful deployment in 87% of cases, a 30-day mortality rate of 5% for elective cases, and paraplegia and endoleak rates of 4% each.[112] The FDA phase II trial data from exclusive deployment of the Gore TAG endograft in 142 patients with TAA revealed similar results: technical success in 98%, a 30-day mortality rate of 1.5%, paraplegia in 3.5%, and endoleak in 8.8%.[111] These results cannot be directly compared with the outcomes of contemporary surgical studies. Most patients with TAA repaired by the endovascular approach in these studies were older and sicker, having been deemed high-risk patients or not suitable for open surgical repair. For example, according to the American Society of Anesthesiologists (ASA) physical status classification; which predicts procedural risk (i.e., low risk, 1 to 2; intermediate risk, 3; high risk, 4 to 5; organ donor, 6), 52% of patients in the combined EUROSTAR and United Kingdom registries were preoperatively classified as ASA 3 or higher.[112]

True comparisons between conventional therapy and the endovascular alternative can be made only after the completion of prospective, randomized, controlled trials. Although these trials are being conducted, a few studies have compared endovascular treatment with anatomically similar open surgery historical controls. As part of the phase II Gore Excluder study, 19 TAA patients who were candidates for open repair received stent graft therapy and were compared with a nonrandomized cohort of 10 patients who had undergone open repair before the availability of thoracic stent grafts.[103] All aneurysms met the same inclusion and exclusion criteria for anatomic involvement. The 1-year survival rate was 89.5% for the endovascular group and 70% for the operative group. As expected, mean hospital stay (6.2 vs. 16.3 days)

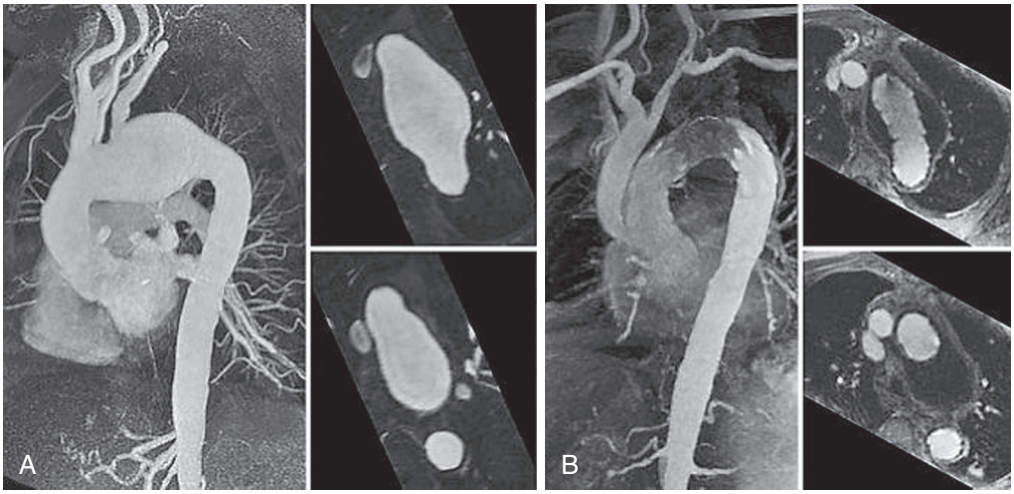


FIGURE 44-11 Contrast-enhanced magnetic resonance angiography of the aorta in a case of an aortic aneurysm. **A,** Aneurysm of the aortic arch involves the supraaortic branches. **B,** Postinterventional surgical result after a hybrid procedure with debranching of the supraaortic vessels and stent graft implantation in the aortic arch.

and length of intervention (155 vs. 256 minutes) were significantly less for those treated endovascularly. In a similar study, Ehrlich and colleagues found a decreased 30-day mortality rate (10% vs. 31%), mean hospital stay (6 vs. 10 days), and mean intervention time (150 vs. 325 minutes) with endovascular repair; the paraplegia rate was also decreased (0% vs. 12%).[98]

Complications and Outcomes

The thoracic aorta has unique anatomic features and a distinctive biomechanical and hemodynamic environment, which explain some of the rare late complications specific to devices used in this location. The descending thoracic aorta, unlike the abdominal aorta, is relatively mobile in the chest and is subject to a complex and vigorous three-dimensional motion. Fixation points are the aortic root, origins of major branches, and a long, mobile aortic segment extending from the LSA to the celiac artery. The thoracic aorta elongates, angulates, and enlarges between these points, and aneurysms may develop.

The mechanical forces exert a complex pattern of dynamic circumferential, radial, and axial forces on thoracic stent grafts, resulting in a stress field significantly different from that exerted on abdominal stent grafts. Development of aneurysms of the dissected aorta after stent graft treatment is an infrequent event. False-lumen thrombosis due to thoracic endografting is essential to prevent late aortic expansion, and close clinical and imaging follow-up are essential to monitor anatomic changes over time.

An unresolved problem, even after successful thoracic stent graft placement, is the fate of the distal aortic segment. In the case of large reentry points, the thoracic-abdominal segment of the false lumen has a tendency to remain patent and remodel completely, setting the stage for late complications such as aneurysmal enlargement at the proximal or distal end of the stent graft. Other complications include perforations of the fragile aortic intima by the ends of the metallic stent, especially in the early phase of acute aortic dissection, and injuries caused by stiff guidewires and devices manipulation, setting the stage for aneurysmal evolution. The risk of these complications seems to be reduced by introducing the more flexible and soft-tip delivery systems with the aid of minimally traumatic thoracic guidewires specifically designed for the interventions. The duration of an endovascular procedure may also correlate with complications such as stroke or bleeding; both of which may be reduced by experienced operators requiring less than 30 minutes to complete a case.

Patency of the abdominal aortic false lumen may be related to persistent communications between the true lumen and false lumen. Treatment of these communications at the level of distal thoracic and abdominal aorta can obliterate the false lumen and reduce the aortic diameter, but in practice, closure is difficult to achieve because of the proximity or involvement of the visceral branches. Another source of late complications is distention of the aorta beyond the portion covered by the stent graft due to the mechanical weakness of the dissected aortic walls. Prevention of these complications can be partially achieved during the primary procedure by ensuring adequate landing zones proximal and distal to the stent graft and by closure of large fenestrations along the length of the false lumen.

Prosthetic graft infection is a rare complication. The diagnosis requires imaging, hematologic, and clinical studies. The findings of air in the aneurysm sac or excessive soft tissue accumulation and progressive enlargement of the aneurysm sac point to a stent infection. Similarly, in the setting of suspicious imaging results, raised levels of systemic inflammation markers may be informative, as are the clinical symptoms of an infection. In most cases, positron emission tomography (PET) radionuclide studies are helpful.

Treatment of thoracic endograft infection depends on the diagnostic certainty, pathogenesis of the organism, extent of infection, and the presenting features and medical comorbidities of the patient. The spectrum of management strategies includes conservative treatment with targeted antibiotics delivered peripherally or by direct puncture and instillation into the perigraft space, insertion of another stent graft inside the infected graft, and excision of the infected stent graft with debridement of the surrounding tissue and in situ or extraanatomic vascular reconstruction.

Treatment of aortic graft infection remains problematic. In the absence of management algorithms that can define treatment in particular conditions based on patient presentation and degree of infection, decisions must be tailored to each patient and weigh the risks of the available options. A decision must be made about whether treatment is intended to be curative or palliative. Curative treatment that requires an aggressive approach with open surgery and that is associated with a relatively high mortality rate may be justified. In cases of palliation, placement of an endovascular graft (graft-in-graft approach) to prevent life-threatening bleeding or fistulation may be considered. Patients with complex graft disease should always be treated in experienced centers that have the required treatment modalities at their disposal.

TABLE 44-4 Summary Data on Studies of Endovascular Repair of Thoracic Aortic Aneurysm

Study	N	Mean Follow-Up (mo)	Devices	Technical Success	30-Day Mortality (%)	Long-Term Survival (%)	Paraplegia (%)	Endoleak (%)
Dake et al, 1998[94]	103	22	Homemade	83% complete thrombosis	9	73 (actuarial 2 yr)	3	24
Ehrlich et al, 1998[98]	10	NA	Talent	80% complete thrombosis	10	NA	0	20
Cartes-Zumelzu et al, 2000[99]	32	16	Excluder, Talent	90.6%	9.4	90.6 (32 mo)	3.1	15.4
Grabenwoger et al, 2000[100]	21	NA	Talent, Prograft	100%	9.5	NA	0	14.3
Greenberg et al, 2000[101]	25	15.4	Homemade	NA	20 (12.5 for elective, 33 for emergent)	NA	12	12
Temudom et al, 2000[102]	14	5.5	Homemade, Vanguard, Excluder	78.6%	14.3	NA	7.1	14.3
Najibi et al, 2002[103]	24	12	Excluder, Talent	94.7%	5.3	89.5 (1 yr)	0	0
Heijmen et al, 2002[104]	28	21	Talent, AneuRx, Excluder	96.4%	0	96.4 (mean, 21 mo)	0	28.6
Schoder et al, 2003[105]	28	22.7	Excluder	100%, 89.3% complete exclusion	0	96.1 (1 yr), 80.2 (3 yr)	0	0 25
Marin et al, 2003[106]	94	15.4	Excluder, Talent	85.1%	NA	NA	NA	24
Lepore et al, 2003[107]	21	12	Excluder, Talent	100%	9.5	76.2 (1 yr)	4.8	19
Sunder-Plassman et al, 2003[106]	45	21	Corvita, Stenford, Vanguard, AneuRx, Talent, Excluder	NA	6.7	NA	2.2	22.2
Ouriel et al, 2003[87]	31	6	Excluder, Talent, Other commercial	NA	12.9	81.6 (1 yr)	6.5	32.3
Bergeron et al, 2003[109]	33	24	Excluder, Talent	NA	9.1	75.8 (mean 24 mo)	0	0
Czerny et al, 2004[110]	54	38	Excluder, Talent	94.4%	9.3	63 (3 yr event free)	0	27.8
Makaroun et al, 2005[111]	142	29.6	TAG	97.9%	1.5	75 (2-yr freedom from death)	3.5	8.8
Leurs et al, 2004[112]	249	1-60	Excluder, Talent, Zenith, EndoFit	87%	10.4 (5.3 for elective, 27.9 for emergent)	80.3 (1 yr)	4	4.2
Greenberg et al, 2005[116]	100	14	Zenith	NA	NA	83 (1 year)	1	6
Wheatley et al, 2006[117]	156	21.5	Gore	98.7%	3.8	76.6 (1 year)	0.6	11.5
Bavaria et al, 2007[172]	140	24	Gore	98%	2.1	NA	2.9	10
Fairman et al, 2008[173]	195	12	Talent	99.5%	2.1	83.9 (1 year, all cause) 96.9 (1 year, aneurysm related)	1.5 (paraplegia) 3.6 (stroke)	NA
Hughes et al, 2010[174]	79	23	Zenith, Gore, Talent	98.7%	5.1	77 (55 mo, overall) 86 (aorta specific)	1.3 (paraplegia) 2.5 (stroke)	2.5
Foley et al, 2012[118]	195	60	Talent	100%	NA	43.9	NA	5.7 (type I, III)
Fossaceca et al, 2013[119]	53	25.6	NA	100%	7.5	39	3.8	22.6
Matsumura et al, 2014[120]	160	60	Zenith	100%	NA	37	NA	5.7

NA, Not applicable.

With avoidance of aortic cross-clamping and prolonged iatrogenic hypotension, endovascular TAA repair was expected to result in lower incidences of paraplegia compared with conventional treatment. The initial concern after stent graft placement was the risk of spinal cord ischemia due to the frequent need to cover multiple intercostal arteries and the artery of Adamkiewicz, usually the only prominent intersegmental branch from the aorta at the lower thoracic or upper lumbar level. Paraplegia rates have ranged from 0% to 5% in endovascular studies,[87,94-112] compared with 5% to 25% for open repair cases.[74,76,81-84] Although low, these rates remain significant, especially because it is impossible to reimplant intercostal arteries in this setting. Some evidence suggests that the occurrence of paraplegia is associated with concomitant or prior surgical AAA repair and increased exclusion length due to the absence of lumbar and hypogastric collateral circulation.[101-121] Adjunctive measures to further reduce spinal cord ischemic complication rates in endovascular TAA repair are being investigated.[122]

Endoleaks are the most prevalent complications after TAA stent graft treatment. However, their observed frequency is substantially less than that reported for AAA endograft repair,[123] and the distribution of endoleak types is also different. TAA endoleaks occur more commonly at the proximal or distal attachment site (type I endoleak), whereas most AAA endoleaks are type II.[124] Type I endoleaks are more serious and require expeditious intervention because they represent direct communications between the aneurysm sac and aortic blood flow.[125]

Treatment options for endoleaks include transcatheter coil or glue embolization, balloon angioplasty, placement of endovascular graft extensions, and open repair.[126,127] Although current anatomic criteria limit thoracic stent graft exclusion to lesions located at least 15 to 25 mm away from the origin of the LSA and celiac trunk, it is common for descending TAAs to be located within the proximal or distal neck length necessary for adequate fixation. At the proximal end, the landing zone can be extended by prophylactic transposition of the LSA to the left carotid artery or by bypass graft placement.[88] Alternatively, the uncovered proximal portion of the Talent endograft can be placed across the LSA origin to achieve fixation without blocking flow. However, case reports of inadvertent coverage of the LSA origin found no resulting complications,[128] and subsequent studies determined that these maneuvers may not be necessary as long as there is no obstruction of the right vertebral or carotid artery and the left internal mammary artery is not used as a coronary bypass conduit.[90-92] Complications such as left arm ischemia have been rare, possibly due to collateral blood supply through retrograde left vertebral flow. Most centers intentionally cover the LSA origin if necessary and reserve secondary revascularization procedures for treatment of related symptoms if they develop.[57,88]

For more proximal TAAs involving the aortic arch, branched and fenestrated stent grafts are being developed to accommodate perfusion through the great vessels.[129,130] Although feasibility has been demonstrated, it is already apparent that the required implantation techniques would be highly complex and would demand considerable technical expertise. Some centers have been investigating techniques to create fenestrations intraoperatively after device deployment and coverage of critical branches.[131]

In contrast, there are no easy management strategies to deal with a short distal neck. In this setting, fenestrated and branched grafts have been used in isolated cases, but the overall experience is limited. Intentional coverage of the celiac artery is not recommended given the risk of hepatic and visceral ischemia. Although a normal superior mesenteric artery may provide collateral flow, no methods exist to predetermine whether the collateral supply would be sufficient. Moreover, the celiac trunk may serve as a prominent source of retrograde endoleak if the artery is covered without adjunctive transcatheter occlusion.

In distal aneurysms that involve the descending thoracic and the abdominal aorta, combined open AAA repair and endovascular TAA exclusion is a novel treatment approach under investigation. Stent grafts are also being used to treat patients with diffuse aneurysmal disease involving the entire thoracic aorta. In these patients, the traditional surgical treatment is a two-stage procedure called the *elephant trunk technique*.[132] In the first stage, the ascending aorta and aortic arch are repaired by a median sternotomy, and an extra-long graft is used for reconstruction, which leaves the excess portion of the graft, the elephant trunk, dangling within the lumen of the remaining diseased aorta. In the second stage, the lesion in the descending aorta is repaired by a left thoracotomy, and the graft replacement is connected to the elephant trunk proximally. To bypass the need for thoracotomy, a few centers have successfully deployed thoracic stent grafts into the elephant trunk extension, replacing the second stage of the traditional elephant trunk procedure.[133]

Following closely on the heels of early clinical experiences with stent grafting for TAA repair, experimental application of the less invasive approach has been extended to a growing number of other pathologies of the thoracic aorta. They include aortic dissection,[5] traumatic aortic injury,[134] penetrating atherosclerotic ulcer,[135] and aortic rupture.[136]

ABDOMINAL AORTIC ANEURYSM

Therapeutic Strategies

Aneurysm of the abdominal aorta represents a potentially life-threatening scenario affecting an increasingly important segment of the aging patient population. With improved overall health care, many patients reach an advanced age despite severe cardiovascular, hypertensive, and pulmonary comorbidities, providing time for an AAA to enlarge to a critical diameter and qualify for open surgical or endovascular treatment.

Although surgical resection and interposition of an abdominal aortic prosthesis (i.e., Dacron or Gore-Tex) have long been considered standard treatment, despite a well-known perioperative mortality risk, endovascular strategies have evolved over the past decade and have become an accepted standard of care for patients considered too sick or too old for open surgery. Advanced technology, ease of use, and the temptation of a fully percutaneous procedure have attracted a new breed of endovascular surgeons propelled by the prospect of avoiding surgical risk and inducing reconstructive remodeling of the aneurysmatic aorta through depressurization and complete exclusion of the aneurysmal sac.

After deployment, the stent graft bridges the region of the aneurysm, excluding it from the circulation while allowing aortic blood flow to continue distally through the prosthetic stent graft lumen. Between 30% and 60% of AAAs are anatomically suitable for endovascular repair. When repair is undertaken, the rate of successful stent graft implantation has ranged from 78% to 94%.

A major technical difficulty associated with the stent graft technique that has yet to be overcome is endoleaks. They occur in 10% to 20% of cases[137] and are seen angiographically as persistent contrast flow into the aneurysmal sac due to failure to completely exclude the aneurysm from the aortic circulation. If left untreated, endoleaks can leave the patient at risk for aneurysmal expansion or rupture. In a follow-up study of outcomes at 12 months or longer for more than 1000 stent graft recipients, the EUROSTAR investigators reported that almost 10% of patients per year required secondary interventions, suggesting that there should be caution in the broad application of endovascular aneurysmal repair (EVAR).[138]

Physicians have embraced EVAR as the method of choice to treat AAAs in high-risk patients. EVAR has great appeal for this older population because it leads to faster recovery with fewer systemic complications than open repair.[139-144] Parodi and colleagues[145] reported the first endovascular repair of an AAA in a human in 1991; they used a graft fashioned from prosthetic vascular grafts and expandable stents. More than 20,000 EVARs take place each year in the United States, representing 36% of all AAA repairs. More than 12% of procedures in Europe involve EVAR, and the expected annual growth rate is 15% (Medtronic Marketing Department, personal communication, 2006). EVAR is the

method of choice for high-risk older patients because of its minimal incisions, shorter operating time, and reduced blood loss.

Indications for Treatment

Most asymptomatic AAAs are discovered serendipitously, often on imaging examinations for other complaints. Increasing evidence indicates that there is value to screening patients for AAA, and it is likely that screening will be approved in the near future.[146]

After the diagnosis of AAA is made, two critical questions need to be answered: when to intervene and how to intervene. The availability of EVAR has made these decisions somewhat more complex while adding a significant treatment option. Studies have questioned whether aneurysms smaller than 5 cm in diameter should be treated.[147] However, the clinical recommendation remains to offer treatment for aneurysms between 5 and 5.5 cm in diameter, depending on the results of clinical trials.[148] An exception to this guideline is that intervention should be offered despite the size of the aneurysm if symptoms develop or the aneurysm increases in size by 1 cm per year.[149] If the patient is a woman with smaller native vessels, the relative size that represents aneurysmal disease may be less than the conventional 5 to 5.5-cm range.

Patient selection has emerged as the most important factor for successful EVAR. Assessment begins with consideration of the body habitus and gender of the patient; small body size and female gender have been associated with a higher risk of procedure abortion.[150,151] The comorbidities of the patient must be assessed, with careful attention to cardiac, pulmonary, and renal conditions. Risk stratification analysis indicates that survival for those at low to minimal risk is excellent over 10 years. Those at highest risk succumb to cardiac disease or cancer, and survival is poorest for those patients.[152] EVAR has shown a reduction in 30-day mortality relative to that achieved with open repair (1.2% vs. 4.6%). Risk stratification determines survival in general and shows that both open surgery and EVAR decrease the risk of death from AAA rupture.[153]

The characteristics of the aneurysm must be matched to the most suitable device; this has a direct impact on outcomes and the complication profile of the procedure. The aneurysm is evaluated from a three-dimensional reconstruction CT scan or aortography with a calibrated catheter. At least four important features must be assessed before a patient's eligibility for EVAR can be determined, and this analysis leads to a list of contraindications[154] (Table 44-5). Experienced interventionists can deal with some of these challenges, but morphologic features of the aneurysm and access vessels may preclude EVAR.

The key features of endovascular repair of AAAs that determine procedural success and long-term outcomes are proximal and distal fixation and sealing. Most devices have a metal skeleton made of stainless steel, nitinol, or Elgiloy. Attachment is facilitated by the use of hooks or radial force. After the graft is inserted through the sheath, it can be deployed by a self-expanding mechanism or by balloon expansion. Some grafts attach superior to the renal arteries (i.e., suprarenal attachment), but most devices require at least 15 mm of proximal neck to achieve fixation and sealing in the infrarenal position. The grafts require different delivery system sizes (i.e., profiles). Low-profile devices permit access through smaller arteries.

Most complications associated with EVAR are minor and can be watched carefully or treated easily with additional interventional procedures. Some complications occur during or soon after the procedure, whereas others may be noticed only during graft surveillance.[155] A study by Ohki and colleages[156] analyzed complication and death rates within 30 days after EVAR and reported them to be 17.6% and 8.5%, respectively. This remains an active and important area of EVAR research, and standards have been developed to facilitate reporting of endovascular abdominal aortic repair complications.[157]

Endoleaks can have substantial clinical significance because they carry an increased risk of symptoms or aneurysmal rupture. The term *endoleak* describes the continuation of blood flow into the extragraft portion of the aneurysm; this flow increases the size of the aneurysmal sac.[158] Endoleaks occur in the acute setting during graft implantation or during the postoperative surveillance period. Most procedural endoleaks disappear without intervention. Endoleaks are graft related or non–graft related, and a classification system has been developed (Table 44-6).[159] Type I endoleaks occur when the attachment is not complete proximally or distally; blood can flow into the aneurysmal sac, and it is not completely occluded by endograft attachment to the arterial wall. Type II endoleaks result from continued backflow from aortic branches, such as the inferior mesenteric artery and lumbar arteries. Flow occurs retrograde into the aneurysmal sac around the endograft. Type III endoleaks are caused by defects in the endograft structure that lead to leakage of blood flow from inside the endograft to the aneurysmal sac. Type IV endoleaks occur early after endograft placement and resolve when the fabric's porosity is decreased by clotted blood.

Because endovascular repair uses a relatively new technology, graft surveillance for complications such as endoleaks is essential. Endoleaks are diagnosed by a variety of techniques: arteriography, pressure monitoring during or after the procedure, CT scanning, and duplex Doppler scanning. CT is the preferred method of detecting endoleaks. An analysis of 2463 patients from the EUROSTAR registry revealed that 171 had an endoleak by the time of their 1-month postoperative evaluation and 317 developed an endoleak at a later date.[160] Of these, 7.8% had a type II endoleak, and 12% had a type I, type III, or combination leak.

Endoleaks are treated by coil embolization, placement of stent graft cuffs and extensions, laparoscopic ligation of inferior mesenteric and lumbar arteries, open surgical repair, and repeat EVAR procedures. Type I and III endoleaks require fairly urgent intervention because blood flow and sac pressure will continue to increase and lead to rupture. Type IV endoleaks usually resolve on their own. The management of type II endoleaks is more controversial because some of them thrombose on their own, whereas others lead to sac enlargement.

TABLE 44-5 Evaluation for Endovascular Aneurysm Repair

Computed tomography assessment for EVAR eligibility
Proximal neck: diameter, length, angle, and presence or absence of thrombus
Distal landing zone: diameter and length
Iliac arteries: aneurysms and occlusive disease
Access arteries: diameter, occlusive disease
Contraindications for EVAR
Short proximal neck
Thrombus in proximal landing zone
Conical proximal neck
Greater than 120-degree angulation of the proximal neck
Critical inferior mesenteric artery
Significant iliac occlusive disease
Tortuosity of iliac vessels

EVAR, Endovascular aneurysm repair.

TABLE 44-6 Classification of Endoleaks

Type I: Attachment-Site Leaks
Proximal end of endograft
Distal end of endograft
Iliac occluder (plug)
Type II: Branch Leaks (Without Attachment-Site Connection)
Simple or to-and-fro (from only one patent branch)
Complex or flow-through (with two or more patent branches)
Type III: Graft Defect
Junctional leak or modular disconnect
Fabric disruption (midgraft hole)
Minor (≤2 mm, such as suture holes)
Major (≥2 mm)
Type IV: Graft Wall (Fabric) Porosity (30 Days After Graft Placement)

Endograft surveillance is important to document normal and abnormal morphologic changes in the repair and in the involved vessels. This process is vital for the detection of endoleaks, increased aneurysm diameter, and device migration.[161] The recommended surveillance routine includes a CT scan at 1, 6, and 12 months and annually thereafter. If an endoleak is detected, scanning frequency increases to every 6 months until resolution of the endoleak is confirmed.

The use of EVAR technology has led to a greater understanding of the basic science of aneurysmal disease. For example, Curci and Thompson[162] have been studying the relationship between the secretion of matrix metalloproteinases (MMPs) and AAAs. They have measured increased levels in the aneurysmal wall compared with the normal arterial wall.

Randomized Trial Data and Analysis

The Endovascular Aneurysmal Repair (EVAR) Study Group has provided important revelations from randomized studies on the treatment of the moving target called AAA in the context of increasing age of patients, continuously refined technology, and improving operator skills. Whereas treatment of large AAAs with EVAR reduced the 30-day mortality rate to 1.7%, compared with 4.7% with open repair ($P < .009$) on an intention-to-treat basis, the investigators were prudent to judge the early benefits only as a license to continue evaluation of EVAR by the use of longer follow-up.[163,164] However, no differences were seen in total mortality or aneurysm-related mortality in the long-term follow-up.[165]

In the Dutch Randomized Endovascular Aneurysm Repair (DREAM) study, 6 years after randomization, endovascular and open repair of AAAs resulted in similar rates of survival (68.9% vs. 69.9%, $P = .97$).[166] Scores for measures of quality of life and sexual functioning favored EVAR only in the early postoperative period but equalized after 6 months compared with open repair, in parallel with a need for continued reinterventions with EVAR. A closer look, however, revealed that many late complications after successful EVAR had low prognostic impact, such as endoleak type II requiring reintervention in only 17 of 79 cases. Severe complications such as graft rupture ($n = 9$), graft migration ($n = 12$), endoleak type I ($n = 27$), and graft thrombosis ($n = 12$), which required reintervention in 35 of 60 cases, were likely to be attributed to technical or procedural problems with the stent graft or unsuitable anatomy, underscoring the inherently immature nature of an emerging technology. Moreover, at least six different brands of endovascular devices were used by surgeons with different levels of experience.

Endovascular repair of AAAs was associated with a significantly lower rate of aneurysm-related mortality than no repair in patients who were ineligible for open repair (adjusted hazard ratio [HR] = 0.53; 95% confidence interval [CI], 0.32 to 0.89; $P = .02$). The 30-day operative mortality was 7.3% in the endovascular repair group. The overall rate of aneurysmal rupture in the no-intervention group was 12.4 (95% CI, 9.6 to 16.2) per 100 person-years. This advantage did not result in any benefit in terms of total mortality (adjusted HR = 0.99; 95% CI, 0.78 to 1.27; $P = 0.97$). A total of 48% of patients who survived endovascular repair had graft-related complications, and 27% required reintervention within the first 6 years. During 8 years of follow-up, endovascular repair was considerably more expensive than no repair (cost difference, £9826 [U.S. $14,867]; 95% CI, 7638 to 12,013 [11,556 to 18,176]).[167,168]

The data presented by the EVAR trialists (30-day and midterm outcomes in EVAR 1 and data from EVAR 2 for patients unfit for open surgery) are sobering, but they also are provocative and revealing. In accordance with the DREAM studies,[164,166,169,170] EVAR 1 showed significant early survival benefit after 30 days with endovascular repair due to reduced periinterventional risk, corroborating previous observational evidence.[37,38,171] Careful analysis of randomized data has provided highly valuable information:

Health status comprising age, comorbidities, and prognostic confounders was the most important denominator of individual prognosis, followed by, to a lesser degree, the nonsurgical nature of EVAR (which can be performed percutaneously with local anesthesia). Assessment of the general state of health of older and sicker patients and serious attempts at improvement should precede EVAR. Examples are cardiopulmonary workup, potentially including percutaneous coronary intervention, and respiratory improvement as integral parts of strategic planning. For some conditions, it appears justified to reject EVAR when conservative care is more appropriate.

The nature of complications requiring reinterventions after EVAR is often related to technical shortcomings with current-generation devices or to unsuitable anatomy. Physicians and the industry must recognize those limitations and develop better devices and improved selection algorithms for treatment with EVAR.

Although the endovascular community should always embrace the *primum non nocere* principle and avoid well-intended but harmful treatment, it should also appreciate the evolving nature of the problem. Some patients considered unfit for surgery do improve and find themselves in a lower-risk category and fit for surgery or EVAR. EVAR technology and interventional skills improve with time and training, and the short-term differential advantage over open surgery is likely to increase.

Elderly patients may express a personal preference for a less traumatic procedure such as EVAR performed by an expert despite the lack of a clear-cut midterm advantage and accept surveillance and interventions during follow-up. The higher costs of follow-up imaging needed with EVAR may be dramatically reduced with a smarter surveillance strategy based on clinical and ultrasound interrogation instead of serial CT or MRI.

Although EVAR may not improve the AAA prognosis compared with classic surgery at midterm, resulting in a current draw after an early advantage, EVAR is here to stay. Better staging and selection of patients, constantly improving technology,[37] and the expertise of centers of excellence for aortic diseases can enhance matching patients with therapeutic options, including EVAR or conservative treatment. It is still wise to use clinical judgment and to offer a holistic approach with intelligent use of prognosticating tools and interdisciplinary cooperation, especially for the growing segment of older patients with multiple comorbidities.

Whether the results of the EVAR trials and the cautious voice of Jonathan Michaels[39] will halt the trend of increasing use of EVAR instead of open surgery remains to be seen. It is certain, however, that the randomized data from EVAR 1 and EVAR 2 will refocus the debate on natural history and patient selection for a forward-moving technology.

REFERENCES

1. Hagan PG, Nienaber CA, Isselbacher EM, et al: The International Registry of Aortic Dissection (IRAD). *JAMA* 283:897–903, 2000.
2. Erbel R, Aboyans V, Boileau C, et al: 2014 ESC guidelines on the diagnosis and treatment of aortic disease: document covering acute and chronic aortic disease of the thoracic and abdominal aorta of the adult. The Task Force for the diagnosis and treatment of aortic diseases of the European Society of Cardiology (ESC). *Eur Heart J* 35:2873–2926, 2014.
3. Kodolitsch Y, Schwartz AG, Nienaber CA: Clinical prediction of acute aortic dissection. *Arch Intern Med* 160:2977–2982, 2000.
4. Ince H, Nienaber CA: The concept of interventional therapy in acute aortic syndrome. *J Card Surg* 17:135–142, 2002.
5. Nienaber CA, Fattori R, Lund G, et al: Nonsurgical reconstruction of thoracic aortic dissection by stent graft placement. *N Engl J Med* 340:1539–1545, 1999.
6. Dake MD, Kato N, Mitchell RS, et al: Endovascular stent graft placement for the treatment of acute aortic dissection. *N Engl J Med* 340:1546–1552, 1999.
7. Walkers PJ, Miller DC: Aneurysmal and ischemic complications of type B (type III) aortic dissections. *Semin Vasc Surg* 5:198–214, 1992.
8. Bossone E, Rampoldi V, Nienaber CA, et al: Usefulness of pulse deficit to predict in-hospital complications and mortality in patients with acute type A aortic dissection. *Am J Cardiol* 89:851–855, 2002.
9. Cambria RP, Brewster DC, Gertler J, et al: Vascular complications associated with spontaneous aortic dissection. *J Vasc Surg* 7:197–209, 1988.
10. Laas J, Heinemann M, Schaefers HJ, et al: Management of thoracoabdominal malperfusion in aortic dissection. *Circulation* 84:20–24, 1991.

11. Miller DC: The continuing dilemma concerning medical versus surgical management of patients with acute type B dissections. *Semin Thorac Cardiovasc Surg* 5:33–46, 1993.
12. Miller DC, Mitchell RS, Oyer PE, et al: Independent determinants of operative mortality for patients with aortic dissections. *Circulation* 70:153–164, 1984.
13. Elefteriades JA, Hartleroad J, Gusberg RJ, et al: Long-term experience with descending aortic dissection: the complication-specific approach. *Ann Thorac Surg* 53:11–20, 1992.
14. Walker PJ, Dake MD, Mitchell RS, et al: The use of endovascular techniques for the treatment of complications of aortic dissection. *J Vasc Surg* 18:1042–1051, 1993.
15. Fann JI, Sarris GE, Mitchell RS, et al: Treatment of patients with aortic dissection presenting with peripheral vascular complications. *Ann Surg* 212:705–713, 1990.
16. Yano H, Ishimaru S, Kawaguchi S, et al: Endovascular stent grafting of the descending thoracic aorta after arch repair in acute type A dissection. *Ann Thorac Surg* 73:288–291, 2002.
17. Kato N, Shimono T, Hirano T, et al: Transluminal placement of endovascular stent grafts for the treatment of type A aortic dissection with an entry tear in the descending thoracic aorta. *J Vasc Surg* 34:1023–1028, 2001.
18. Iannelli G, Piscione F, Di Tommaso L, et al: Thoracic aortic emergencies: impact of endovascular surgery. *Ann Thorac Surg* 77:591–596, 2004.
19. Saito S, Arai H, Kim K, et al: Percutaneous fenestration of dissecting intima with a transseptal needle: a new therapeutic technique for visceral ischemia complicating acute aortic dissection. *Cathet Cardiovasc Diagn* 26:130–135, 1992.
20. Nienaber CA, Ince H, Petzsch M, et al: Endovascular treatment of thoracic aortic dissection and its variants. *Acta Chir Belg* 102:292–298, 2002.
21. Nienaber CA, Ince H, Weber F, et al: Emergency stent graft placement in thoracic aortic dissection and evolving rupture. *J Card Surg* 18:464–470, 2003.
22. Beregi JP, Haulon S, Otal P, et al: Endovascular treatment of acute complications associated with aortic dissection: midterm results from a multicenter study. *J Endovasc Ther* 10:486–493, 2003.
23. Bortone AS, Schena S, D'Agostino D, et al: Immediate versus delayed endovascular treatment of post-traumatic aortic pseudoaneurysms and type B dissections: retrospective analysis and premises to the upcoming European trial. *Circulation* 106:234–240, 2002.
24. Diethrich EB, Ghazoul M, Wheatley GH, et al: Surgical correction of ascending type a thoracic aortic dissection: simultaneous endoluminal exclusion of the arch and distal aorta. *J Endovasc Ther* 12:660–666, 2005.
25. Svensson LG, Kouchoukos NF, Miller DC, et al: Expert consensus document on the treatment of descending thoracic aortic disease using endovascular stent grafts. *Ann Thorac Surg* 85:S1–S41, 2008.
26. Kodama K, Nishigami K, Sakamoto T, et al: Tight heart rate control reduces secondary adverse events in patients with type B acute aortic dissection. *Circulation* 118(Suppl 1):S167–S170, 2008.
27. Tsai TT, Fattori R, Trimarchi S, et al: Long-term survival in patients with type B acute aortic dissection: insight from the International Registry of Acute Aortic Dissection. *Circulation* 114:2226–2231, 2006.
28. Tang DG, Dake MD: TEVAR for acute uncomplicated aortic dissection: immediate repair versus medical therapy. *Semin Vasc Surg* 22:145–151, 2009.
29. Estrera AL, Miller CC, Safi H, et al: Outcomes of medical management of acute type B aortic dissection. *Circulation* 114(Suppl I):384–389, 2006.
30. Trimarchi S, Nienaber CA, Rampoldi V, et al: Role and results of surgery in acute type B aortic dissection: insights from the International Registry of Acute Aortic Dissection (IRAD). *Circulation* 114(Suppl I):I357–I364, 2006.
31. Fattori R, Tsai TT, Myrmel T, et al: Complicated acute type B dissection: is surgery still the best option? *JACC Cardiovasc Interv* 1:395–402, 2008.
32. Nienaber CA, Kische S, Zeller T, et al: Provisional extension to induce complete attachment after stent graft placement in type B aortic dissection: the PETTICOAT concept. *J Endovasc Ther* 13:738–746, 2006.
33. Parker JD, Golledge J: Outcome of endovascular treatment of acute type B aortic dissection. *Ann Thorac Surg* 86:1707–1712, 2008.
34. Xiong J, Jiang B, Guo W, et al: Endovascular stent graft placement in patients with type B aortic dissection: a meta-analysis in China. *J Thorac Cardiovasc Surg* 138:865–872, 2009.
35. Demers P, Miller DC, Mitchell RS, et al: Midterm results of endovascular repair of descending thoracic aortic aneurysms with first-generation stent grafts. *J Thorac Cardiovasc Surg* 127: 664–673, 2004.
36. Dialetto G, Cocino FE, Scognamiglio G, et al: Treatment of type B aortic dissection: endoluminal repair or conventional medical therapy? *Eur J Cardiothorac Surg* 27:826–830, 2005.
37. Lee WA, Carter JW, Upchurch G, et al: Perioperative outcomes after open and endovascular repair of intact abdominal aortic aneurysms in the United States during 2001. *J Vasc Surg* 39:491–496, 2004.
38. Hua HT, Campria RP, Chuang SK, et al: Early outcomes of endovascular versus open abdominal aortic aneurysm repair in the National Surgical Quality Improvement Program-Private Sector (NSQIP-PS). *J Vasc Surg* 41:382–389, 2005.
39. Michaels J: The future of endovascular aneurysm repair. *Eur J Vasc Endovasc Surg* 30:115–118, 2005.
40. Xu S, Hunag F, Yang J, et al: Endovascular repair of acute type B aortic dissection: early and mid-term results. *J Vasc Surg* 43:489–498, 2006.
41. Verhoye JP, Miller DC, Sze D, et al: Complicated acute type B aortic dissection: midterm results of emergency endovascular stent grafting. *J Thorac Cardiovasc Surg* 136:424–430, 2008.
42. Szeto WY, McGarvey M, Pochettino A, et al: Endovascular repair of acute type B aortic dissection: early and mid-term results. *J Vasc Surg* 43:1090–1095, 2006.
43. Shu C, He H, Li QM, et al: Endovascular repair of complicated acute type-B aortic dissection with stentgraft: early and mid-term results. *Eur J Vasc Endovasc Surg* 42:448–453, 2011.
44. Ehrlich MP, Rousseau H, Heijmen R, et al: Midterm results after endovascular treatment of acute, complicated type B aortic dissection: the Talent Thoracic Registry. *J Thorac Cardiovasc Surg* 145:159–165, 2013.
45. Wiedemann D, Ehrlich M, Amabile P, et al: Emergency endovascular stent grafting in acute complicated type B dissection. *J Vasc Surg* 60:1204–1208, 2014.
46. Massmann A, Kunihara T, Fries P, et al: Uncovered stent implantation in complicated acute aortic dissection type B. *J Thorac Cardiovasc Surg* 148:3003–3011, 2014.
47. Eggebrecht H, Herold U, Kuhnt O, et al: Endovascular stent graft treatment of aortic disection: determinants of postinterventional outcome. *Eur Heart J* 26:489–497, 2005.
48. Winnerkvist A, Lockowandt U, Rasmussen E, et al: A prospective study of medically treated acute type B aortic dissection. *Eur J Vasc Endovasc Surg* 32:356–357, 2006.
49. Shimono T, Kato N, Yasuda F, et al: Transluminal stent graft placements for the treatment of acute onset and chronic aortic dissections. *Circulation* 106:1241–1247, 2002.
50. Fattori R, Tsai TT, Myrmel T, et al: Complicated acute type B dissection: is surgery still the best option? A report from the International Registry of Acute Aortic Dissection. *JACC Cardiovasc Interv* 1(4):395–402, 2008.
51. Nienaber CA, Kische S, Rousseau H, et al: Endovascular repair of type B aortic dissection: long-term results of the randomized investigation of stent grafts in aortic dissection trial. *Circ Cardiovasc Interv* 6:407–416, 2013.
52. Andersen ND, Keenan JE, Ganapathi AM, et al: Current management and outcome of chronic type B aortic dissection: results with open and endovascular repair since the advent of thoracic endografting. *Ann Cardiothorac Surg* 3:264–274, 2014.
53. Nienaber CA, Rousseau H, Eggebrecht H, et al: Randomized comparison of strategies for type B aortic dissection: the Investigation of STEnt grafts in Aortic Dissection (INSTEAD) trial. *Circulation* 120:2519–2528, 2009.
54. Nienaber CA, Kische S, Rousseeau H, et al: Endovascular repair of type B aortic dissection: long-term results of the randomized investigation of stent grafts in aortic dissection trial. *Circ Cardiovasc Interv* 6:407–416, 2013.
55. Nienaber CA, Kische S, Rehders TC, et al: Rapid pacing for better placing: comparison of techniques for precise deployment of endografts in the thoracic aorta. *J Endovasc Ther* 14:506–512, 2007.
56. Koschyk DH, Nienaber CA, Knap M, et al: How to guide stent graft implantation in type B aortic dissection? Comparison of angiography, transesophageal echocardiography, and intravascular ultrasound. *Circulation* 112(Suppl I):I-260–I-264, 2005.
57. Rehders TC, Petzsch M, Ince H, et al: Intentional occlusion of the left subclavian artery during endovascular stent graft implantation in the thoracic aorta: risk and relevance. *J Endovasc Ther* 11:659–666, 2004.
58. Eggebrecht H, Thompson M, Rousseau H, et al: European Registry on Endovascular Aortic Repair Complications. Retrograde ascending aortic dissection during or after thoracic aortic stent graft placement: insight from the European registry on endovascular aortic repair complications. *Circulation* 120(Suppl 11): S276–S281, 2009.
59. Dong ZH, Fu WG, Wang YQ, et al: Retrograde type A aortic dissection after endovascular stent graft placement of type B dissection. *Circulation* 119:735–741, 2009.
60. Hata M, Sezai A, Niino T, et al: Prognosis for patients with type B acute aortic dissection: risk analysis of early requirement for elective surgery. *Circ J* 71:1279–1282, 2007.
61. Jing QM, Han YL, Wang XZ, et al: Endovascular stent grafts for acute and chronic type B aortic dissection: comparison of clinical outcomes. *Chin Med J* 121:2213–2217, 2008.
62. Kato N, Hirano T, Ishida M, et al: Acute and contained rupture of the descending thoracic aorta: treatment with endovascular stent grafts. *J Vasc Surg* 37:100–105, 2003.
63. Clouse WD, Hallett JW, Jr, Schaff HV, et al: Improved prognosis of thoracic aortic aneurysms: A population-based study. *JAMA* 280:1926–1929, 1998.
64. Bickerstaff LK, Pairolero PC, Hollier LH, et al: Thoracic aortic aneurysms: a population-based study. *Surgery* 92:1103–1108, 1982.
65. Gloviczki P, Pairolero P, Welch T, et al: Multiple aortic aneurysms: the results of surgical management. *J Vasc Surg* 11:19–27, 1990.
66. Thomson MM, Bell PR: ABC of arterial and venous disease: arterial aneurysms. *BMJ* 320:1193–1196, 2000.
67. Coady MA, Rizzo JA, Goldstein LJ, et al: Natural history, pathogenesis, and etiology of thoracic aortic aneurysms and dissections. *Cardiol Clin* 17:615–635, 1999.
68. Crawford ES, DeNatale RW: Thoracoabdominal aortic aneurysm: observations regarding the natural course of the disease. *J Vasc Surg* 3:578–582, 1986.
69. McNamara JJ, Pressler VM: Natural history of arteriosclerotic thoracic aortic aneurysms. *Ann Thorac Surg* 26:468–473, 1998.
70. Davies RR, Goldstein LJ, Coady MA, et al: Yearly rupture or dissection rate for thoracic aortic aneurysms: simple prediction based on size. *Ann Thorac Surg* 73:17–27, 2002.
71. Juvonen T, Ergin MA, Galla JD, et al: Prospective study of the natural history of thoracic aortic aneurysms. *Ann Thorac Surg* 63:1533–1545, 1997.
72. Johansson G, Markstrom U, Swedenborg J: Ruptured thoracic aortic aneurysms: a study of incidence and mortality rates. *J Vasc Surg* 21:985–988, 1995.
73. Olsson C, Thelin S, Ståhle E, et al: Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002. *Circulation* 114:2611–2618, 2006.
74. DeBakey ME, McCollum CH, Graham JM: Surgical treatment of aneurysms of the descending thoracic aorta: Long-term results in 500 patients. *J Cardiovasc Surg (Torino)* 19:571–576, 1998.
75. Hilgenberg AD, Rainer WG, Sadler TR, Jr: Aneurysm of the descending thoracic aorta: Replacement with the use of a shunt or bypass. *J Thorac Cardiovasc Surg* 81:818–824, 1981.
76. Moreno-Cabral CE, Miller DC, Mitchell RS, et al: Degenerative and atherosclerotic aneurysms of the thoracic aorta: determinants of early and late surgical outcome. *J Thorac Cardiovasc Surg* 88:1020–1032, 1984.
77. Muhs BE, Vincken KL, van Prehn J, et al: Dynamic cine-CT angiography for the evaluation of the thoracic aorta: insight in dynamic changes with implications for thoracic endograft treatment. *Eur J Vasc Endovasc Surg* 32:532–536, 2006.
78. Pressler V, McNamara JJ: Thoracic aortic aneurysm: natural history and treatment. *J Thorac Cardiovasc Surg* 79:489–498, 1980.
79. Fann JI: Descending thoracic and thoracoabdominal aortic aneurysms. *Coron Artery Dis* 13:93–102, 2002.
80. Svensson LG, Crawford ES, Hess KR, et al: Variables predictive of outcome in 832 patients undergoing repairs of the descending thoracic aorta. *Chest* 104:1248–1253, 1993.
81. Borst HG, Jurmann M, Buhner B, et al: Risk of replacement of descending aorta with a standardized left heart bypass technique. *J Thorac Cardiovasc Surg* 105:126–132, 1994.
82. Pressler V, McNamara JJ: Aneurysm of the thoracic aorta: review of 260 cases. *J Thorac Cardiovasc Surg* 89:50–54, 1985.
83. Svensson LG, Crawford ES, Hess KR, et al: Experience with 1509 patients undergoing thoracoabdominal aortic operations. *J Vasc Surg* 17:357–368, 1993.
84. Livesay JJ, Cooley DA, Ventemiglia RA, et al: Surgical experience in descending thoracic aneurysmectomy with and without adjuncts to avoid ischemia. *Ann Thorac Surg* 39:37–46, 1985.
85. Berg P, Kaufmann D, van Marrewijk CJ, et al: Spinal cord ischaemia after stent graft treatment for infra-renal abdominal aortic aneurysms: analysis of the EUROSTAR database. *Eur J Vasc Endovasc Surg* 22:342–347, 2001.
86. Rosenthal D: Spinal cord ischemia after abdominal aortic operation: is it preventable? *J Vasc Surg* 30:391–397, 1999.
87. Ouriel K, Greenberg RK: Endovascular treatment of thoracic aortic aneurysms. *J Card Surg* 18:455–463, 2003.
88. Dake MD: Endovascular stent graft management of thoracic aortic diseases. *Eur J Radiol* 39:42–49, 2001.
89. Gravereaux EC, Faries PL, Burks JA, et al: Risk of spinal cord ischemia after endograft repair of thoracic aortic aneurysms. *J Vasc Surg* 34:977–1003, 2001.
90. Burks JA, Jr, Faries PL, Gravereaux EC, et al: Endovascular repair of thoracic aortic aneurysms: stent graft fixation across the aortic arch vessels. *Ann Vasc Surg* 16:24–28, 2002.
91. Gorich J, Asquan Y, Seifarth H, et al: Initial experience with intentional stent graft coverage of the subclavian artery during endovascular thoracic aortic repairs. *J Endovasc Ther* 9(Suppl 2):II39–II43, 2002.
92. Tiesenhausen K, Hausegger KA, Oberwalder P, et al: Left subclavian artery management in endovascular repair of thoracic aortic aneurysms and aortic dissections. *J Card Surg* 18:429–435, 2003.
93. Dake MD, Miller DC, Semba CP, et al: Transluminal placement of endovascular stent grafts for the treatment of descending thoracic aortic aneurysms. *N Engl J Med* 331:1729–1734, 1994.
94. Dake MD, Miller DC, Mitchell RS, et al: The "first generation" of endovascular stent grafts for patients with aneurysms of the descending thoracic aorta. *J Thorac Cardiovasc Surg* 116:689–703, 1998.
95. Fann JI, Miller DC: Endovascular treatment of descending thoracic aortic aneurysms and dissections. *Surg Clin North Am* 79:551–574, 1999.
96. Kazui T, Washiyamoi N, Muhammod BA, et al: Improved results of atherosclerotic arch aneurysm operation with a refined technique. *J Thorac Cardiovasc Surg* 121:491–499, 2001.
97. Spielvogel D, Holstead JC, Meies M, et al: Aortic arch replacement using a trifurcated graft: simple, versatile and safe. *Ann Thorac Surg* 80:90–95, 2005.

98. Ehrlich M, Grabenwoeger M, Cartes-Zumelzu F, et al: Endovascular stent graft repair for aneurysms on the descending thoracic aorta. *Ann Thorac Surg* 66:19–24, 1998.
99. Cartes-Zumelzu F, Lammer J, Kretschmer G, et al: Endovascular repair of thoracic aortic aneurysms. *Semin Interv Cardiol* 5:53–57, 2000.
100. Grabenwoger M, Hutschala D, Ehrlich MP, et al: Thoracic aortic aneurysms: treatment with endovascular self-expandable stent grafts. *Ann Thorac Surg* 69:421–425, 2000.
101. Greenberg R, Resch T, Nyman U, et al: Endovascular repair of descending thoracic aortic aneurysms: an early experience with intermediate-term follow-up. *J Vasc Surg* 31:147–156, 2000.
102. Temudom T, D'Ayala M, Marin ML, et al: Endovascular grafts in the treatment of thoracic aortic aneurysms and pseudoaneurysms. *Ann Vasc Surg* 14:230–238, 2000.
103. Najibi S, Terramani TT, Weiss VJ, et al: Endoluminal versus open treatment of descending thoracic aortic aneurysms. *J Vasc Surg* 36:732–737, 2002.
104. Heijmen RH, Deblier IG, Moll FL, et al: Endovascular stent grafting for descending thoracic aortic aneurysms. *Eur J Cardiothorac Surg* 21:5–9, 2002.
105. Schoder M, Cartes-Zumelzu F, Grabenwoger M, et al: Elective endovascular stent graft repair of atherosclerotic thoracic aortic aneurysms: clinical results and midterm follow-up. *AJR Am J Roentgenol* 180:709–715, 2003.
106. Marin ML, Hollier LH, Ellozy SH, et al: Endovascular stent graft repair of abdominal and thoracic aortic aneurysms: a ten-year experience with 817 patients. *Ann Surg* 238:586–593, 2003.
107. Lepore V, Lonn L, Delle M, et al: Treatment of descending thoracic aneurysms by endovascular stent grafting. *J Card Surg* 18:416–423, 2003.
108. Sunder-Plassmann L, Scharrer-Pamler R, Liewald F, et al: Endovascular exclusion of thoracic aortic aneurysms: mid-term results of elective treatment and in contained rupture. *J Card Surg* 18:367–374, 2003.
109. Bergeron P, De Chaumaray T, Gay J, et al: Endovascular treatment of thoracic aortic aneurysms. *J Cardiovasc Surg (Torino)* 42:349–361, 2003.
110. Czerny M, Cejna M, Hutschala D, et al: Stent graft placement in atherosclerotic descending thoracic aortic aneurysms: midterm results. *J Endovasc Ther* 11:26–32, 2004.
111. Makaroun MS, Dillavou ED, Kee ST, et al: Endovascular treatment of thoracic aortic aneurysms: results of the phase II multicenter trial of the GORE TAG thoracic endoprosthesis. *J Vasc Surg* 41:1–9, 2005.
112. Leurs LJ, Bell R, Degrieck Y, et al: Endovascular treatment of thoracic aortic diseases: Combined experience from the EUROSTAR and United Kingdom Thoracic Endograft registries. *J Vasc Surg* 40:670–679, 2004.
113. Khoynezhad A, Donayre CE, Omari BO, et al: Midterm results of endovascular treatment of complicated acute type B aortic dissection. *J Thorac Cardiovasc Surg* 138:625–631, 2009.
114. Alves CM, da Fonseca JH, de Souza JA, et al: Endovascular treatment of type B aortic dissection: the challenge of late success. *Ann Thorac Surg* 87:1360–1365, 2009.
115. Parsa CJ, Schroder JN, Danehmand MA, et al: Midterm results for endovascular repair of complicated acute and chronic type B aortic dissection. *Ann Thorac Surg* 89:97–104, 2010.
116. Greenberg RK, O'Neill S, Walker E, et al: Endovascular repair of thoracic aortic lesions with the Zenith TX1 and TX2 thoracic grafts: intermediate-term results. *J Vasc Surg* 41:589–596, 2005.
117. Wheatley GH, III, Gurbuz AT, Rodriguez-Lopez JA, et al: Midterm outcome in 158 consecutive Gore TAG thoracic endoprostheses: single center experience. *Ann Thorac Surg* 81:1570–1577, 2006.
118. Foley PJ, Criado FJ, Farber MA, et al: Results with the Talent thoracic stent graft in the VALOR trial. *J Vasc Surg* 56:1214–1221, 2012.
119. Fossaceca R, Guzzardi G, Cerini P, et al: Endovascular treatment of thoracic aortic aneurysm: a single-center experience. *Ann Vasc Surg* 27:1020–1028, 2013.
120. Matsumura JS, Melissano G, Cambria RP, et al: Five-year results of thoracic endovascular aortic repair with the Zenith TX2. *J Vasc Surg* 60:1–10, 2014.
121. Mitchell RS, Miller DC, Dake MD: Stent graft repair of thoracic aortic aneurysms. *Semin Vasc Surg* 10:257–271, 1997.
122. Carroccio A, Marin ML, Ellozy S, et al: Pathophysiology of paraplegia following endovascular thoracic aortic aneurysm repair. *J Card Surg* 18:359–366, 2003.
123. Thurnher SA, Grabenwoger M: Endovascular treatment of thoracic aortic aneurysms: a review. *Eur Radiol* 12:1370–1387, 2002.
124. Resch T, Koul B, Dias NV, et al: Changes in aneurysm morphology and stent graft configuration after endovascular repair of aneurysms of the descending thoracic aorta. *J Thorac Cardiovasc Surg* 122:47–52, 2001.
125. Buth J, Harris PL, van Marrewijk C, et al: The significance and management of different types of endoleaks. *Semin Vasc Surg* 16:95–102, 2003.
126. Chuter TA, Faruqi RM, Sawhney R, et al: Endoleak after endovascular repair of abdominal aortic aneurysm. *J Vasc Surg* 34:98–105, 2001.
127. Kato N, Semba CP, Dake MD: Embolization of perigraft leaks after endovascular stent graft treatment of aortic aneurysms. *J Vasc Interv Radiol* 7:805–811, 1996.
128. Hausegger KA, Oberwalder P, Tiesenhausen K, et al: Intentional left subclavian artery occlusion by thoracic aortic stent grafts without surgical transposition. *J Endovasc Ther* 8:472–476, 2001.
129. Stanley BM, Semmens JB, Lawrence-Brown MM, et al: Fenestration in endovascular grafts for aortic aneurysm repair: new horizons for preserving blood flow in branch vessels. *J Endovasc Ther* 8:16–24, 2001.
130. Inoue K, Hosokawa H, Iwase T, et al: Aortic arch reconstruction by transluminally placed endovascular branched stent graft. *Circulation* 100(Suppl II):II-316–II-321, 1999.
131. McWilliams RG, Murphy M, Hartley D, et al: In situ stent graft fenestration to preserve the left subclavian artery. *J Endovasc Ther* 11:170–174, 2004.
132. Heinemann MK, Buehner B, Jurmann MJ, Borst HG: Use of the "elephant trunk technique" in aortic surgery. *Ann Thorac Surg* 60:2–6, 1995.
133. Fann JI, Dake MD, Semba CP, et al: Endovascular stent grafting after arch aneurysm repair using the "elephant trunk". *Ann Thorac Surg* 60:1102–1105, 1995.
134. Kato N, Dake MD, Miller DC, et al: Traumatic thoracic aortic aneurysm: treatment with endovascular stent grafts. *Radiology* 205:657–662, 1997.
135. Eggebrecht H, Baumgart D, Schmermund A, et al: Penetrating atherosclerotic ulcer of the aorta: treatment by endovascular stent graft placement. *Curr Opin Cardiol* 18:431–435, 2003.
136. Kato N, Hirano T, Ishida M, et al: Acute and contained rupture of the descending thoracic aorta: treatment with endovascular stent grafts. *J Vasc Surg* 37:100–105, 2003.
137. Brewster DC, Cronenwett JL, Hallett JW, Jr, et al: Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery: guidelines for the treatment of abdominal aortic aneurysms: report of a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. *J Vasc Surg* 37:1106–1117, 2003.
138. Laheij RJ, Buth J, Harris PL, et al: Need for secondary interventions after endovascular repair of abdominal aortic aneurysms: intermediate-term follow-up results of a European collaborative registry (EUROSTAR). *Br J Surg* 87:1666–1673, 2000.
139. Criado FJ, Fairman RM, Becker GJ: Talent LPS AAA stent graft: results of a pivotal clinical trial. *J Vasc Surg* 37:709–715, 2003.
140. Matsumura JS, Brewster DC, Makaroun MS, et al: A multicenter controlled clinical trial of open versus endovascular treatment of abdominal aortic aneurysm. *J Vasc Surg* 37:262–271, 2003.
141. Ouriel K, Clair DG, Greenberg RK, et al: Endovascular repair of abdominal aortic aneurysms: device-specific outcome. *J Vasc Surg* 37:971–978, 2003.
142. Moore WS: The Guidant Ancure bifurcation endograft: five-year follow-up. *Semin Vasc Surg* 16:139–143, 2003.
143. Zarins CK, White RA, Moll FL, et al: The AneuRx stent graft: four-year results and worldwide experience 2000. *J Vasc Surg* 33:S135–S145, 2001.
144. Greenberg RK, Chuter TA, Sternbergh WC, III, et al: Zenith AAA endovascular graft: intermediate-term results of the US multicenter trial. *J Vasc Surg* 39:1209–1218, 2004.
145. Parodi JC, Palmaz JC, Barone HD: Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. *Ann Vasc Surg* 5:491–497, 1991.
146. Kent KC, Zwolak RM, Jaff MR, et al: Screening for abdominal aortic aneurysm: a consensus statement. *J Vasc Surg* 39:267–269, 2004.
147. The UK Small Aneurysm Trial Participants: Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. *Lancet* 352:1649–1655, 1998.
148. Powell JT, Greenhalgh RM: Clinical practice: small abdominal aortic aneurysms. *N Engl J Med* 348:1895–1901, 2003.
149. Scott RA, Tisi PV, Ashton HA, et al: Abdominal aortic aneurysm rupture rates: a 7-year follow-up of the entire abdominal aortic aneurysm population detected by screening. *J Vasc Surg* 28:124–128, 1998.
150. Mathison M, Becker GJ, Katzen BT, et al: The influence of female gender on the outcome of endovascular abdominal aortic aneurysm repair. *J Vasc Interv Radiol* 12:1047–1051, 2001.
151. Mathison MN, Becker GJ, Katzen BT, et al: Implications of problematic access in transluminal endografting of abdominal aortic aneurysm. *J Vasc Interv Radiol* 14:33–39, 2003.
152. Becker GJ, Kovacs M, Mathison MN, et al: Risk stratification and outcomes of transluminal endografting for abdominal aortic aneurysm: 7-year experience and long-term follow-up. *J Vasc Interv Radiol* 12:1033–1046, 2001.
153. Huber TS, Wang JG, Derrow AE, et al: Experience in the United States with intact abdominal aortic aneurysm repair. *J Vasc Surg* 33:304–310, 2001.
154. Ohki T, Veith FJ: Patient selection for endovascular repair of abdominal aortic aneurysms: changing the threshold for intervention. *Semin Vasc Surg* 12:226–234, 1999.
155. Elkouri S, Gloviczki P, McKusick MA, et al: Perioperative complications and early outcome after endovascular and open surgical repair of abdominal aortic aneurysms. *J Vasc Surg* 39:497–505, 2004.
156. Ohki T, Veith FJ, Shaw P, et al: Increasing incidence of midterm and long-term complications after endovascular graft repair of abdominal aortic aneurysms: a note of caution based on a 9-year experience. *Ann Surg* 234:323–334, 2001.
157. Chaikof EL, Blankensteijn JD, Harris PL, et al: Reporting standards for endovascular aortic aneurysm repair. *J Vasc Surg* 35:1048–1060, 2002.
158. White GH, Yu W, May J: Endoleak: a proposed new terminology to describe incomplete aneurysm exclusion by an endoluminal graft. *J Endovasc Surg* 3:124–125, 1996.
159. Veith FJ, Baum RA, Ohki T, et al: Nature and significance of endoleaks and endotension: summary of opinions expressed at an international conference. *J Vasc Surg* 35:1029–1035, 2002.
160. van Marrewijk C, Buth J, Harris PL, et al: Significance of endoleaks after endovascular repair of abdominal aortic aneurysms: the EUROSTAR experience. *J Vasc Surg* 35:461–473, 2002.
161. Corriere MA, Feurer ID, Becker SY, et al: Endoleak following endovascular abdominal aortic aneurysm repair: implications for duration of screening. *Ann Surg* 239:800–805, 2004.
162. Curci JA, Thompson RW: Adaptive cellular immunity in aortic aneurysms: cause, consequence, or context? *J Clin Invest* 114:168–171, 2004.
163. Greenhalgh RM, Brown LC, Kwong GP, et al: Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1)—30-day operative mortality results: randomised controlled trial. *Lancet* 364:843–848, 2004.
164. EVAR trial participants: Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. *Lancet* 365:2179–2186, 2005.
165. Greenhalgh RM, Brown LC, Powel JT, et al: for The United Kingdom EVAR Trial Investigators. Endovascular versus open repair of abdominal aortic aneurysm. *N Engl J Med* 362:1863–1871, 2010.
166. DeBruin JL, Baas AF, Buth J, et al: for the DREAM Study Group: Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. *N Engl J Med* 362:1881–1889, 2010.
167. EVAR Trial Participants: Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial. *Lancet* 365:2187–2192, 2005.
168. Greenhalgh RM, Brown LC, Powel JT, et al: for The United Kingdom EVAR Trial Investigators: Endovascular repair of aortic aneurysm in patients physically ineligible for open repair. *N Engl J Med* 362:1872–1880, 2010.
169. Prinssen M, Verhoeven ELG, Buth J, et al: A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. *N Engl J Med* 351:1607–1618, 2004.
170. Blankensteijn JD, de Jong SE, Prinssen M, et al: Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. *N Engl J Med* 352:2398–2405, 2005.
171. Anderson PL, Arons RR, Moskowitz AJ, et al: A statewide experience with endovascular abdominal aortic aneurysm repair: rapid diffusion with excellent early results. *J Vasc Surg* 39:10–19, 2004.
172. Bavaria JE, Appoo JJ, Makaroun MS, et al: Endovascular stent grafting versus open surgical repair of descending thoracic aortic aneurysms in low-risk patients: a multicenter comparative trial. *J Thorac Cardiovasc Surg* 1333:369–377, 2007.
173. Fairman RM, Criado F, Farber M, et al: Pivotal results of the Medtronic Vascular Talent Thoracic Stent Graft System: the VALOR Trial. *J Vasc Surg* 48:546–554, 2008.
174. Hughes CC, Lee SM, Daneshmand MA, et al: Endovascular repair of descending thoracic aneurysms: results with "on-label" application in the post Food and Drug Administration approval era. *Ann Thorac Surg* 90:83–89, 2010.

Venous Intervention

45

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KEY POINTS

- Venous disease, both acute (deep venous thrombosis [DVT], pulmonary embolism [PE]) and chronic (postthrombotic syndrome, ulcers, varicose veins), is widely prevalent, affecting up to one-quarter of the population.
- The superior vena cava syndrome manifests as severe congestion and edema of the face, arms, and upper thorax and may progress to dyspnea, cognitive dysfunction, and headache. It is commonly associated with malignancy, indwelling catheters, or pacemaker leads.
- The use of thrombolytic therapy before endovascular stenting of superior vena cava syndrome often minimizes the length of stent required.
- Patients with Paget-Schroetter syndrome develop spontaneous DVT of the upper extremity, usually in the dominant arm, after strenuous physical activity. Heavy repetitive exertion causes microtrauma to the vessel intima and leads to activation of the coagulation cascade.
- Upper extremity deep vein thrombosis (UEDVT) not associated with indwelling catheters or pacemaker leads should prompt further workup for a vascular compression syndrome.
- Duplex ultrasonography is usually the initial test of choice for the diagnosis of DVT because of its widespread availability, portability, reproducibility, and cost. However, it has a limited role in central venous stenosis.
- Clinical PE has a high prevalence in patients with untreated proximal DVT and is associated with a high mortality rate. With treatment, the incidence of PE decreases to 5% and the mortality rate to less than 1%.
- For lower extremity DVT, catheter-directed thrombolysis (CDT), or the delivery of thrombolytic agents directly into a thrombus, offers significant advantages when compared with systemic therapy, which may fail to reach and penetrate an occluded venous segment.
- Retrievable inferior vena cava filters are important adjuncts in the care of patients with contraindications to anticoagulation or recurrent PE. They can also be beneficial in the treatment of "free-floating" iliac vein thrombus and in patients with compromised cardiopulmonary reserve.
- Percutaneous mechanical thrombectomy is an important adjunct to CDT and may result in a shorter time to vein patency, shorter length of hospitalization, reduction in hemorrhagic risk, and overall cost savings.

As interventional cardiologists have expanded their skill set from coronary interventions to the endovascular management of peripheral arterial disease, venous intervention has also gradually become a common part of the repertoire of the "global cardiovascular interventionalist." With greater recognition of the high prevalence, morbidity, and mortality associated with venous disease, more interventional cardiologists have become interested in the management of venous disorders, including both medical and catheter-based treatment of central venous stenosis, upper extremity and lower extremity DVT, and the insertion and retrieval of inferior vena cava filters.

THE VENOUS SYSTEM: BASIC HISTOLOGY AND PHYSIOLOGY

Veins are larger in caliber and more numerous than arteries. Arteries of the extremities run in the deep compartments, protected from superficial injury. Veins, on the other hand, course in both deep and superficial spaces. Additionally, the venous system has a much greater volume capacity than the arterial system, with thinner and less elastic walls. Most anatomists distinguish three layers in the walls of veins: tunica intima, tunica media, and tunica adventitia. Although the distinctions between the layers are subtle, in general the venous internal elastic membrane is poorly defined, and the tunica media is much less developed compared with that of arteries.

As in the arterial system, veins are commonly categorized into three major groups: large veins, medium-size veins, and venules and small veins. Only medium- and large-size veins are discussed in this chapter; for a complete review of venous embryology and anatomy, please refer to an anatomy textbook.

Medium-size veins range between 2 and 9 mm in diameter. They include veins from extremities distal to the axillary or inguinal crease and cutaneous veins. The intima consists of endothelium, basal lamina, and reticular fibers. The media consists of a very thin layer of circular smooth muscle and few collagen fibers. The adventitia, the thickest of all the layers, consists of both collagen and elastic fibers.

The large veins comprise veins that are central to the axillary or inguinal crease, the superior vena cava (SVC), the inferior vena cava (IVC), renal veins, hepatic veins, and azygos veins. The intima is similar to that of the medium-size veins. The tunica media is lacking in most of the large veins, with the exception of the gravid uterus and pulmonary veins. A thick adventitia makes up the greater part of the thickness of the wall. This layer is rich in elastic fibers and longitudinally oriented collagen. The IVC is exceptional in that its adventitia contains scattered longitudinal bundles of smooth muscle. Large veins, similar to large arteries, get their nutrient blood supply from very small penetrating vessels called *vasa vasorum*.

Vein Valves

Valve leaflets consist of a thin fold of the intima, with a thin layer of collagen and a network of elastic fibers that extend toward the intima of the vessel wall. Anatomically, valves are typically bicuspid in structure and are more numerous in the veins of the lower extremity, where the force of gravity is greatest. In general, small- and large-size veins have no valves. The wall of the vessel becomes thinner and slightly expanded just above the attachment of each valve cusp, creating a cavity called the *valve sinus*. When competent, the valves are forced shut by the weight of the column of blood above and the manner in which this column interacts with the valve sinus. This interaction causes valvule coaptation, preventing venous reflux (Fig. 45-1).

Only medium-size veins have valves, because their predominant function is to ensure the antegrade flow of blood—both peripheral to central flow and superficial to deep flow. Unidirectional valves prevent retrograde flow of blood away from the heart.

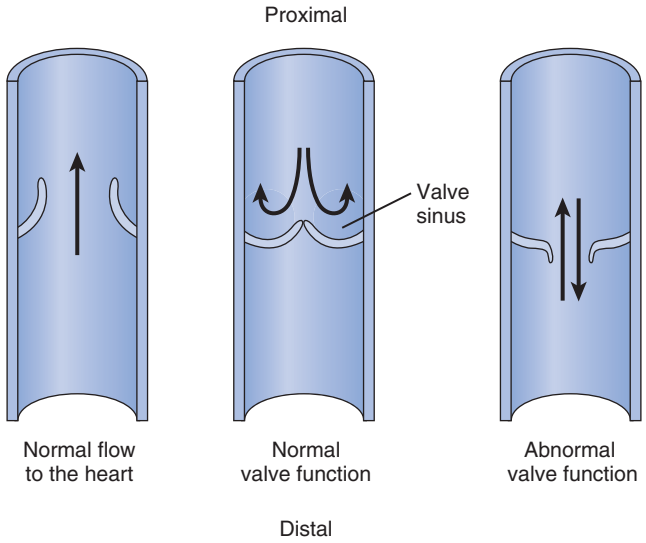

FIGURE 45-1 Venous valves with schematic representation of normal and abnormal function.

Physiology

The venous system has a large capacity, accounting for approximately two thirds of the systemic blood volume. Veins, because of their unique vascular structure, can undergo a large change in volume with minimal change in transmural pressure. This characteristic is called *venous capacitance*.

Because of their low elastic tissue content and collagen-dense adventitia, veins are actually stiffer than arteries when compared at the same distending pressure. A person standing at rest has significantly elevated venous pressures at the level of the feet and calves, accumulating a large volume of blood in the lower extremities. The calf muscles augment venous return by working as a hydraulic pump. During walking or exercise, calf muscle contractions push the accumulated blood toward the heart, decreasing the venous pressures to near-zero. The venous pressure remains low even during calf muscle relaxation. At this time, the unidirectional venous valves prevent backflow of blood but allow antegrade flow toward the heart. The venous valves must be competent for the calf pump system to work efficiently. A normal pump system reduces venous pressures and volume in the exercising muscle, increases venous return, and improves arterial perfusion.

Varicose Veins

Incompetent valves in the saphenous system permit reflux of blood from the central veins to the peripheral veins. The superficial veins dilate once the volume of retrograde flow exceeds their capacity; this ultimately leads to poor coaptation and venous valve incompetence. This valve incompetence can occur in the deep and the superficial systems, creating a standing column of blood with a constant increase in pressure. The transmission of an elevated venous pressure into the superficial system leads to the characteristic clinical sequelae known as varicose veins.

Chronic Venous Disease

Chronic venous insufficiency is a significant problem in the United States, affecting as many as 25 to 40 million people. Venous valve incompetence is central to the venous hypertension that appears to underlie most or all signs of chronic venous disease. Chronic venous disease afflicts a large segment of the population, and the morbidity of edema, leg pain, and ulceration may result in lifestyle alterations, loss of work, and frequent hospitalizations. The prevalence of venous ulcerations is not restricted to the elderly but certainly increases with age.[1] Venous ulcers have had a major negative economic impact, with an estimated loss of approximately 2 million working days and treatment costs of approximately $3 billion dollars per year in the United States.[2] The chief clinical manifestations of chronic venous disease are aching, leg pain, heaviness, a sensation of swelling, itching, cramping, and restless legs.

Chronic venous disease can be graded according to the descriptive clinical, etiologic, anatomic, and pathophysiologic (CEAP) classification, which provides an orderly framework for communication and decision making (Table 45-1).[3] The pathophysiology of chronic venous disease in regard to its clinical expression has been well described; it involves venous valve incompetence, structural changes in the vein wall (manifested as hypertrophy), and the roles of elevated venous pressure and shear stress.[4] Much newer work has been done in understanding the pathophysiology of the skin changes of chronic venous disease. These studies have validated that chronic inflammation has a key role in the skin changes of chronic venous disease. Support for the role of chronic inflammation in chronic venous disease has come to be known as the microvascular leukocyte-trapping hypothesis; elegant studies have shown elevated numbers of macrophages, T lymphocytes, and mast cells in skin biopsy specimens from lower limbs affected by chronic venous disease.[5] The chronic inflammatory state in patients with chronic venous disease is related to the skin changes that are typical of the condition.[4] Increased expression and activity of matrix

TABLE 45-1 Revised CEAP Classification of Chronic Venous Disorders

Clinical Classification	
C_0	No visible or palpable signs of venous disease
C_1	Telangiectasias, reticular veins, malleolar flares
C_2	Varicose veins
C_3	Edema without skin changes
C_4	Skin changes ascribed to venous disease (e.g., pigmentation, venous eczema, lipodermatosclerosis)
C_{4a}	Pigmentation or eczema
C_{4b}	Lipodermatosclerosis or atrophie blanche
C_5	Skin changes as defined above with healed ulceration
C_6	Skin changes as defined above with active ulceration
S	Symptomatic, including ache, pain, tightness, skin irritation, heaviness, muscle cramps, and other complaints attributable to venous dysfunction
A	Asymptomatic
Etiologic Classification	
Ec	Congenital
Ep	Primary
Es	Secondary (postthrombotic)
En	No venous cause identified
Anatomic Classification	
As	Superficial veins
Ap	Perforator veins
Ad	Deep veins
An	No venous location identified
Pathophysiologic Classification	
Pr	Reflux
Po	Obstruction
Pr,o	Reflux and obstruction
Pn	No venous pathophysiology identifiable

Adapted from Eklof B, Rutherford R, Bergan J, et al: Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg* 40:1248, 2004.

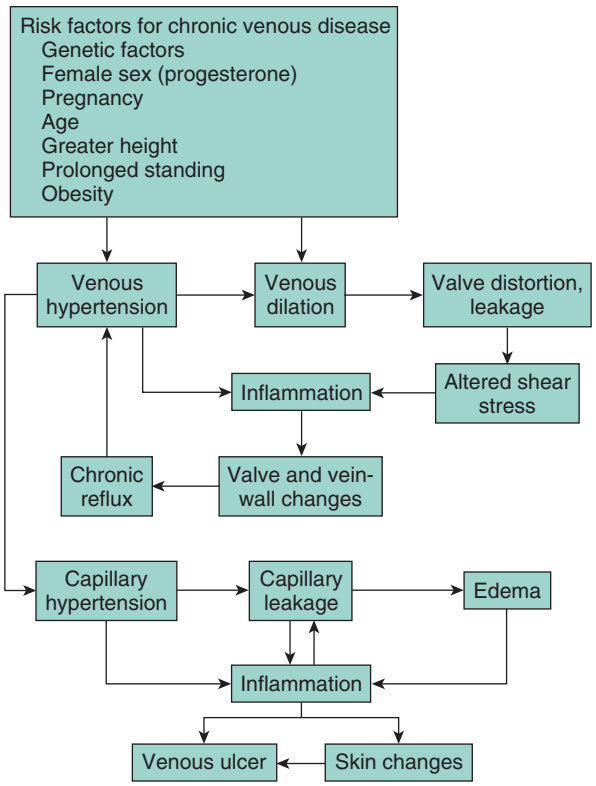

FIGURE 45-2 Venous hypertension as the hypothetical cause of the clinical manifestations of chronic venous disease, emphasizing the importance of inflammation.

metalloproteinases (MMPs), especially MMP2, has been reported in lipodermatosclerosis,[6] venous leg ulcers,[7] and wound fluid from non-healing ulcers.[8]

The treatment of chronic venous disease is beyond the scope of this chapter, but would be aimed at preventing venous hypertension, venous reflux, and chronic inflammation (Fig. 45-2). Compression stockings and devices are certainly the mainstay of controlling venous hypertension. However, endovenous ablation procedures utilizing laser energy or radiofrequency are available to treat venous reflux and are becoming a common part of the armamentarium used to combat venous disease. Clinical research is now being actively pursued to develop pharmacotherapy to alleviate the chronic inflammatory state of chronic venous disease, particularly targeting the interaction of leukocytes and endothelial cells.

CENTRAL VENOUS STENOSIS

SVC syndrome is a serious disorder resulting from impeded venous return from the upper body caused by obstruction of the SVC. The symptoms include severe congestion and edema of the face (facial plethora), arms, and upper thorax and may progress to dyspnea, headache, and, ultimately, cognitive dysfunction. A clinical classification system has been used to classify symptom severity (Table 45-2). SVC syndrome is usually caused by extrinsic or intrinsic obstruction of the SVC, although bilateral obstruction of both brachiocephalic venous segments can result in a similar clinical syndrome. Extrinsic compression caused by mediastinal malignancy or lymphadenopathy is the most common cause of true SVC syndrome.[9] The syndrome can also result from extension of central DVT to the SVC, usually in the presence of bilateral subclavian vein stenosis. Other etiologies include (1) thrombosis caused by underlying stenosis from long-term indwelling central venous catheters or other transvenous instruments

TABLE 45-2 Clinical Scoring System for Central Venous Stenosis

Signs and Symptoms	Grade
Neurologic Symptoms	
Stupor, coma, blackout	4
Blurry vision, headache, dizziness, amnesia	3
Changes in mentation	2
Uneasiness	1
Laryngotracheal or Thoracic Symptoms	
Orthopnea, laryngeal edema	3
Stridor, hoarseness, dysphagia, shortness of breath	2
Cough, pleural effusion	1
Nasal and Facial Signs or Symptoms	
Lip edema, nasal stiffness, epistaxis, rhinorrhea	2
Facial swelling	1
Venous Dilation	
Neck vein or arm vein distention, upper extremity swelling or upper body plethora	1

Modified from Kish K, Sonomura T, Mitsuzane K, et al: Self-expandable metallic stent therapy for superior vena cava syndrome: clinical observations. *Radiology* 189:531-535, 1993.

(see later discussion) and (2) benign compressive or constrictive conditions of the mediastinum, such as adenopathy from earlier histoplasmosis, fibrosing mediastinitis, previous irradiation, tuberculosis, and histiocytosis.[10–14]

Diagnosis of Central Venous Stenosis

The clinical presentation of SVC syndrome is relatively consistent and can be verified with multiple diagnostic modalities. Computed tomography (CT) is helpful for the initial workup of SVC syndrome and often gives enough information to proceed directly to an endovascular procedure.[15] An upper extremity venogram will reveal multiple collaterals if the obstruction is of long standing, but with acute SVC obstruction there are often surprisingly few collaterals. In most cases, the venogram demonstrates the level of involvement, but it can overestimate the length of involvement of the innominate veins and even the SVC because of the high resistance to flow.

Magnetic resonance (MR) imaging is helpful for the evaluation of SVC syndrome, and procedure planning can be based solely on MR imaging findings.[16] MR imaging shows excellent, detailed anatomic information regarding the extent of occlusion and collateral flow. Ultrasound is not accurate in pinpointing the location of the central obstruction, especially when the obstruction is more proximal than the subclavian veins, because of poor acoustic penetration. However, the Doppler signal will raise a suspicion of obstruction because of the flattened character of the waveform as a result of loss of venous pulsatility and respiratory phasicity. Ultrasound with Doppler can be a useful tool for follow-up after endovascular repair; obstructive changes in the waveform will raise suspicion of recurrent narrowing or occlusion of the recanalized vessel.

Technique

Endovascular therapy has emerged as the first-line treatment for central vein stenosis.[17] It is important to have a plan of approach before attempting SVC recanalization or stent placement. Taking into account the patient's clinical presentation and preprocedure noninvasive imaging findings is essential to a successful outcome.

Many operators have used femoral vein access, but others have used jugular, subclavian,[18] and arm vein or even transhepatic venous approaches for stent delivery.[19] One may use any combination of these approaches, but it is always paramount to have a guidewire "through

and through," especially if the stenosis is severe and difficult to pass.[20] A guidewire externalized from two separate access points allows for better overall support and control during stent delivery and deployment. This is particularly important in regard to preventing stent migration into the right side of the heart or pulmonary artery when the stenosis is near the SVC and right atrial junction. The stent is more likely to stay on the wire and can be more safely manipulated, removed, or moved to a different location.

Initially, accessing the SVC from the anterograde direction (e.g., right internal jugular vein, upper extremity veins) has several benefits. First, manipulation is easier because of the limited space in the internal jugular vein compared with the right atrium, which one has to work through when coming from a femoral vein access. Second, the distance from the access site to the obstruction is shorter, often making it easier to cross chronic total occlusions. Finally, accessing from the anterograde direction allows for good contrast visualization during injections. Other upper extremity access points, such as the brachial or basilic veins, are also viable options, especially in patients with short or obese necks. The entire venous intervention can be performed from this access, including thrombolysis, angioplasty, and stent placement in most cases.[21] This approach is also comfortable and well tolerated by most patients. Hemostasis is not usually problematic; placing a pressure dressing for 20 minutes or holding pressure for 5 to 10 minutes is usually successful. If double-barrel stenting is required to treat the SVC, bilateral upper extremity access is ideal, with the stents each traversing the brachiocephalic veins.

Several operators advocate use of the common femoral vein for access, but it can be difficult to access an occluded or severely narrowed SVC from the femoral vein because of the anatomic relationship with the right atrium.[22,23] From this direction, gentle wire manipulation often results in prolapse across the tricuspid valve, and aggressive wire manipulation risks right atrial perforation. Some operators have therefore crossed the obstruction from the internal jugular or brachial veins, creating a through-and-through access from the femoral vein access by snaring the wire and pulling it through the femoral vein.[24] In addition, double-barrel stents into each of the brachiocephalic veins can be easily placed from bilateral common femoral vein access using a similar technique if necessary.

Some experience with the use of thrombolytic therapy before, and in conjunction with, SVC stent placement has been reported. Isolated pharmacomechanical thrombolysis plus primary stenting is a combined procedure that opens an acutely thrombosed SVC rapidly to alleviate symptoms in seriously ill patients with SVC syndrome. O'Sullivan and colleagues[25] reported a case series in which all patients received isolated pharmacomechanical thrombolysis with tissue plasminogen activator (tPA) delivered in a Trellis Peripheral Infusion System (Covidien, Mansfield, MA) that removed obstructive clot in minutes, compared with the 24 to 48 hours required for traditional catheter-directed thrombolysis (CDT). In each patient, stents were deployed immediately after pharmacomechanical thrombolysis in a combined procedure lasting less than 1 hour. In the appropriate clinical setting, thrombolysis for SVC syndrome before endovascular therapy can have great utility, especially if the clinical scenario suggests the coexistence of acute thrombosis in addition to mechanical obstruction. By resolving the acute thrombus, one needs only to stent the underlying stenosis, which is typically shorter than the occluded segment that was occupied by thrombus. Because a shorter segment of vessel has to be stented, the number of stents used is reduced, as is, ultimately, the potential thrombogenic stent surface.

Gray and associates[26] reviewed the outcomes from thrombolysis of SVC thrombus in 16 patients and reported no major complications and complete success in 56% without stents. Thrombolysis was effective in 73%. Stents were not used in any of the patients, which may explain many of the poor clinical outcomes. Many patients with SVC syndrome have central venous catheters in place, on which they are dependent. In these patients, it may be necessary to temporarily remove the catheter before stenting, then reinsert the catheter through the stent immediately after the procedure.[27]

Stent Selection

Early reports of SVC stenting described the use of Gianturco stents (now known as the Cook-Z stent; Cook Medical, Bloomington, IN). This was the first self-expanding stent in wide use, and it had diameters that were acceptable. Although few complications have been reported, large sheath introducers (14 to 16 Fr) are required for this stent, and it is now used only in cases where inflow vessels must be covered because of the large spaces between the stent's interstices. Similarly, the Palmaz stent (now called the Palmaz Genesis stent; Cordis Corporation, Miami, FL) was once commonly used for treatment of SVC syndrome but is now rarely used in this anatomic location. This stent is balloon-expandable and has a higher radial force than self-expanding stents. However, when extra radial force is needed, it can be used either primarily or secondarily within a deployed self-expanding stent that cannot sustain the radial force of SVC recoil.

In today's era of endovascular therapy, self-expanding stent delivery systems are now mostly used for SVC stenting (Fig. 45-3).[28,29] The newer self-expanding stent delivery systems are easily deployed and come on a small (6-7 Fr) delivery system. The WALLSTENT (Boston Scientific Corporation, Natick, MA) was one of the earlier versions of a self-expanding stent, and it is still widely used for SVC intervention. Its main shortcoming is that it foreshortens significantly on delivery, which makes precise placement difficult. Recent generations of self-expanding stents are made of nitinol, a shape-memory superelastic alloy that offers greater flexibility and vessel adaptability. A few examples of self-expanding nitinol stents are the S.M.A.R.T. stents (Cordis Corporation, Miami, FL), the E-LUMINEXX (Bard Peripheral Vascular, Tempe, AZ), the Zilver (Cook Medical), and the Absolute Pro (Abbott Laboratories, Abbott Park, IL). Additionally, endovascular stent grafts are available in larger diameters and may result in better long-term patency compared with uncovered stents, although more study and experience is needed.[30] For the SVC, a 12- to 16-mm stent diameter is usually adequate, but intravascular ultrasound (IVUS) can be a useful adjunct to both the diagnosis and the treatment of SVC syndrome.[28]

Complications

In a group of 59 patients with malignant disease, Lanciego and colleagues reported 6 reocclusions, all of which were treated successfully with restenting in combination with thrombolysis.[29] One of the patients in their series had stent migration to the right atrium, which was successfully treated.

Hemopericardium has been reported by several operators in the literature. This complication most often occurs during the procedure itself or immediately after stent placement,[31] but delayed bleeding into the pericardium has also been described.[32,33] The pericardial reflection can extend very high in the mediastinum, and the position is unpredictable. In this regard, it is advisable to place stents high in the SVC without compromising clinical results. If there is a high index of suspicion for hemopericardium, an echocardiogram or right heart catherization should be performed immediately.

DEEP VENOUS THROMBOSIS OF THE UPPER EXTREMITY

Upper extremity deep venous thrombosis (UEDVT) is an increasingly important clinical condition with potential consequences of significant morbidity and mortality. Subclinical pulmonary embolism (PE) may be present in 33% of patients with a UEDVT, but symptomatic PE is detected in only 4% to 9% of such patients.[34,35] The venous pathway of the upper limb is less likely to develop a DVT compared with the lower limb because of the relatively high blood flow rate, gravitational effects, and lack of stasis.

Named after James Paget and Leopold von Schroetter, Paget-Schroetter syndrome remains a leading cause of primary UEDVT. Also known as *effort thrombosis* or *thoracic outlet syndrome (TOS)*, this

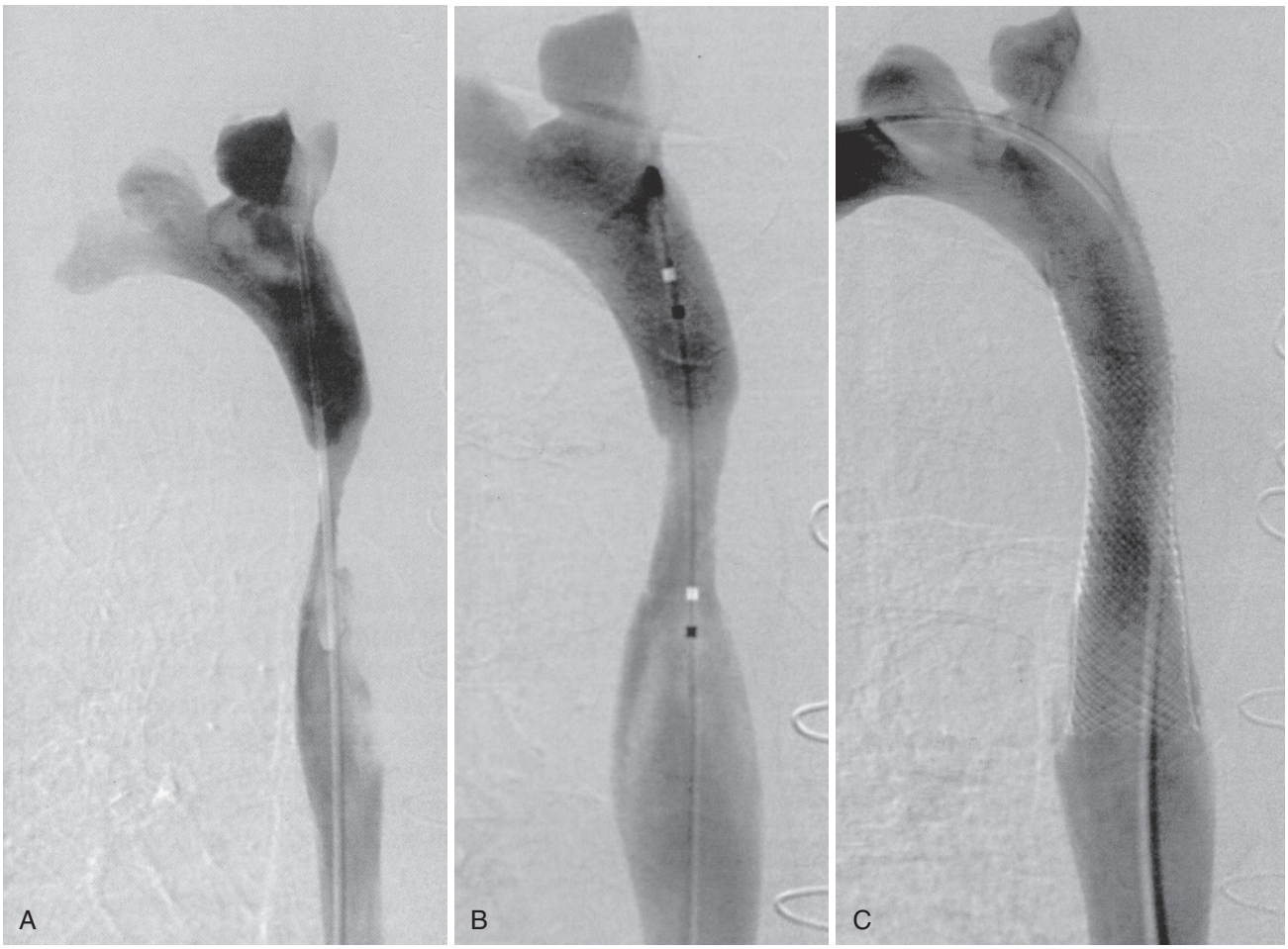

FIGURE 45-3 **A,** Venogram of significant superior vena cava (SVC) stenosis. **B,** Venogram of SVC after use of a 12-mm diameter balloon for angioplasty. **C,** Venogram after use of a 14-mm WALLSTENT (Boston Scientific Corporation, Natick, MA).

syndrome was often regarded as a benign condition. As available case reports and literature grew in the 1990s, UEDVT was increasingly regarded as a more common and less benign disease with potential for increased PE, postthrombotic syndrome (PTS), and mortality.[36-38] This change in view regarding UEDVT has been reflected by a higher degree of clinical awareness, more sensitive and ubiquitous noninvasive diagnostic techniques, and more effective contemporary treatments.[39-41]

Primary UEDVT remains a rare disorder (1 to 2 cases per 100,000 persons per year).[42,43] The term comprises effort thrombosis (Paget-Schroetter syndrome), venous TOS, and idiopathic UEDVT. Patients with effort thrombosis develop spontaneous UEDVT, usually in their dominant arm, after repetitive strenuous activities such as rowing, wrestling, weight lifting, or baseball pitching, but they are otherwise young and healthy.[44] The heavy exertion causes microtrauma to the vessels' intima, leading to activation of the coagulation cascade. Significant thrombosis may occur with repeated insults to the vein wall, especially if mechanical compression of the vessel is also present.[45]

TOS refers to compression of the neurovascular bundle (brachial plexus, subclavian artery, subclavian vein) as it exits the thoracic inlet (Fig. 45-4).[46,47] Although this disorder may initially cause intermittent positional extrinsic vein compression, repeated trauma to the vessel can result in the formation of dense perivascular fibrous scar tissue that will persistently compress the vein.[46] Compression of the subclavian vein typically develops in young athletes with hypertrophied muscles who do heavy lifting or frequently abduct their arms. Cervical ribs, long transverse processes of the cervical spine, musculofacial bands, and clavicular or first rib anomalies are sometimes found in these patients. Therefore plain films of the cervical spine and chest should be obtained in all patients undergoing evaluation for TOS.[46] Presenting signs and symptoms of UEDVT are shown in Table 45-3.

TABLE 45-3 Signs and Symptoms of Deep Venous Thrombosis of the Upper Extremity*

	Symptoms	Signs
Axillary or subclavian vein thrombosis	Vague shoulder or neck discomfort Arm or hand edema	Supraclavicular fullness Palpable cord Arm or hand edema Extremity cyanosis Diluted cutaneous veins Jugular venous distention Unable to access central venous catheter
Thoracic outlet syndrome	Pain radiating to arm/forearm Hand weakness	Brachial plexus tenderness Arm or hand atrophy Positive Adson† or Wright‡ maneuver

*These are nonspecific and may be recognized with provocative maneuvers.
†Adson maneuver: The examiner extends the patient's arm on the affected side while the patient extends the neck and rotates the head toward the same side. The test is positive if there is weakening of the radial pulse with deep inspiration and suggests compression of the subclavian artery.
‡Wright's maneuver: The patient's shoulder is abducted and the humerus externally rotated. The test is positive if symptoms are reproduced and there is weakening of the radial pulse.

Secondary UEDVT is associated with both exogenous and endogenous risk factors and usually develops in older, ill patients, with a slight preponderance among women.[48] Among exogenous risk factors,

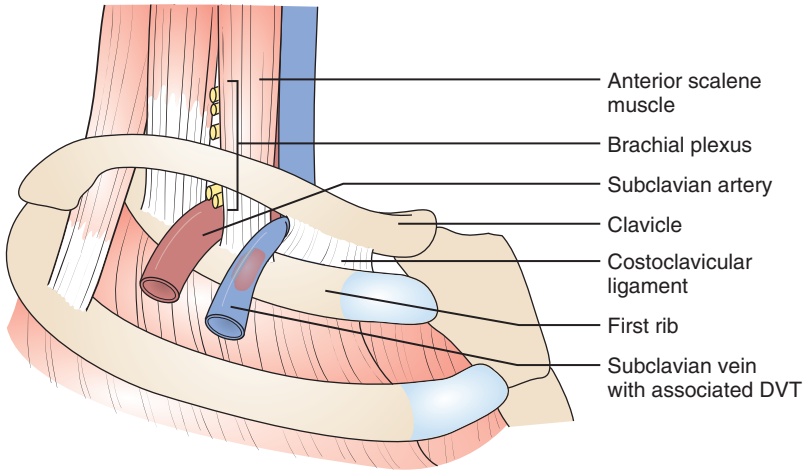

FIGURE 45-4 Illustration of the thoracic outlet anatomy. Notice the relationship of the subclavian vein to the surrounding structures: the anterior scalene muscle posteriorly, the first rib inferiorly, the clavicle superiorly, and the costoclavicular ligament anteriorly. In this example, the costoclavicular ligament is abnormal and is constricting venous flow. *DVT,* Deep venous thrombosis. (Modified from Urschel HC, Patel AN: Surgery remains the most effective treatment for Paget-Schroetter syndrome: 50 years' experience, *Ann Thorac Surg* 86[1]:254-260, Fig. 2, 2008.)

the positioning of central venous lines, malignancy, previous or actual episodes of lower extremity deep venous thrombosis (LEDVT), treatment with oral contraceptives, and trauma appear to have the greatest impacts on the development of UEDVT. Patients with indwelling central venous catheters constitute a particularly high-risk population, especially when undergoing chemotherapy, invasive hemodynamic monitoring, chronic parenteral nutrition, hemodialysis, or transvenous pacing, with a more than 60% prevalence of either symptomatic or asymptomatic UEDVT.[49-51] In fact, ispilateral catheter-related UEDVT may account for up to 70% of all secondary UEDVT cases.[48] Malignancy, either overt or undiagnosed, is also frequently associated with UEDVT (>30% of cases).[43,52] The discovery of an otherwise unexplained UEDVT in an older patient should prompt a malignancy workup; some data indicate that occult malignancy, especially lung cancer or lymphoma, may be discovered during follow-up in as many as 24% of patients with UEDVT, mostly during the first week of hospital admission.[53]

A history of previous episodes or an ongoing DVT of the lower extremities is associated with UEDVT in up to 18% of cases.[48] In an ultrasound surveillance study, almost 30% of high-risk trauma patients developed UEDVT during the course of hospitalization, and UEDVT was asymptomatic in up to 30% of the cases.[54] Treatment with oral contraceptives may also represent a significant risk factor in females (up to 14%) although the data are conflicting.[55] Infrequently, UEDVT arises in carriers of peripheral venous catheters, usually from a superficial phlebitis that has spread to the deep venous system,[51] or is associated with intravenous drug abuse, especially of cocaine.[56]

The prevalence of hypercoagulable states in patients with UEDVT is uncertain because observational studies report varying results, but the best available data estimates range as high as 24%.[43,57] Screening for coagulation disorders is controversial and has never been shown to be cost-effective.[58] The yield of these tests is highest for patients with idiopathic UEDVT; a family history of DVT; a history of recurrent, unexplained pregnancy loss; or a prior DVT.

Finally, the increasing use of device therapy in cardiac patients has undoubtedly led to an increased prevalence of UEDVT and other venous obstructive complications. Unlike catheter-associated complications, which may be transient and treatable with removal of the device, placement of cardiac pacemaker or defibrillator leads is usually permanent. Moreover, it is now common to have two or even three leads traversing the subclavian vein, and repeat procedures for device upgrades or lead revisions are frequent. In some studies, the incidence of angiographic venous lesions after pacemaker implantation was approximately 64%, with UEDVT incidence as high as 23%.[59,60] The majority of these UEDVTs are asymptomatic. Advanced age (≥65 years), left ventricular ejection fraction 0.40 or less, and atrial fibrillation have all been associated with increased risk for subclavian vein obstruction after pacemaker implantation.[59,61,62]

Diagnostic Testing

Historically, the gold standard for the diagnosis of UEDVT, which involves direct imaging of the whole deep venous system of the arm, is contrast venography. In contemporary practice, however, contrast venography has a limited initial role due to its invasive nature, inconvenience for patients, technical difficulty in performance and interpretation, and possible contrast dye-related complications.

Instead, several noninvasive imaging modalities that are widely available serve as alternatives to contrast venography; these are highlighted in the following sections.

Contrast Venography

Contrast venography is the standard reference for the diagnosis of UEDVT. Ideally, contrast injections should be made into the medial antecubital vein or more distally (e.g., in the back of the hand), and imaging should be captured using digital subtraction angiography (DSA) techniques with modern equipment. This will ensure adequate opacification of the brachial, axillary, and subclavian veins. Manual (by hand) injections are preferred over power injectors to reduce the risk of serious contrast extravasation. A common pitfall of contrast venography is nonfilling of the cephalic vein segment, and isolated thrombosis of this venous segment may go unnoticed. When imaging the central veins, it is essential to perform contrast opacification of the SVC during a single breath hold. If DSA imaging is inadequate due to poor patient cooperation or inability to maintain a breath hold, traditional cineangiography may be necessary. Contrast venography may not be feasible in up to 20% of patients because of inaccessibility of arm veins and contraindications for contrast agents (e.g., renal failure, hypersensitivity).

Despite some apparent disadvantages, venography may be required to confirm the diagnosis of UEDVT if suspicion for thrombosis remains high despite a negative noninvasive test. Venography is also required as a prelude to endovascular intervention, and it is used to assess response to these treatments, including thrombolytic therapy.

Duplex Ultrasonography

Duplex ultrasound has largely replaced invasive venography for the initial diagnosis of DVT. Its most advantageous features include no requirement for nephrotoxic contrast agents, its noninvasive nature, and the absence of ionizing radiation. In addition, it is widely available, portable, inexpensive, and can readily be performed at the bedside. Duplex ultrasonography has a high sensitivity and specificity for peripheral (jugular, distal subclavian, axillary) UEDVT.[63] However, acoustic shadowing from the clavicle limits visualization of a segment of subclavian vein and may result in a false-negative study.[64] Some technical recommendations regarding the use of duplex ultrasonography for the diagnosis of UEDVT include using a combination of

real-time compression gray-scale ultrasonography, color Doppler, and flow measurements using duplex technique with a 7.5-MHz linear-array probe.

In considering the diagnosis of UEDVT with the use of duplex ultrasonography, the definition of thrombosis is critical. It is widely accepted that noncompressibility of a venous segment with or without visible thrombus constitutes thrombosis. There is a building body of evidence regarding the use of isolated flow abnormalities as predictors of venous thrombosis. Because of acoustic shadowing from the clavicle, these flow abnormalities can be crucial clues to underlying thrombosis that is otherwise not well visualized in the venous segments beyond the clavicle.[64] These flow abnormalities seen on duplex ultrasound are only suggestive of thrombosis; contrast venography may be necessary if there is a high clinical index of suspicion for UEDVT. No studies have specifically addressed interobserver and intraobserver variability, but it is widely accepted in clinical practice that duplex ultrasonography is operator dependent and that some patients are more difficult to investigate, especially those with extensive edema or morbid obesity.

Magnetic Resonance Imaging

MR venography is an accurate, noninvasive method for detecting thrombus in the central chest veins, such as the SVC and brachiocephalic veins. MR venography provides a complete evaluation of central collaterals, central veins, and blood flow patterns. The correlation with traditional contrast venography is very good; therefore MR venography is a valuable imaging modality for the diagnosis of UEDVT when contrast venography is contraindicated or impossible. However, the increased use of pacemakers and internal defibrillators, the longer time required for image acquisition, and claustrophobia are potential drawbacks to MR venography. Although it was once considered a preferred alternative to contrast dye–based techniques such as contrast venography or CT venography for patients with renal disease, the recognition of nephrogenic systemic fibrosis and its association with gadolinium has slowed the widespread adoption of MR venography.[65,66]

Computed Tomography Venography

Already a mature technology, CT continues to evolve with the use of multidetector CT equipment that allows coronal and sagittal slice reformation and three-dimensional reconstruction. Moreover, the ability for rapid image acquisition gated to the cardiac cycle provides for high-resolution imaging without motion artifact. This imaging modality will likely play a greater role in the management of UEDVT going forward. One major advantage of CT venography is the ability to assess for the presence of pulmonary emboli and other anatomic abnormalities that may underlie a patient's upper extremity complaints (e.g., malignancy). Limitations to this technology include the need for a contrast agent, the use of ionizing radiation, and overall cost.

Treatment Options

The optimal approach for the treatment of UEDVT remains unknown, but in general there are two overarching goals: first, to prevent thrombus propagation and second, to restore normal venous anatomy. Arresting further thrombus formation reduces the risk of secondary events such as pulmonary embolization or disease recurrence. Restoration of normal venous anatomy is achieved typically by recanalization of existing thrombus and is important in the prevention of PTS. It is quite likely that henceforth more patients with UEDVT will be approached with a multimodal effort. Treatment options will include, either individually or in combination, anticoagulant therapy, thrombolytic therapy, endovascular intervention, and vascular surgery.

Anticoagulation

Anticoagulation represents the mainstay of therapy for UEDVT. Anticoagulation helps maintain the patency of venous collaterals and reduces thrombus propagation even in the absence of complete thrombus resolution.[67] However, anticoagulation alone rarely achieves vessel recanalization, and the result is permanent obstruction of the upper extremity veins. Collateral veins typically develop, but they are generally not accessible for placement of intravenous lines and are usually inadequate for the normal efflux of venous blood from the arm. Standard anticoagulation typically includes unfractionated heparin or low-molecular-weight heparin (LMWH) for 5 to 7 days, as a "bridge" to oral warfarin. Warfarin is typically continued for a minimum of 3 months, with a goal international normalized ratio (INR) of 2.0 to 3.0. A longer duration of warfarin anticoagulation may be indicated if some form of coagulation abnormality is detected or if an underlying mechanical etiology is not definitively treated. Alternatives to warfarin in contemporary practice include the new oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, and apixaban in the treatment of DVT.[68]

Thrombolytic Therapy

Because many patients with UEDVT are young, active, and healthy, thrombolytic therapy rather than conservative anticoagulation should be strongly considered on a case-by-case basis. Certainly, a young healthy patient with UEDVT may have significant long-term morbidity if treated with only anticoagulation.[69] In this regard, thrombolysis restores venous patency early, minimizes damage to the endothelium, and reduces the risk of long-term complications, especially the development of PTS, with its disabling chronic aching and swelling of the arm and hand. The obvious disadvantage of thrombolytic therapy is greater risk of a bleeding complication.

The ideal candidate for thrombolytic therapy for UEDVT is an otherwise healthy young patient with a primary UEDVT or a patient with an indwelling central venous catheter in whom it is essential to maintain patency for central venous access.

Results from a large series of patients with UEDVT who were treated with CDT showed that treatment restored venous drainage, with subsequent low frequency of mild postthrombotic syndrome at follow-up.[70] No intracerebral bleeding, clinical PE, or death occurred during treatment follow-up.[70] Thrombolysis has the best chance of success if it is used within 4 to 6 weeks after symptom onset; older, organized thrombus is more resistant to thrombolysis. When one is performing CDT, the catheter should be placed directly within the entire length of visible thrombus; otherwise, the potential for collateral circulation to divert drug distribution away from the thrombus may lead to an unsuccessful procedure.

There are no randomized, prospective, controlled clinical trials comparing different thrombolytic agents for treatment of UEDVT. At our tertiary referral center, catheter-directed reteplase (Retavase) or tenecteplase (TNKase) are administered at 0.25 to 0.5 U per hour for 8 hours.[71] Clinical examination and serial venography are used to assess response to treatment. We often use a percutaneous mechanical thrombectomy (PMT) device in combination with thrombolytic therapy. This adjunctive catheter-based thrombectomy technique has the benefit of accomplishing thrombus extraction before thrombolytic therapy; this often initiates some blood flow, thereby improving drug distribution and reducing the dose and duration of thrombolytic therapy.[72] (See "Percutaneous Mechanical Thrombectomy" for a complete description.)

The time required to achieve complete thrombolysis in subclavian vein thrombosis can be as long as 72 hours, but it is not unusual to get much quicker or even immediate, on-the-table results depending on the age of the thrombus. Oral anticoagulants such as warfarin or a NOAC should be used for 3 to 6 months after successful thrombolysis for UEDVT. Certainly, duration of warfarin therapy should be individualized on a case-by-case basis depending on the clinical situation.

Interventional Therapy

Catheter-based mechanical thrombectomy is an important adjunct to thrombolytic therapy, as stated earlier. The ability to perform instant thrombus removal and thereby restore some anterograde flow through the DVT allows for better overall drug distribution and delivery. Moreover, the ability to deliver thrombolytic agents directly into the clot instead of systemically reduces both the dose and treatment time.[73]

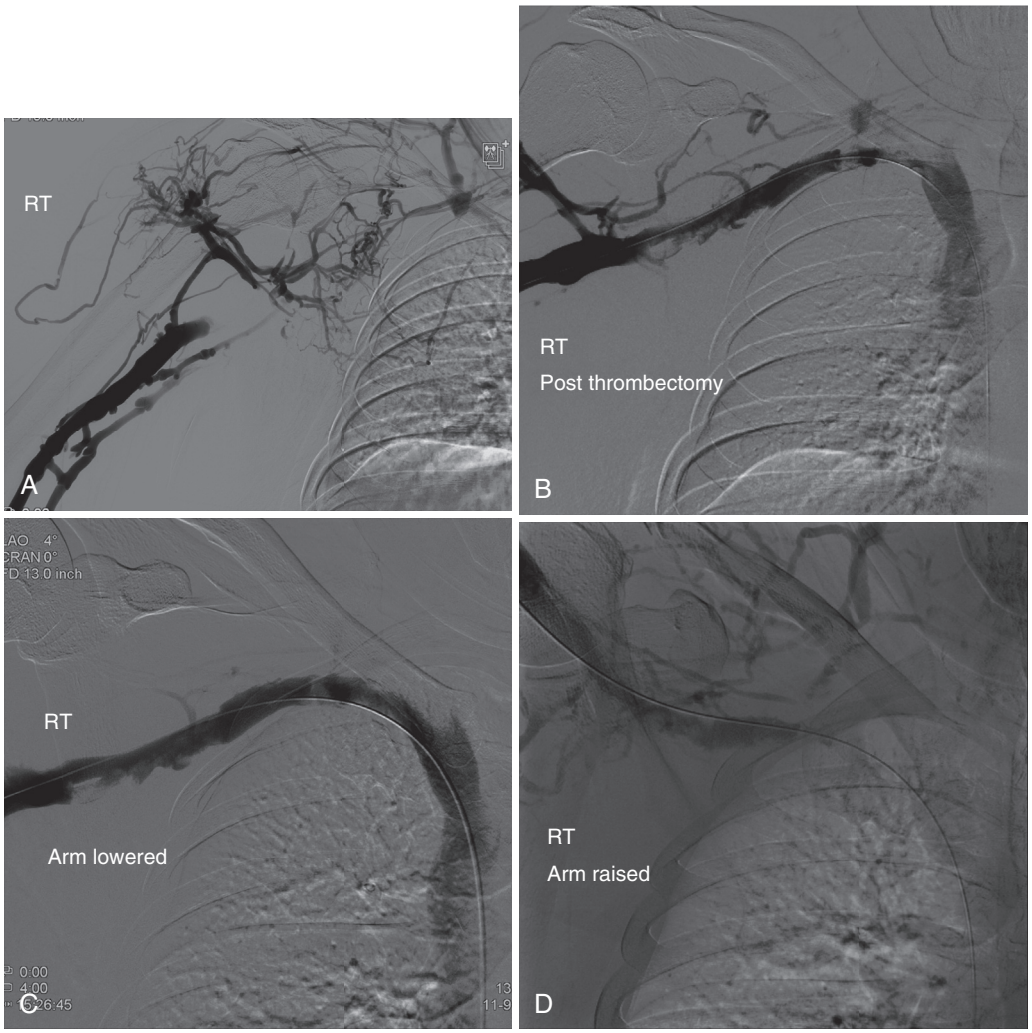

FIGURE 45-5 **A,** Right upper extremity venogram of a 42-year-old right-handed painter with acute right subclavian vein deep venous thrombosis. **B,** Venogram in same patient after successful "on-the-table" catheter-directed thrombolysis and rheolytic thrombectomy. Provocative maneuvers show excellent flow with the arm in a neutral position after treatment (**C**) but provoked outlet obstruction with the arm in the raised and externally rotated position (**D**), as evidenced by cessation of venous flow despite successful treatment.

Adjunctive percutaneous transluminal angioplasty (PTA) or stenting of the subclavian vein has utility, especially for catheter-related stenosis when a hemodynamically significant pressure gradient remains after successful thrombolytic therapy.[74] A flexible, self-expanding, oversized nitinol stent is best suited for this location, but caution must be used, especially in the treatment of TOS, because the extrinsic compressive forces may lead to stent fracture and failure.[47,75] Intravascular ultrasound has proved to be very useful in determining stent sizing when treating subclavian vein stenosis. Figure 45-5 demonstrates CDT of an acute right UEDVT in a patient with classic effort thrombosis.

Subclavian vein stenosis resulting from transvenous permanent pacemaker or internal cardiac defibrillator leads is becoming increasingly common. Although these patients can have UEDVT or even SVC syndrome at presentation,[76] the stenosis is more often discovered during elective upgrade of the cardiac device or during the addition or revision of leads. In such instances, the predominant role of interventional therapy is to assist with lead delivery through what is often a chronically occluded or near-occluded vein composed of dense, scar-like adhesions. In this scenario, balloon angioplasty to facilitate sheath insertion across the stenosis is usually adequate to provide a path through which the electrophysiologist can work.

Surgical Therapy

Subclavian vein compression in patients with primary UEDVT represents an important cause of recurrent thrombosis and long-term morbidity.[77] After successful treatment of an acute UEDVT, it is paramount that some form of imaging be undertaken to evaluate for the presence of vein compression. After successful thrombolysis, venography in the neutral and shoulder-abducted positions can help demonstrate vein compression. Recent surgical series recommend surgical correction of extrinsic vein compression,[77] which typically requires resection of part of the first rib or clavicle. Lysis of adhesions around the subclavian vein may also be required if anatomic anomalies have caused chronic, repeated trauma to the subclavian vein. Today, surgical thrombectomy is rarely required because of advancements in pharmacologic and catheter-based therapies. However, in symptomatic patients who are refractory to other therapies, surgical thrombectomy can restore venous patency.

Treatment of UEDVT is aimed at preserving the venous anatomy, preventing potentially fatal PE, and decreasing the risk of PTS. Treatment depends on the cause, the duration of thrombosis, and the clinical circumstances. For most patients with UEDVT, 3 to 6 months of oral anticoagulation is usually sufficient, especially for reversible conditions such as catheter-associated UEDVT. However, there is a

tendency to be more aggressive with thrombolytic therapy and catheter-based thrombectomy in individual cases, especially in younger patients who are at risk of chronic venous insufficiency or in an effort to minimize long-term morbidity and optimize functionality. A structured physical therapy program aimed at loosening the muscles compressing the subclavian vein and weight loss, if indicated, is another important adjunct to complete therapy.

DEEP VENOUS THROMBOSIS OF THE LOWER EXTREMITY

DVT is a process that can affect any of the deep veins of the body, but it is most frequently seen in the deep veins of the lower extremity. Venous thrombus formation is initiated by intravascular clotting and is increased in the presence of several risk factors. These risk factors were postulated more than 100 years ago by Virchow and are summarized by his classic triad of coagulation abnormalities, endothelial damage, and stasis. The main contributing risk factors for DVT of the lower extremities include advanced age, prolonged bed rest, and major surgery—particularly large abdominal operations and orthopedic procedures. Other commonly described risk factors include previous DVT, malignancy, trauma, varicose veins, chronic venous insufficiency, smoking, high estrogen states (e.g., pregnancy and the postpartum period, estrogen-containing contraceptive devices or pills), and hypercoagulable states, either primary or secondary.

The major complications of LEDVT include PE and PTS, and the treatment paradigms are aimed largely at preventing both. The incidence of venous thromboembolism in the general population may reach 1.92 per 1000 person-years. Almost half of all cases are idiopathic. For those patients with a first episode of venous thromboembolism, the 28-day mortality rate may reach 11% and may be as high as 25% in cancer-associated subgroups.[78] Clinical PE occurs in 26% to 67% of the cases of untreated proximal DVT and is associated with a mortality rate of 11% to 23% if untreated. With treatment, the incidence of PE decreases to 5% and the mortality rate to less than 1%.

However, PTS is a cause of increased morbidity and disability as well. Up to two thirds of patients with iliofemoral DVT develop edema and pain, and 5% develop venous ulcers despite adequate anticoagulation.[69] Early diagnosis and treatment of DVT is essential to prevent mortality and morbidity from PE and PTS.

Diagnosis of Acute Deep Venous Thrombosis of the Lower Extremity

Venous Duplex Ultrasound

The clinical diagnosis of LEDVT is notoriously inaccurate: The classic signs and symptoms of DVT are as common in patients without DVT as they are in those with confirmed DVT. Objective confirmation of clinically suspected DVT is therefore required. Despite its many limitations, contrast venography has historically been considered the "gold standard" for the diagnosis of acute DVT. However, it is invasive, not easily reproducible, and impossible to perform or interpret in 9 to 14% of patients; it fails to visualize all venous segments in 10% to 30% of studies; and it is associated with interobserver disagreements in 4% to 10% of studies. Therefore contrast venography has been replaced by venous duplex ultrasound as the most widely used diagnostic test for acute DVT. In comparison with contrast venography, duplex ultrasound has the advantages of being widely available, noninvasive, portable, inexpensive, and easily repeatable. A complete ultrasound evaluation of the lower extremities includes an assessment of venous compressibility, intraluminal echogenic signals, venous flow characteristics, and luminal color filling. Venous incompressibility, or failure to completely coapt the venous walls with gentle probe compression, is the most widely used diagnostic criterion for acute DVT.[79] Normal flow in the proximal veins should be spontaneous and should vary with respiration, increasing during expiration and decreasing during inspiration. Adjunctive gray-scale imaging may allow for more subtle characterization of the thrombus including the degree of intraluminal echogenicity, surrounding tissue edema, and amount of venous dilation, all of which may assist the provider in determining the age of the DVT.

Other noninvasive imaging techniques for the diagnosis of LEDVT include MR venography and CT venography. These modalities are comparable to conventional contrast venography but are subject to the multitude of limitations described previously.

Diagnostic Testing and Clinical Risk Stratification

D-dimer, which is formed as a byproduct in the degradation of cross-linked fibrin by plasmin, reflects thrombus formation and has been proposed as an alternative or adjunct to initial diagnostic testing. Although D-dimer is sensitive for the diagnosis of DVT, D-dimer measurements are nonspecific, and elevated levels may be associated with preeclampsia, malignancy, infection, trauma, age, or recent surgery. The high sensitivity of D-dimer measurement and its favorable negative predictive value make it advantageous for exclusion of DVT when used in the correct patient population and typically in conjunction with other predictive models[80]; however, the low specificity and positive predictive value necessitate confirmatory noninvasive testing for positive results. A combined strategy using an assessment of clinical probability, D-dimer testing, and venous duplex ultrasound may hold the greatest diagnostic promise. The utility of this approach relies on the observation that its negative predictive value approaches 100% in outpatients with a low pretest clinical probability for DVT.[81]

Goals of Therapy

As understanding of the pathophysiology of venous thromboembolism has evolved, along with the constant refinement of endovascular devices and thrombotic therapy, so too have the overall goals of care. There are four general treatment goals for patients with LEDVT: (1) diminishing the severity and duration of lower extremity symptoms, (2) preventing PE, (3) minimizing the risk of recurrent venous thrombosis, and (4) preventing PTS. To successfully achieve these goals, a comprehensive treatment approach using multiple modalities is typically employed. This may be as simple as a brief duration of anticoagulation, compression stockings, an avoidance of prolonged immobility in some patients. In others, it may include an extensive biologic workup for inherited thrombophilias, pharmacomechanical CDT, and IVC filter placement.

Detailed monographs and practice guidelines regarding the medical management of LEDVT are numerous and readily available.[82] There is uniform agreement that adequate initial anticoagulation therapy is required to arrest further thrombus propagation and PE. Intravenous unfractionated heparin remains in widespread use but is gradually being replaced by LMWH as the anticoagulant of choice for the initial treatment of LEDVT. Both agents are relatively safe and effective when used in this context, with LMWH suitable for outpatient therapy because of improved bioavailability and more predictable anticoagulant response. Serious potential complications of heparin therapy, such as heparin-induced thrombocytopenia and osteoporosis, seem less common with LMWH.

Although medical therapy with anticoagulation is the mainstay of the initial management of LEDVT, many patients, particularly those with large proximal iliofemoral DVTs, have persistent leg edema, pain, and difficulty ambulating. Some patients progress to develop phlegmasia cerulea dolens, a rare condition marked by severe venous hypertension, cyanosis, venous gangrene, compartment syndrome, and eventually limb loss or circulatory collapse. These morbid symptoms arise from venous hypertension caused by outflow obstruction, and demand a treatment strategy more aggressive than simple anticoagulation. Indeed, anticoagulation alone is associated with thrombus regression in only 50% of patients,[83]a fact that severely limits anticoagulation monotherapy, particularly in patients with very proximal DVTs.

Fortunately the modern evolution of endovascular techniques (including CDT, mechanical thrombectomy, and stenting) have significantly increased the number of viable treatment options for LEDVT.[84,85]

The details of endovascular venous interventions—which are targeted to restore venous patency, preserve valvular function, and minimize the risk of late postthrombotic complications—are discussed in the following sections.

Inferior Vena Cava Filters

The primary indications for IVC filter placement include absolute contraindications to anticoagulation and recurrent thromboembolism while receiving therapeutic doses of anticoagulation for LEDVT. IVC filters may also be placed in the setting of massive or submassive PE when it is believed that any further pulmonary emboli may be lethal because of a compromised cardiopulmonary reserve. Although IVC filters are effective in reducing the risk of further pulmonary embolization, they do not afford protection from further DVT. In fact, IVC filters may result in an increased risk of secondary DVT. In a study of high-risk patients with proximal DVT, Decousus and coworkers found that the initial beneficial effect of IVC filters for prevention of PE was counterbalanced by an excess of recurrent DVT (20.8%) compared with standard anticoagulation (11.6%), without any difference in mortality.[86]

Today, IVC filters are designed to be either permanent or optionally retrievable (Fig. 45-6). Optionally retrievable filters are approved for permanent placement but are designed to facilitate retrieval once the risk of further PE or contraindication to anticoagulation has passed. Currently, 11 permanent or optionally retrievable IVC filters have been approved by the U.S. Food and Drug Administration (FDA). Percutaneous transjugular or transfemoral insertion is most commonly used. Smaller delivery sheaths and lower device profiles have also facilitated access via the brachial vein or the popliteal vein. The choice of filter depends on IVC size and the required duration of insertion anticoagulation can be safely started. The popularity of IVC filters has increased dramatically over the last decade because of expanding indications for insertion, particularly for primary prevention, and because of the increasing use of retrievable filters.

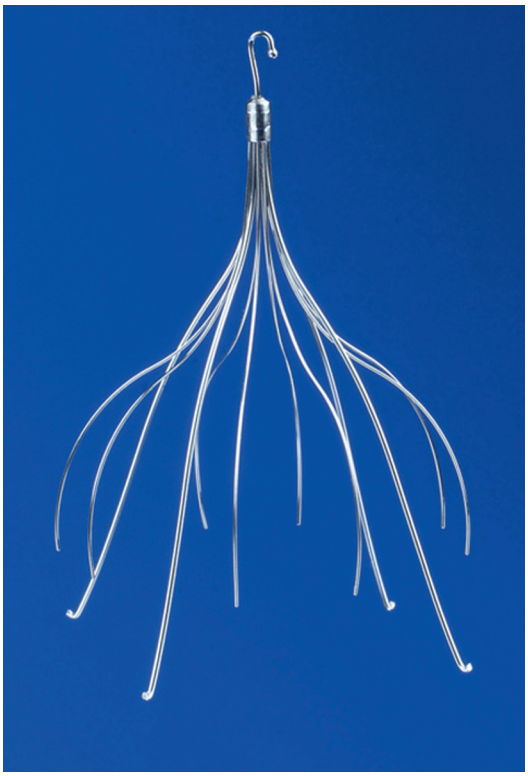

FIGURE 45-6 Cook Celect retrievable inferior vena cava (IVC) filter, which has nitinol construction, is used in IVCs up to 30 mm in diameter and is delivered via a 7-Fr delivery sheath. (Courtesy Cook Medical, Bloomington, IN.)

Manufacturer-recommended retrieval times vary by product, with some filters having on-label retrieval times for up to 1 year after implantation. In August 2010, the FDA mandated that implanting physicians and clinicians responsible for the ongoing care of patients with retrievable IVC filters consider removing the filter as soon as protection from PE is no longer needed.

Complications of IVC filters fall into three categories: procedure-related, device-related, and thrombosis-related. Procedure-related complications include primarily insertion site complications. Device-related complications include malpositioning, tilting, failure of complete deployment, migration, fracture, and IVC perforation. These device-related complications affect the efficacy of the filter in secondary PE prevention. Thrombotic complications include PTS, recurrent DVT, and IVC thrombosis. The seriousness of these complications highlights the importance of appropriate case selection when IVC filter placement is being considered as an adjuvant treatment in the patient's overall care.

Catheter-Directed Thrombolysis

In the early 1990s, Semba and Dake first reported the feasibility of CDT for iliofemoral vein thrombosis as an alternative to systemic anticoagulation, systemic thrombolysis, or surgical venous thrombectomy.[87] CDT, or the delivery of thrombolytic agents directly into the thrombus, offers significant advantages over systemic therapy, which may fail to reach and penetrate an occluded venous segment. Because thrombolytic agents activate plasminogen within the thrombus, local delivery of the drug directly into the thrombus enhances its overall effectiveness. Focused delivery of higher concentrations of the drug can improve lysis rates, reduce the duration of treatment, and minimize complications associated with exposure of the patient to systemic thrombolytic therapy. Furthermore, with enhanced removal of obstructive thrombus, it is believed that venous valvular function will remain preserved and the incidence of PTS will therefore be reduced. In addition, successful CDT facilitates detection and correction of any underlying venous obstructive lesions with balloon angioplasty and/or stent placement.

Currently, no thrombolytic agents are approved for CDT by the FDA. The use of thrombolytic agents in CDT for venous thrombosis constitutes an "off-label" use. Although many thrombolytic agents are available in the United States for use in CDT, contemporary use involves mostly alteplase and tenecteplase. Although the various agents have unique properties that might theoretically confer an advantage of one over another, there remains no peer-reviewed consensus on a superior agent for CDT in cases of venous thrombosis. The literature on CDT for venous thrombosis has a paucity of prospective randomized comparative trials. Therefore the choice of thrombolytic agent is individualized to the physician's discretion.

There is a large, ongoing, prospective multicenter randomized trial aimed at determining whether CDT should routinely be used in the treatment of proximal DVT for the prevention of PTS.[88] The largest published experience with CDT to date has come from the National Venous Thrombolysis Registry,[87] which included 287 patients who were treated with urokinase and monitored for 1 year. Overall, 71% of the patients were treated for iliofemoral DVT. Complete dissolution of thrombus was achieved in 31% of cases, and partial thrombus dissolution was reported in an additional 52%. Primary patency at 1 year was 60%. Preservation of valvular competence was demonstrated in 72% of those patients with complete thrombolysis. Table 45-4 reviews the available clinical experience with CDT for the treatment of DVT.

The location of the LEDVT and the patient's symptoms determine the access technique. For most cases of iliofemoral DVT, the ipsilateral popliteal vein is favored if the clinical situation allows. With the patient prone on the angiographic table, the popliteal vein should be accessed under ultrasound guidance, typically with a small-gauge

micropuncture echogenic needle, and care should be taken to avoid inadvertent puncture of the popliteal artery. Should the popliteal vein be thrombosed, the ipsilateral posterior tibial vein may be accessed, a technique that confers the advantage of maintaining the patient in a supine position. After popliteal vein cannulation, a 5- to 6-Fr short sheath is introduced, through which all subsequent catheters can be exchanged. Next, a baseline venogram is obtained through the venous sheath using standard DSA imaging techniques. Then a combination of 0.035-inch straight and curved hydrophilic guidewires are used to cross the occluded venous segment. After wire and then catheter traversal of the occluded venous segment, venography is repeated to confirm the intraluminal position of the catheter.

At this point, modern techniques generally favor moving directly to mechanical thrombectomy (described later), followed by the insertion of an infusion catheter with multiple sideholes for dedicated, prolonged administration of thrombolytics, if necessary. When placing an infusion catheter for the direct delivery of thrombolytic agents, it is essential to position the delivery system directly across the thrombus in order to maximize plasminogen activation at the site of obstruction. Figure 45-7 illustrates the endovascular management of an acute left common iliac DVT. Patients are closely monitored in an interventional recovery unit during thrombolytic infusion. It is common for the duration of therapy to exceed 24 hours, particularly in cases with an extensive thrombus burden. Follow-up venography should be performed every 8 to 12 hours to assess the infusion catheter and reposition as necessary. Weighing the risks versus the benefits of thrombolytic therapy, the infusion should ideally be continued until complete lysis is achieved.

In patients in whom venous patency has been restored and there is no underlying stenotic or occlusive lesion, thrombolysis is discontinued and anticoagulation is initiated. Hemodynamically significant lesions that are uncovered in the iliac veins should be considered for endovascular stenting, although the long-term benefits of venous stenting are not well described. However, if left untreated, a significant iliac vein stenosis appears to pose a substantial risk of early rethrombosis. Often these stenoses are actually caused by extrinsic compression of the iliac vein, typically the left common iliac vein, by the crossing of the right iliac artery at the iliocaval junction. This anatomic configuration, termed the *May-Thurner syndrome*, classically involves the left common iliac vein, but other variants have been described.[89] Because these lesions result from chronic, extrinsic compressive forces, balloon angioplasty alone is rarely successful, and the deployment of nitinol self-expanding stents is preferred because of their longitudinal flexibility and ability to conform to various venous configurations. Care should be exercised to avoid stenting across the common femoral vein, particularly at the saphenofemoral junction. IVC filter placement during CDT for LEDVT should be used according to standard indications (described previously). Routine use of IVC filter placement during CDT has always been controversial because of the low incidence of complications observed when thrombolysis is performed without filter protection. Acknowledging this controversy, we have generally been using retrievable IVC filters during CDT for LEDVT, especially in patients in whom the venogram has defined a true "free-floating" iliac vein thrombus or in patients with a documented pulmonary embolus and limited cardiopulmonary reserve.

TABLE 45-4 Single-Center Case Studies Supporting Catheter-Directed Thrombolysis for Deep Venous Thrombosis*

Author	*N*	Agent	Outcome (% lysis)	Hemorrhage (%)
Molina et al	12	Urokinase	95	0
Comerota et al	7	Urokinase	71	0
Semba & Dake	27	Urokinase	92	0
Bjarnason et al	87	Urokinase	86	6.9 major/14.9 minor
Patel et al	10	Urokinase	100	0
Ouriel et al	11	Reteplase	73	0
Castenada et al	25	Reteplase	92	4
Chang et al	10	Alteplase	90	0
Horne et al	10	Alteplase	90	30 minor
Razavi et al	36	Tenecteplase	83	2.7 major/8.3 minor

N, Number of patients.
*Series evaluating catheter-directed thrombolysis for deep venous thrombosis.

Percutaneous Mechanical Thrombectomy

Several drawbacks to CDT as a monotherapy for LEDVT include the time required for thrombolysis, the need for intensive care monitoring, associated hemorrhagic risks, cost, and lack of prospective, randomized clinical trials. With these issues in mind, PMT is conceptually attractive because such a technique may obviate or reduce the time required for thrombolytic drug administration. In turn, this may result in a shorter time to vein patency, shorter length of stay, reduction in hemorrhagic risk, and overall cost savings. From a mechanistic standpoint, PMT devices can be categorized as rotational, hydrodynamic, or ultrasound-facilitated. *Pharmacomechanical thrombectomy* is a term used to describe the treatment of thrombosis using both thrombolytic drugs and mechanical thrombectomy during the same procedure. Some PMT devices are able to deliver thrombolytics directly into the thrombus, whereas others may be used only as an adjuvant before the use of a standard multi-sidehole infusion catheter.

Rotational thrombectomy devices employ a high-speed rotating basket or impeller to pulverize or fragment thrombus. Preclinical evaluations of these devices have focused on clot removal and assessment of potential valve injury. In one such study, the Arrow-Trerotola percutaneous thrombectomy device (Arrow International, Reading, PA) did not cause physiologically significant damage to valves 7 mm or larger in diameter.[90]

Hydrodynamic or rheolytic recirculation devices have become a common treatment modality for LEDVT. The AngioJet Thrombectomy System (Boston Scientific, Marlborough, MA) is the prototypical device in this category, which works based on the Venturi effect. Rapidly flowing saline jets are directed backward from the tip of the device to outflow channels in a coaxial fashion; this generates a vacuum force that draws thrombus into the catheter (Fig. 45-8). One major advantage of this PMT device is that the thrombectomy catheter can be delivered through a 6-Fr introducer sheath, which reduces access-site complications. Newer iterations of this device also include the ability to spray thrombolytic agents directly into areas of thrombus using the Power Pulse technology, making it a simple device for pharmacomechanical thrombectomy (Fig. 45-9). Using Power Pulse, the operator delivers the thrombolytic agent after a standard thrombectomy run and then allows the drug to dwell, typically for 20 to 30 minutes. After the dwell period, a final "clean up" run is performed, again using the standard thrombectomy settings. Two contemporary series using pharmacomechanical thrombectomy and the Power Pulse technique reported high technical success rates with acceptable safety and long-term improved functional outcomes.[91,92]

The Trellis Peripheral Infusion System (Covidien, Dublin, Ireland), which also combines pharmacologic and mechanical thrombectomy, consists of a catheter with proximal and distal occlusion balloons (Fig. 45-10) and a sheath designed to aspirate contents between the balloons. A sinusoidal nitinol wire placed between the balloons is rotated by an included battery-operated motor unit to mix the blood between the balloons. The wire oscillates at varying rates ranging from 500 to 3000 revolutions per minute and is controlled by the operator. The Trellis device, which combines a high concentration of locally delivered thrombolytic medication with mechanical disruption of thrombus, has been used with success to treat patients with DVT.[93] The occlusion

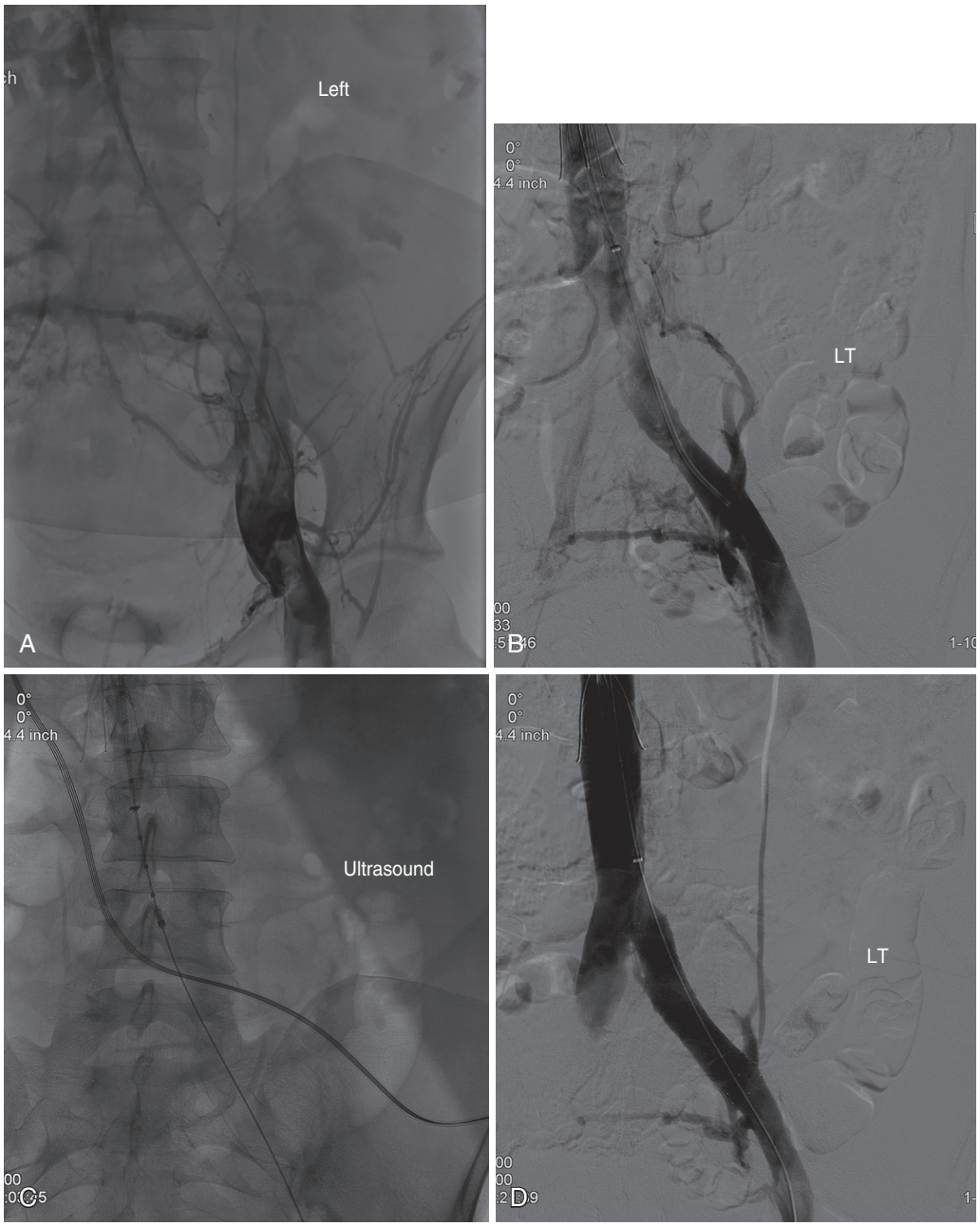

FIGURE 45-7 **A,** Extensive thrombotic occlusion of the left common and external iliac veins with some extension into the common femoral veins. Notice the severely dilated iliac veins. **B,** After pharmacomechanical thrombolysis using rheolytic thrombectomy and the Power Pulse feature of the AngioJet Thrombectomy System (Boston Scientific, Marlborough, MA) with a 20-minute dwell time. **C,** Intravascular ultrasound (IVUS) is used to confirm extrinsic compression of the left common iliac vein and to assist with stent sizing. **D,** Final venogram of the left common and external iliac vein after deployment of 14 × 60 S.M.A.R.T. Control nitinol self-expanding stent (Cordis Corp., Miami, FL).

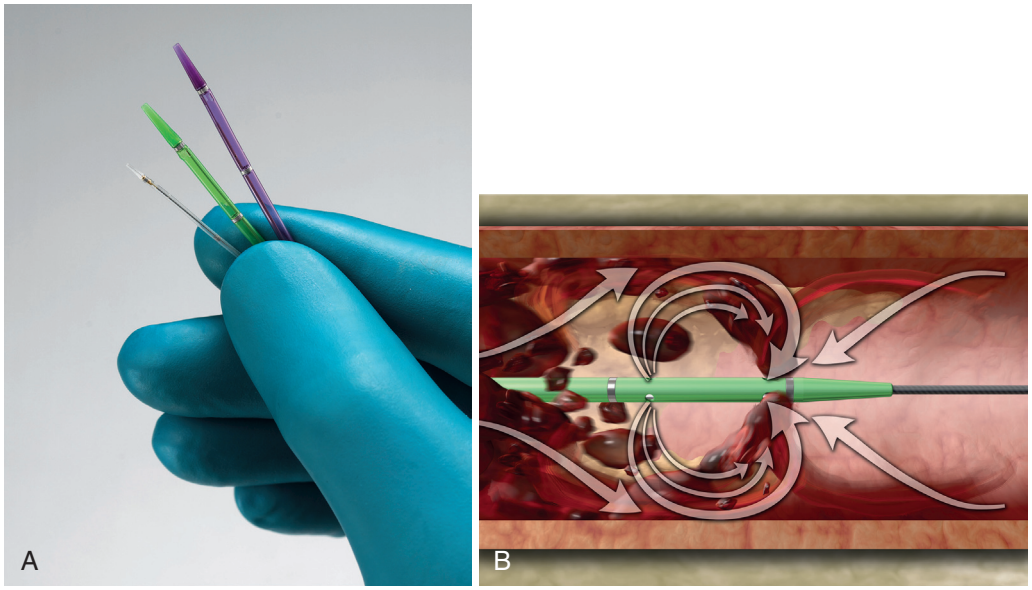

FIGURE 45-8 **A,** The AngioJet Thrombectomy System (Boston Scientific, Marlborough, MA) comes in multiple sizes and emits high-velocity saline jets that are directed backward from the tip of the device to outflow channels in a coaxial fashion. **B,** This generates a vacuum force that draws the thrombus into the catheter by the Venturi effect. (Image courtesy Boston Scientific. © 2014 Boston Scientific Corporation or its affiliates. All rights reserved.)

FIGURE 45-9 **A,** AngioJet Thrombectomy System (Boston Scientific, Marlborough, MA) with a simplified set-up process. **B,** It also has the ability to directly spray thrombolytics onto the clot using the Power Pulse spray feature. (Image courtesy Boston Scientific. © 2014 Boston Scientific Corporation or its affiliates. All rights reserved.)

balloons limit leakage of thrombolytic agent into the systemic circulation, potentially reducing the risk of bleeding complications, and reduce embolization of particulate matter to the pulmonary circulation. Figure 45-11 illustrates the use of the Trellis 8 system to treat a right brachial and axillary DVT.

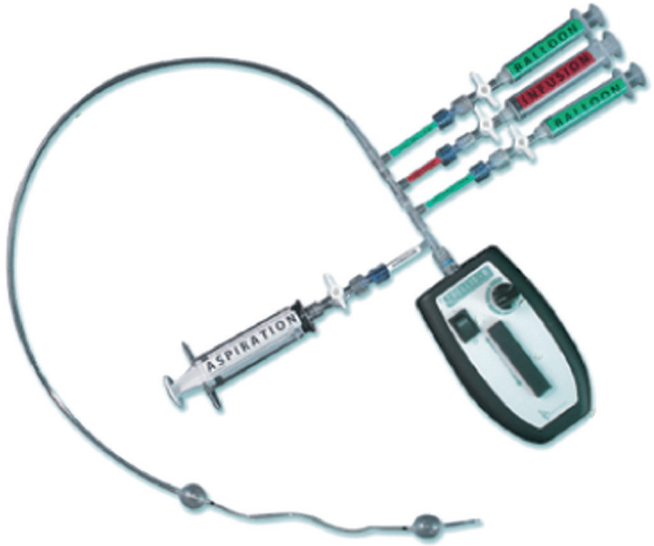

FIGURE 45-10 The Trellis 8 Peripheral Infusion System (Covidien, Dublin, Ireland) consists of proximal and distal occlusion balloons with balloon inflation syringes, a thrombolysis infusion port, the thrombus aspiration syringe, and a drive unit for mechanical dispersion of the thrombolytic agent.

Despite great advances in PMT technologies, complete on-the-table thrombus resolution rarely occurs, and adjunctive thrombolytic therapy is often required. Penetration of thrombolytics into the clot is often difficult with a passive infusion catheter. In an effort to improve thrombolytic penetration and enhance thrombus disruption, an ultrasound-based infusion system, the EkoSonic Endovascular System (EKOS Corporation, Bothell, WA) was developed. The EkoSonic catheter combines high-frequency, low-power ultrasound with simultaneous CDT to accelerate clot dissolution. The exposure of the clot to nonfragmenting ultrasound has no thrombolytic effect on it own. However, the combination of directed ultrasound and local thrombolytic infusion accelerates the thrombolytic process.[94] Mechanistically, it is thought that the ultrasound waves work by loosening the fibrin matrix, increasing clot permeability and ultimately driving the thrombolytic agent deep into the thrombus for better drug distribution. In addition, the ultrasound energy is atraumatic with regard to the venous valves, a property that is theoretically important in the prevention of PTS. The EkoSonic catheter system consists of a 5.2-Fr, multilumen drug delivery catheter with one central lumen and three separate infusion ports (Fig. 45-12). Each catheter has a matched ultrasound core wire that is placed in the central lumen and delivers the ultrasound energy evenly along the entire infusion pathway. After the catheter is positioned in the thrombus, an infusion of thrombolytic agent is started, along with saline to serve as a coolant. Ultrasound energy is then started and delivered simultaneously with the thrombolytic agent infusion. In a multicenter series of 53 patients, ultrasound-accelerated thrombolysis was shown to be a safe and efficacious treatment for DVT, with a high incidence of complete thrombolysis and a reduction in bleeding rates.[95] This device has recently gained FDA approval for the use in the pulmonary arteries for treatment of PE.[96]

These exciting combination strategies continue to be developed and investigated; with further follow-up and study these interventions will be better defined for use in the evolving treatment paradigms for DVT.

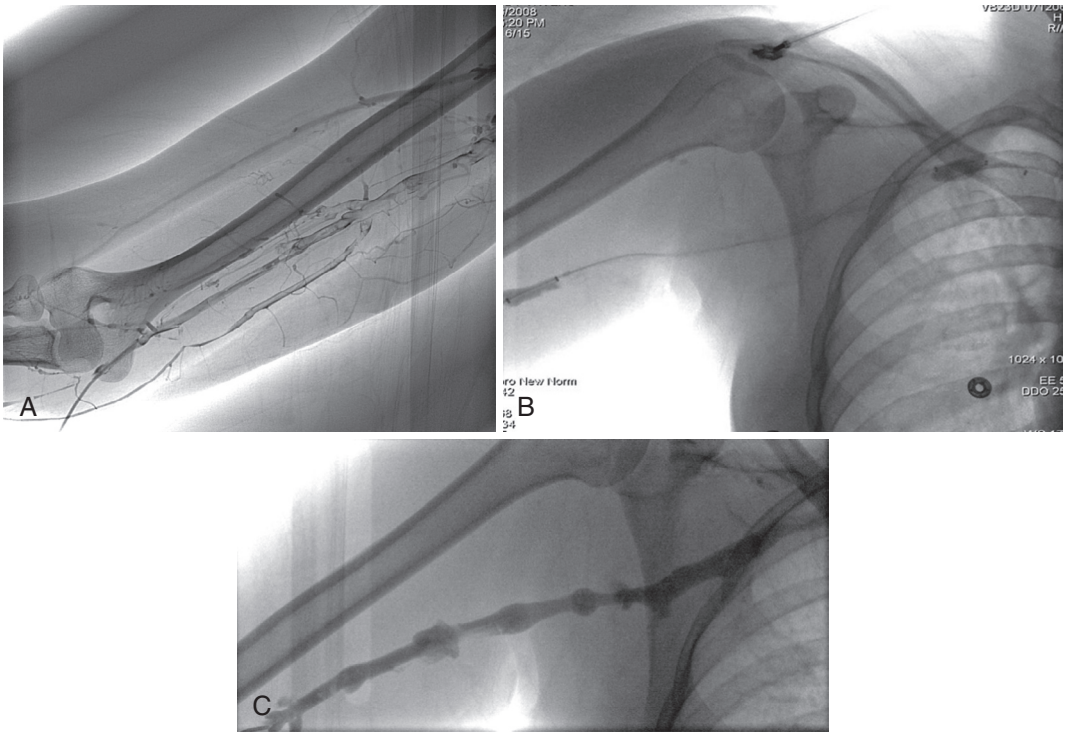

FIGURE 45-11 **A,** Acute right upper extremity deep venous thrombosis with classic intraluminal filling defects in right brachial and axillary veins. **B,** The Trellis 8 system is deployed in the right brachial and axillary vein using a 30-cm treatment zone. **C,** Completion venogram demonstrates complete resolution of thrombus in right brachial and axillary veins after pharmacomechanical thrombectomy using the Trellis 8 thrombolysis catheter (Covidien, Dublin, Ireland).

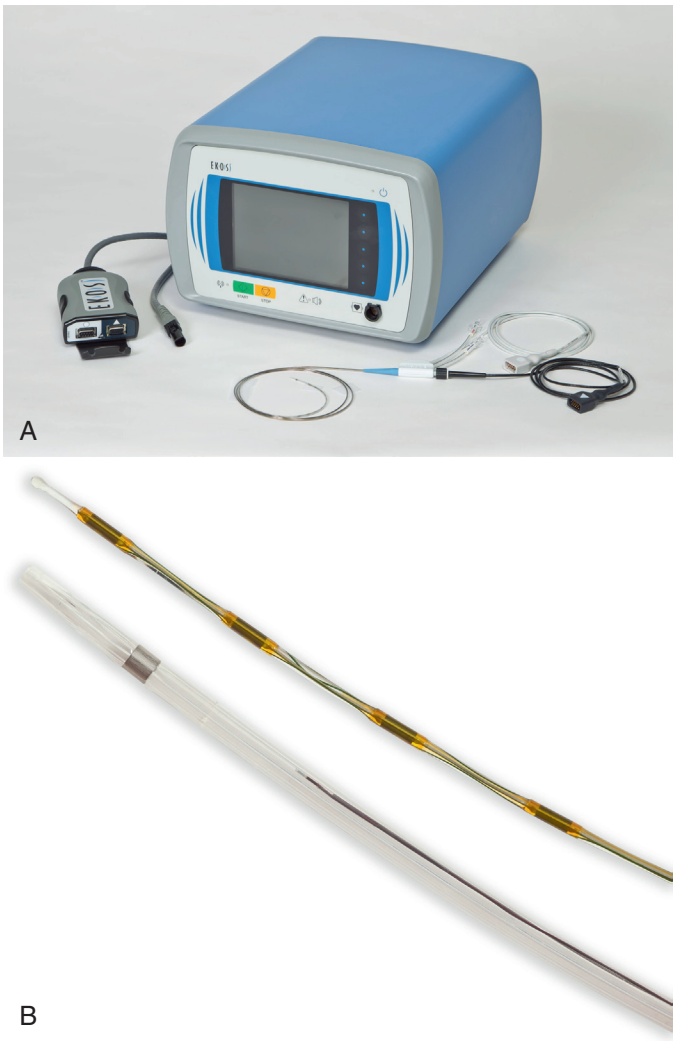

FIGURE 45-12 **A,** The EkoSonic Endovascular System (EKOS Corporation, Bothell, WA) has an ultrasound-generating console with simplified set-up. **B,** The catheter is placed directly into the thrombus, where microtransducers transmit high-frequency, low-power sound waves.

REFERENCES

1. Moffatt CJ, Franks PJ, Doherty DC, et al: Prevalence of leg ulceration in a London population. *QJM* 97:431–437, 2004.
2. McGuckin M, Waterman R, Brooks J, et al: Validation of venous leg ulcer guidelines in the United States and United Kingdom. *Am J Surg* 183:132–137, 2002.
3. Eklöf B, Rutherford RB, Bergan JJ, et al: Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg* 40(6):1248–1252, 2004.
4. Bergan JJ, Schmid-Schonbein GW, Smith PDC, et al: Chronic venous disease. *N Engl J Med* 355:488–498, 2006.
5. Wilkinson LS, Bunker C, Edwards JCW, et al: Leukocytes: their role in the etiopathogenesis of skin damage in venous disease. *J Vasc Surg* 17:669–675, 1993.
6. Herouy Y, May AE, Pornschtegel G, et al: Lipodermatosclerosis is characterized by elevated expression and activation of matrix metalloproteinases: implications for venous ulcer formation. *J Invest Dermatol* 111:822–827, 1998.
7. Norgauer J, Hildenbrand T, Idzko M, et al: Elevated expression of extracellular matrix metalloproteinase inducer (CD147) and membrane-type matrix metalloproteinases in venous leg ulcers. *Br J Dermatol* 147:1180–1186, 2002.
8. Mwaura B, Mahendran B, Hynes N, et al: The impact of differential expression of extracellular matrix metalloproteinase inducer, matrix metalloproteinase-2, tissue inhibitor of matrix metalloproteinase-2 and PDGF-AA on the chronicity of venous leg ulcers. *Eur J Vasc Endovasc Surg* 31:306–310, 2006.
9. Kee ST, Kinoshita L, Razavi MK, et al: Superior vena cava syndrome: treatment with catheter-directed thrombolysis and endovascular stent placement. *Radiology* 206:187–193, 1998.
10. Chamorro H, Rao G, Wholey MH: Superior vena cava syndrome: a complication of transvenous pacemaker implantation. *Radiology* 126:377–378, 1978.
11. Mocherla S, Wheat LJ: Treatment of histoplasmosis. *Semin Respir Infect* 16:141–148, 2001.
12. Rossi SE, McAdams HP, Rosado-de-Christenson ML, et al: Fibrosing mediastinitis. *Radiographics* 21(3):737–757, 2001.
13. Mahajan V, Strimlan V, Ordstrand HS, Loop FD: Benign superior vena cava syndrome. *Chest* 68:32–35, 1975.
14. Connell JV, Muhm JR: Radiographic manifestations of pulmonary histoplasmosis: a 10-year review. *Radiology* 121:281–285, 1976.
15. Qanadli SD, El Hajjam M, Bruckert F, et al: Helical CT phlebography of the superior vena cava: diagnosis and evaluation of venous obstruction. *AJR Am J Roentgenol* 172:1327–1333, 1999.
16. Hartnell GG, Hughes LA, Finn JP, Longmaid HE: Magnetic resonance angiography of the central chest veins: a new gold standard? *Chest* 107:1053–1057, 1995.
17. Rizvi AZ, Kalra M, Bjarnason H, et al: Benign superior vena cava syndrome: stenting is now the first line of treatment. *J Vasc Surg* 47:372–380, 2008.
18. Miller JH, McBride K, Little F, Price A: Malignant superior vena cava obstruction: stent placement via the subclavian route. *Cardiovasc Intervent Radiol* 23:155–158, 2000.
19. Petersen BD, Uchida BT: Long-term results of treatment of benign central venous obstructions unrelated to dialysis with expandable Z stents. *J Vasc Interv Radiol* 10:757–766, 1999.
20. Link J, Brossmann J, Müller-Hülsbeck S, Heller M: Venous stent application with a simultaneous cubitofemoral approach. *Rofo* 163:81–83, 1995.
21. Smayra T, Otal P, Chabbert V, et al: Long-term results of endovascular stent placement in the superior caval venous system. *Cardiovasc Intervent Radiol* 24:388–394, 2001.
22. Chatziioannou A, Alexopoulos T, Mourikis D, et al: Stent therapy for malignant superior vena cava syndrome: should be first line therapy or simple adjunct to radiotherapy. *Eur J Radiol* 47:247–250, 2003.
23. Courtheoux P, Alkofer B, Al Refaï M, et al: Stent placement in superior vena cava syndrome. *Ann Thorac Surg* 75:158–161, 2003.
24. Hennequin LM, Fade O, Fays JG, et al: Superior vena cava stent placement: results with the Wallstent endoprosthesis. *Radiology* 196:353–361, 1995.
25. O'Sullivan GJ, Mhuircheartaigh JN, Ferguson D, et al: Isolated pharmacomechanical thrombolysis plus primary stenting in a single procedure to treat acute thrombotic superior vena cava syndrome. *J Endovasc Ther* 17:115–123, 2010.
26. Gray BH, Olin JW, Graor RA, et al: Safety and efficacy of thrombolytic therapy for superior vena cava syndrome. *Chest* 99:54–59, 1991.
27. Perno J, Putnam SG, Cohen GS, Ball D: Endovascular treatment of superior vena cava syndrome without removing a central venous catheter. *J Vasc Interv Radiol* 10(7):917–918, 1999.
28. Kitamura J, Murakami Y, Shimada T, et al: Morphological observation by intravascular ultrasound in superior vena cava syndrome after pacemaker implantation. *Cathet Cardiovasc Diagn* 37:83–85, 1996.
29. Lanciego C, Chacon JL, Julian A, et al: Stenting as first option for endovascular treatment of malignant superior vena cava syndrome. *AJR Am J Roentgenol* 177:585–593, 2001.
30. Gwon DI, Ko G-Y, Kim JH, et al: Malignant superior vena cava syndrome: a comparative cohort study of treatment with covered stents versus uncovered stents. *Radiology* 266:979–987, 2013.
31. Da Ines D, Chabrot P, Motreff P, et al: Cardiac tamponade after malignant superior vena cava stenting: two case reports and brief review of the literature. *Acta Radiol* 51:256–259, 2010.

32. Smith SL, Manhire AR, Clark DM: Delayed spontaneous superior vena cava perforation associated with a SVC Wallstent. *Cardiovasc Intervent Radiol* 24:286–287, 2001.
33. Siani A, Marcucci G, Accrocca F, et al: Endovascular central venous stenosis treatment ended with superior vena cava perforation, pericardial tamponade, and exitus. *Ann Vasc Surg* 26(5): 733.e9–733.e12, 2012.
34. Sajid MS, Ahmed N, Desai M, et al: Upper limb deep vein thrombosis: a literature review to streamline the protocol for management. *Acta Haematol* 118:10–18, 2007.
35. Muñoz FJ, Mismetti P, Poggio R, et al: Clinical outcome of patients with upper-extremity deep vein thrombosis: results from the RIETE registry. *Chest* 133(1):143–148, 2008.
36. Prandoni P, Polistena P, Bernardi E, et al: Upper-extremity deep vein thrombosis: risk factors, diagnosis, and complications. *Arch Intern Med* 157:57–62, 1997.
37. Hingorani A, Ascher E, Lorenson E, et al: Upper extremity deep venous thrombosis and its impact on morbidity and mortality rates in a hospital-based population. Presented at the Ninth Annual Meeting of the American Venous Forum, San Antonio, TX, February 20-24, 1997. *J Vasc Surg* 26:853–860, 1997.
38. Becker DM, Philbrick JT, Walker FB: Axillary and subclavian venous thrombosis: prognosis and treatment. *Arch Intern Med* 151:1934–1943, 1991.
39. Knudson GJ, Wiedmeyer DA, Erickson SJ, et al: Color Doppler sonographic imaging in the assessment of upper-extremity deep venous thrombosis. *AJR Am J Roentgenol* 154:399–403, 1990.
40. Fraser JD, Anderson DR: Deep venous thrombosis: recent advances and optimal investigation with US. *Radiology* 211:9–24, 1999.
41. Fielding JR, Nagel JS, Pomeroy O: Upper extremity DVT: correlation of MR and nuclear medicine flow imaging. *Clin Imaging* 21:260–263, 1997.
42. Lindblad B, Tengborn L, Bergqvist D: Deep vein thrombosis of the axillary-subclavian veins: epidemiologic data, effects of different types of treatment and late sequelae. *Eur J Vasc Surg* 2:161–165, 1988.
43. Isma N, Svensson PJ, Gottsäter A, Lindblad B: Upper extremity deep venous thrombosis in the population-based Malmö thrombophilia study (MATS): epidemiology, risk factors, recurrence risk, and mortality. *Thromb Res* 125(6):e335–e338, 2010.
44. Zell L, Kindermann W, Marschall F, et al: Paget-Schroetter syndrome in sports activities: case study and literature review. *Angiology* 52:337–342, 2001.
45. Thompson RW, Schneider PA, Nelken NA, et al: Circumferential venolysis and paraclavicular thoracic outlet decompression for "effort thrombosis" of the subclavian vein. *J Vasc Surg* 16:723–732, 1992.
46. Parziale JR, Akelman E, Weiss AP, Green A: Thoracic outlet syndrome. *Am J Orthop* 29:353–360, 2000.
47. Urschel HC, Patel AN: Surgery remains the most effective treatment for Paget-Schroetter syndrome: 50 years' experience. *Ann Thorac Surg* 86(1):254–260, discussion 260, 2008.
48. Marinella MA, Kathula SK, Markert RJ: Spectrum of upper-extremity deep venous thrombosis in a community teaching hospital. *Heart Lung* 29(2):113–117, 2000.
49. Lokich JJ, Becker B: Subclavian vein thrombosis in patients treated with infusion chemotherapy for advanced malignancy. *Cancer* 52:1586–1589, 1983.
50. Monreal M, Raventos A, Lerma R, et al: Pulmonary embolism in patients with upper extremity DVT associated to venous central lines: a prospective study. *Thromb Haemost* 72:548–550, 1994.
51. Timsit JF, Farkas JC, Boyer JM, et al: Central vein catheter-related thrombosis in intensive care patients: incidence, risks factors, and relationship with catheter-related sepsis. *Chest* 114:207–213, 1998.
52. Girolami A, Prandoni P, Zanon E, et al: Venous thromboses of upper limbs are more frequently associated with occult cancer as compared with those of lower limbs. *Blood Coagul Fibrinolysis* 10:455–457, 1999.
53. Martinelli I, Cattaneo M, Panzeri D, et al: Risk factors for deep venous thrombosis of the upper extremities. *Ann Intern Med* 126:707–711, 1997.
54. Hammers LW, Cohn SM, Brown JM, et al: Doppler color flow imaging surveillance of deep vein thrombosis in high-risk trauma patients. *J Ultrasound Med* 15:19–24, 1996.
55. Héron E, Lozinguez O, Alhenc-Gelas M, et al: Hypercoagulable states in primary upper-extremity deep vein thrombosis. *Arch Intern Med* 160:382–386, 2000.
56. Lisse JR, Davis CP, Thurmond-Anderle M: Cocaine abuse and deep venous thrombosis. *Ann Intern Med* 110(7):571–572, 1989.
57. Leebeek FWG, Stadhouders NAM, Van Stein D, et al: Hypercoagulability states in upper-extremity deep venous thrombosis. *Am J Hematol* 67:15–19, 2001.
58. Ruggeri M, Castaman G, Tosetto A, Rodeghiero F: Low prevalence of thrombophilic coagulation defects in patients with deep vein thrombosis of the upper limbs. *Blood Coagul Fibrinolysis* 8:191–194, 1997.
59. Da Costa SS, do C, Scalabrini Neto A, et al: Incidence and risk factors of upper extremity deep vein lesions after permanent transvenous pacemaker implant: a 6-month follow-up prospective study. *Pacing Clin Electrophysiol* 25:1301–1306, 2002.
60. Van Rooden CJ, Molhoek SG, Rosendaal FR, et al: Incidence and risk factors of early venous thrombosis associated with permanent pacemaker leads. *J Cardiovasc Electrophysiol* 15(11):1258–1262, 2004.
61. Bulur S, Vural A, Yacici M, et al: Incidence and predictors of subclavian vein obstruction following biventricular device implantation. *J Interv Card Electrophysiol* 29:199–202, 2010.
62. Korkeila P, Nyman K, Ylitalo A, et al: Venous obstruction after pacemaker implantation. *Pacing Clin Electrophysiol* 30:199–206, 2007.
63. Baarslag H-J, van Beek EJR, Koopman MMW, Reekers JA: Prospective study of color duplex ultrasonography compared with contrast venography in patients suspected of having deep venous thrombosis of the upper extremities. *Ann Intern Med* 136:865–872, 2002.
64. Haire WD, Lynch TG, Lund GB, et al: Limitations of magnetic resonance imaging and ultrasound-directed (duplex) scanning in the diagnosis of subclavian vein thrombosis. *J Vasc Surg* 13:391–397, 1991.
65. Grobner T: Gadolinium: a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 21(4):1104–1108, 2006.
66. Marckmann P, Skov L, Rossen K, et al: Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol* 17(9):2359–2362, 2006.
67. Urschel HC, Razzuk MA: Paget-Schroetter syndrome: what is the best management? *Ann Thorac Surg* 69:1663–1669, 2000.
68. Yeh CH, Gross PL, Weitz JI: Evolving use of new oral anticoagulants for treatment of venous thromboembolism. *Blood* 124:1020–1028, 2014.
69. Strandness DE, Langlois Y, Cramer M, et al: Long-term sequelae of acute venous thrombosis. *JAMA* 250:1289–1292, 1983.
70. Vik A, Holme PA, Singh K, et al: Catheter-directed thrombolysis for treatment of deep venous thrombosis in the upper extremities. *Cardiovasc Intervent Radiol* 32:980–987, 2009.
71. Razavi MK, Wong H, Kee ST, et al: Initial clinical results of tenecteplase (TNK) in catheter-directed thrombolytic therapy. *J Endovasc Ther* 9(5):593–598, 2002.
72. Kasirajan K, Gray B, Ouriel K: Percutaneous AngioJet thrombectomy in the management of extensive deep venous thrombosis. *J Vasc Interv Radiol* 12:179–185, 2001.
73. Martinez Trabal JL, Comerota AJ, LaPorte FB, et al: The quantitative benefit of isolated, segmental, pharmacomechanical thrombolysis (ISPMT) for iliofemoral venous thrombosis. *J Vasc Surg* 48(6):1532–1537, 2008.
74. Agarwal AK, Patel BM, Haddad NJ: Central vein stenosis: a nephrologist's perspective. *Semin Dial* 20(1):53–62, 2007.
75. Lee JT, Karwowski JK, Harris EJ, et al: Long-term thrombotic recurrence after nonoperative management of Paget-Schroetter syndrome. *J Vasc Surg* 43:1236–1243, 2006.
76. Rozmus G, Daubert JP, Huang DT, et al: Venous thrombosis and stenosis after implantation of pacemakers and defibrillators. *J Interv Card Electrophysiol* 13(1):9–19, 2005.
77. Lee MC, Grassi CJ, Belkin M, et al: Early operative intervention after thrombolytic therapy for primary subclavian vein thrombosis: an effective treatment approach. *J Vasc Surg* 27:1101–1107, discussion 1107–1108, 1998.
78. Cushman M, Tsai AW, White RH, et al: Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. *Am J Med* 117(1):19–25, 2004.
79. Lensing AW, Prandoni P, Brandjes D, et al: Detection of deep-vein thrombosis by real-time B-mode ultrasonography. *N Engl J Med* 320(6):342–345, 1989.
80. Wells PS, Anderson DR, Rodger M, et al: Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med* 349(13):1227–1235, 2003.
81. Shields GP, Turnipseed S, Panacek EA, et al: Validation of the Canadian clinical probability model for acute venous thrombosis. *Acad Emerg Med* 9:561–566, 2002.
82. Kearon C, Akl EA, Comerota AJ, et al: Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141(2 Suppl): e419S–e494S, 2012.
83. Breddin HK, Hach-Wunderle V, Nakov R, Kakkar V: Effects of a low-molecular-weight heparin on thrombus regression and recurrent thromboembolism in patients with deep-vein thrombosis. *N Engl J Med* 344:626–631, 2001.
84. Nazir SA, Ganeshan A, Nazir S, Uberoi R: Endovascular treatment options in the management of lower limb deep venous thrombosis. *Cardiovasc Intervent Radiol* 32:861–876, 2009.
85. Shi HJ, Huang YH, Shen T, Xu Q: Percutaneous mechanical thrombectomy combined with catheter-directed thrombolysis in the treatment of symptomatic lower extremity deep venous thrombosis. *Eur J Radiol* 71:350–355, 2009.
86. Decousus H, Leizorovicz A, Parent F, et al: A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prévention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. *N Engl J Med* 338(7):409–415, 1998.
87. Semba CP, Dake MD: Iliofemoral deep venous thrombosis: aggressive therapy with catheter-directed thrombolysis. *Radiology* 191:487–494, 1994.
88. Vedantham S, Goldhaber SZ, Kahn SR, et al: Rationale and design of the ATTRACT study: a multicenter randomized trial to evaluate pharmacomechanical catheter-directed thrombolysis for the prevention of postthrombotic syndrome in patients with proximal deep vein thrombosis. *Am Heart J* 165(4):523–530.e3, 2013.
89. Raju S, Neglen P: High prevalence of nonthrombotic iliac vein lesions in chronic venous disease: a permissive role in pathogenicity. *J Vasc Surg* 44(1):136–143, discussion 144, 2006.
90. McLennan G, Trerotola SO, Davidson D, et al: The effects of a mechanical thrombolytic device on normal canine vein valves. *J Vasc Interv Radiol* 12(1):89–94, 2001.
91. Gasparis AP, Labropoulos N, Tassiopoulos AK, et al: Midterm follow-up after pharmacomechanical thrombolysis for lower extremity deep venous thrombosis. *Vasc Endovascular Surg* 43(1):61–68, 2009.
92. Rao AS, Konig G, Leers SA, et al: Pharmacomechanical thrombectomy for iliofemoral deep vein thrombosis: an alternative in patients with contraindications to thrombolysis. *J Vasc Surg* 50:1092–1098, 2009.
93. Hilleman DE, Razavi MK: Clinical and economic evaluation of the Trellis-8 Infusion Catheter for deep vein thrombosis. *J Vasc Interv Radiol* 19:377–383, 2008.
94. Braaten JV, Goss RA, Francis CW: Ultrasound reversibly disaggregates fibrin fibers. *Thromb Haemost* 78:1063–1068, 1997.
95. Parikh S, Motarjeme A, McNamara T, et al: Ultrasound-accelerated thrombolysis for the treatment of deep vein thrombosis: initial clinical experience. *J Vasc Interv Radiol* 19(4):521–528, 2008.
96. Kucher N, Boekstegers P, Müller OJ, et al: Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation* 129:479–486, 2014.

Carotid and Cerebrovascular Intervention

46

R. KEVIN ROGERS | IVAN P. CASSERLY

KEY POINTS

- Cerebrovascular intervention for the treatment of atherosclerotic disease has evolved considerably. The potential for serious neurologic complications during such procedures places a premium on careful studies documenting the overall clinical efficacy of intervention compared with medical therapy.
- Carotid bifurcation disease and intracranial atherosclerosis account for 15% to 20% of all ischemic strokes and represent an important target for stroke prevention.
- Contemporary carotid bifurcation intervention involves the use of self-expanding stents with embolic protection systems to reduce the risk of distal embolization. The technique has proved to be equivalent to carotid endarterectomy in high-risk patients. There remains debate on the interpretation of randomized trial data for carotid stenting and on Medicare reimbursement in normal-risk patients.
- Proximal vertebral artery disease may account for up to 10% of posterior circulation ischemic events. Intervention at this site is straightforward and safe but has not proved to be superior to medical therapy alone.
- Intracranial intervention, when practiced by skilled and experienced operators, is technically feasible and reasonably safe. Randomized studies documenting superiority over medical therapy are needed.
- Further refinements in technique, technology, and patient selection, together with dedicated randomized controlled trials, will allow cerebrovascular intervention to realize its true potential in patients with stroke.

Stroke is the leading cause of adult disability and the third leading cause of death in North America, Europe, South America, and Asia. Most strokes (80% to 85%) are ischemic in etiology. In the United States, atherosclerotic disease affecting the extracranial and intracranial arterial circulation accounts for approximately 20% of ischemic strokes (Fig. 46-1) and thus is an important target for stroke prevention.[1] Cerebrovascular intervention has evolved largely for the treatment of atherosclerotic disease with the goal of stroke prevention. Based on dramatic technological advances and increased operator expertise, these procedures can now be performed with a high rate of technical success. However, because of the potential for serious neurologic complications from endovascular intervention in the cerebrovascular circulation, clear documentation of the safety of these procedures and their overall clinical efficacy is of paramount importance. These considerations have raised the bar for cerebrovascular intervention compared with other peripheral vascular procedures.

In the field of cerebrovascular intervention, carotid bifurcation intervention is unique in that the natural history of carotid artery bifurcation disease has been well defined and large randomized trials have previously documented the clinical effectiveness of surgical revascularization for this disease. There is already a large evidence base supporting carotid intervention in specific patient subgroups, and several randomized trials are ongoing in the remaining patient populations. With more than 140,000 carotid endarterectomy (CEA) procedures performed each year in the United States, and more than 280,000 worldwide, the potential impact of percutaneous revascularization has captured the interest of endovascular specialists who are keen to offer an alternative to surgery.

In contrast, endovascular intervention in the cerebrovascular circulation outside of the carotid bifurcation has been hampered by two important considerations: the natural history of non–carotid bifurcation cerebrovascular disease is less well defined, and there is a notable absence of randomized data documenting the benefit of revascularization compared with medical therapy alone. Despite these obstacles, however, dramatic advances in the technical aspects of these interventions have been made, and there is an increased recognition of the need for well-designed clinical studies that address these deficiencies. What is often underappreciated is that non–carotid bifurcation cerebrovascular disease is responsible for at least the same number of ischemic strokes as carotid bifurcation disease and represents an equally important target for stroke prevention.

This chapter summarizes the current status of carotid bifurcation intervention and the most frequently performed non–carotid bifurcation cerebrovascular interventions, notably proximal vertebral artery (VA) and intracranial intervention.

CAROTID BIFURCATION INTERVENTION

Carotid Bifurcation Atherosclerosis and Stroke

The carotid bifurcation has a remarkable predilection for the development of atherosclerosis, which is typically located at the origin of the internal carotid artery (ICA) (Fig. 46-2). This plaque is similar to that found at other sites throughout the arterial system in that it contains a dense cap of connective tissue with embedded smooth muscle cells and an underlying core of lipid and necrotic debris.[2] Histologic studies of plaque from the carotid bifurcation of symptomatic and asymptomatic individuals have revealed features associated with the development of symptoms that are similar to those associated with plaque vulnerability in the coronary circulation: reduced amounts of collagen, increased inflammation, thinning of the fibrous cap, and increased cholesterol in the necrotic core.[2,3] Based on our current understanding, these processes result in plaque fissuring or rupture at the carotid bifurcation, causing either occlusive or nonocclusive thrombus formation. The dominant mechanism of stroke is believed to result from distal thromboembolism to the anterior cerebral circulation. However, a number of considerations, such as the size and composition of the embolus, the presence of contralateral disease, the anatomy of the circle of Willis, and the activity of fibrinolytic pathways, may attenuate or accentuate the clinical consequence of the pathologic event. Consequently, the same pathologic event may result in a reversible neurologic deficit (i.e., transient ischemic attack [TIA]), an irreversible neurologic deficit (i.e., stroke), or no symptoms at all.

Natural History of Carotid Artery Bifurcation Disease

In clinical practice, two dominant factors are used to determine the risk of ischemic complications from a lesion of the carotid artery bifurcation: the symptomatic status of the lesion and the severity of stenosis. Although many of these data are derived from the medical arms of the large randomized CEA trials performed between the late 1980s and early 2000s, these considerations continue to be used as the major

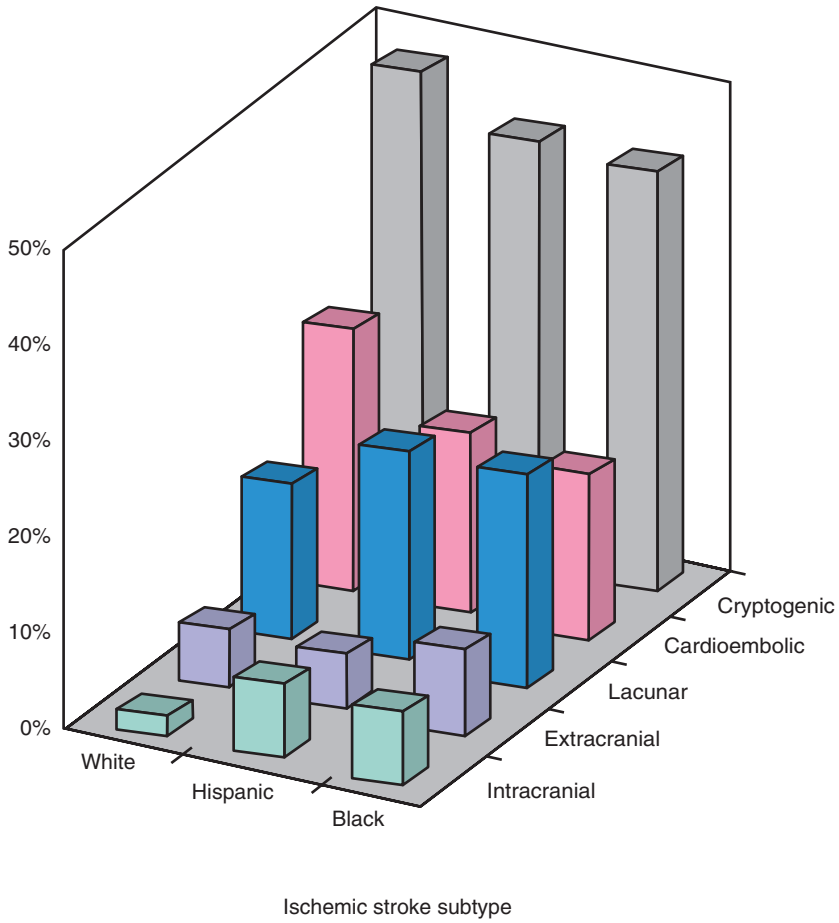

FIGURE 46-1 Proportion of ischemic stroke subtypes according to race in the Northern Manhattan Study. (Adapted from White H, Boden-Albala B, Wang C, et al: Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study, *Circulation* 111[10]:1327-1331, 2005.)

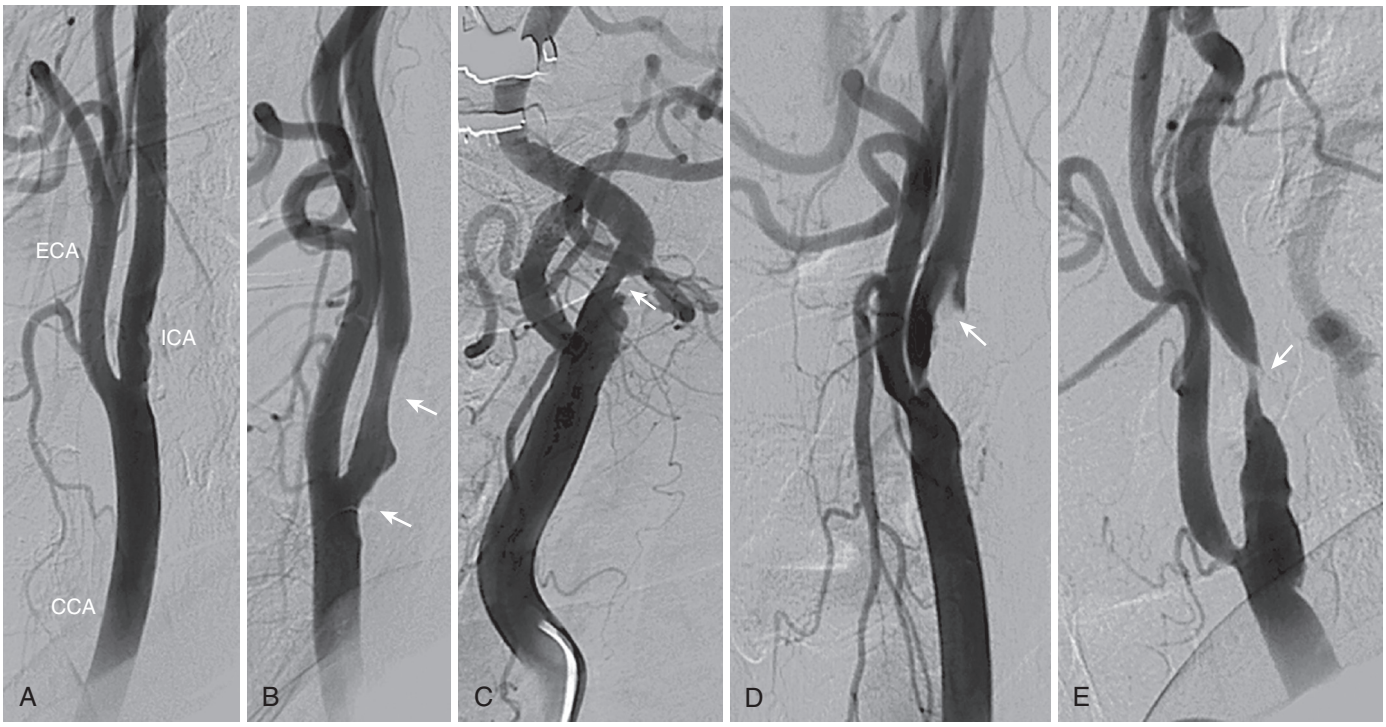

FIGURE 46-2 Angiographic images from the carotid bifurcation show the spectrum of atherosclerotic disease at this site. **A,** Minimal disease at the origin of the internal carotid artery (ICA). **B,** Mild stenosis extending from the distal common carotid artery (CCA) into the proximal ICA. **C,** Moderate eccentric stenosis in the proximal portion of the ICA. **D,** A thrombotic lesion in the proximal portion of the ICA in a patient with recent stroke. **E,** High-grade stenosis in the proximal portion of the ICA. Notice that atherosclerotic plaque tends to accumulate in the posterior aspect of the ICA. *Arrows* indicate location of plaque. *ECA,* External carotid artery.

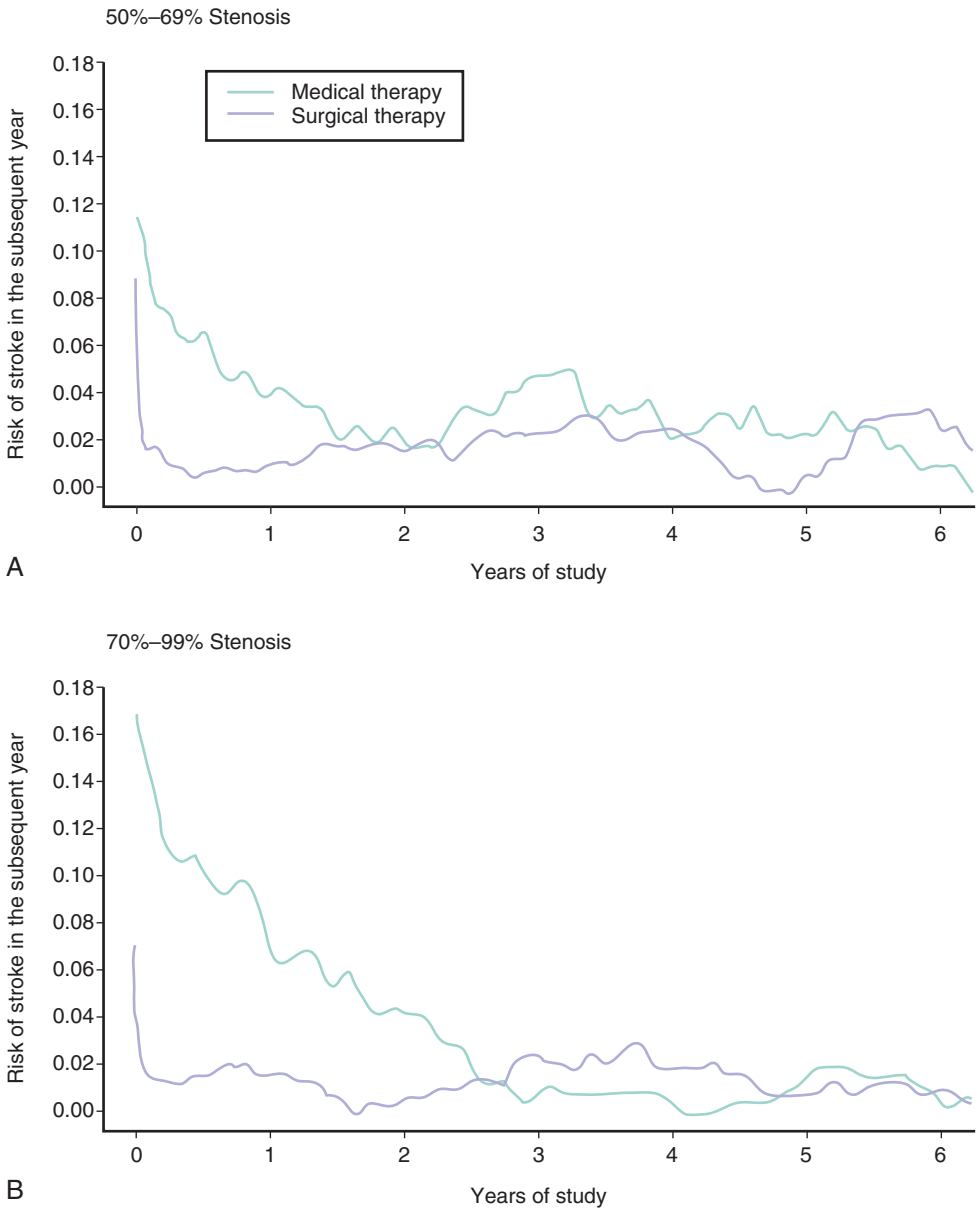

FIGURE 46-3 Change in risk of ipsilateral stroke over time in medically treated *(green line)* and surgically treated *(purple line)* patients with symptomatic stenosis of 50% to 69% (**A**) or 70% to 79% (**B**) in the NASCET trial (North American Symptomatic Carotid Endarterectomy Trial). (Adapted from Barnett HJ, Taylor DW, Eliasziw M, et al: Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 339[20]:1415-1425, 1998.)

criteria for choosing patients for endovascular procedures and for enrolling subjects in carotid endovascular trials.

Symptomatic lesions of the carotid bifurcation are associated with a high risk of recurrent ischemic stroke. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the risk of any ipsilateral stroke at 2-year follow-up in medically treated patients with symptomatic stenoses of 70% to 99% was 26%.[4] Among patients with symptomatic stenoses of 50% to 69%, the 5-year risk of any ipsilateral stroke was 22.2%.[5] There is a close temporal relationship between these recurrent strokes and the index event, with a steep exponential decline in risk within the first months, followed by a more gradual decline and ultimate normalization of risk at 2 to 3 years (Fig. 46-3).

By contrast, asymptomatic lesions of the carotid bifurcation are associated with a much lower risk of ischemic stroke. Over a 5-year period after an asymptomatic carotid stenosis was diagnosed (more than 60% by ultrasound), the risk of any stroke among medically treated patients in the Asymptomatic Carotid Surgery Trial (ACST) was 11%.[6] Not surprisingly, the risk of stroke was constant over the duration of the study. The implication from these findings is that carotid revascularization should be performed as expediently as possible after a neurologic event caused by a culprit symptomatic stenosis, whereas intervention for an asymptomatic lesion may be approached in a more elective fashion.[7]

Among symptomatic patients, a close relationship between the severity of stenosis as assessed by careful angiographic methods and subsequent risk of ipsilateral stroke has been demonstrated.[8] The relationship is nonlinear, with a steep increase in risk associated with the tightest degree of stenosis (Fig. 46-4). However, for symptomatic patients with "near-occlusion" of the ICA—defined as a stenosis causing obstruction to flow sufficient to result in a decrease in the ICA diameter beyond the lesion (Fig. 46-5)—there are data to suggest that the risk of recurrent stroke is reduced compared with patients with severe stenosis without features of near-occlusion.[9] One potential explanation for this finding is the reduced likelihood of distal cerebral

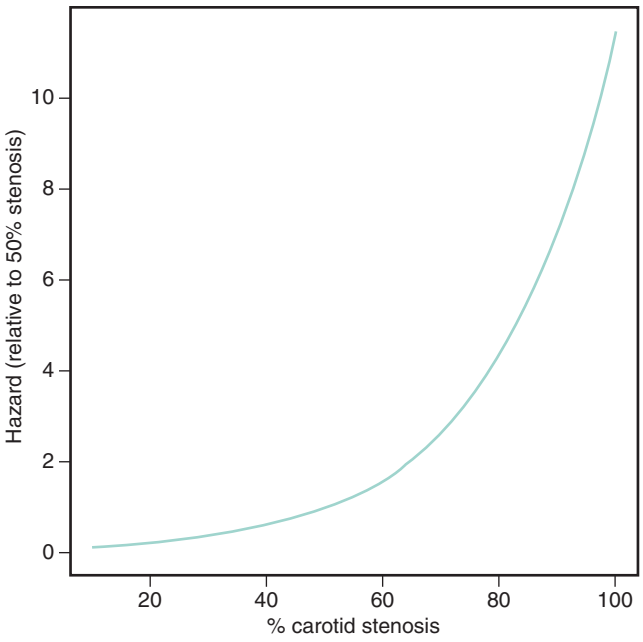

FIGURE 46-4 Hazard of ipsilateral ischemic stroke within 3 years after index transient ischemic attack or stroke as a function of the percent of carotid stenosis, determined with the use of biplane angiographic views. (Adapted from Cuffe RL, Rothwell PM: Effect of nonoptimal imaging on the relationship between the measured degree of symptomatic carotid stenosis and risk of ischemic stroke. *Stroke* 37:1785-1791, 2006.)

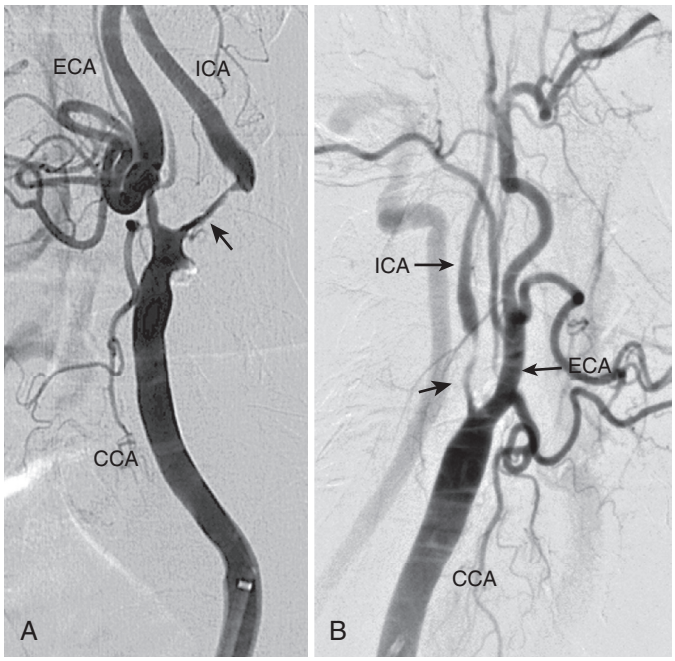

FIGURE 46-5 Angiographic appearance of "near-occlusion" of the internal carotid artery (ICA). **A,** Reduction in diameter of the ICA compared with the external carotid artery (ECA) reflects a mild form of near-occlusion of ICA *(arrow)*. **B,** Major collapse of the ICA beyond critical stenosis *(arrow)* reflects a severe form of near-occlusion of the ICA and is often referred to as a string sign. *CCA,* Common carotid artery.

embolization caused by diminished flow distal to a critical stenosis. Among asymptomatic patients, the association between stenosis severity and risk of subsequent stroke has been inconsistent.[6,10] This finding likely underscores the heterogeneous nature of carotid plaque histology in asymptomatic patients and suggests that assessments of plaque vulnerability may be a more potent predictor of recurrent events than severity of stenosis in this patient group.

Today there are more sophisticated models to predict the risk of stroke in patients with carotid disease, particularly for symptomatic patients.[11,12] In addition to stenosis severity, these models incorporate variables such as age, sex, nature of the presenting symptomatic event, time since the index event, plaque surface morphology, and transcranial Doppler findings to provide a more individualized estimate of risk. However, these models have yet to be incorporated into patient selection criteria in randomized trials to more fully establish their clinical relevance.

Benefit of Carotid Revascularization

The benefit of carotid revascularization in patients with carotid artery disease has been documented in several randomized controlled trials (RCTs) comparing medical therapy with surgical revascularization (i.e., CEA). These data are extremely important in any discussion of endovascular therapy for carotid bifurcation disease because they form the cornerstone justifying revascularization in certain subsets of patients. In a pooled analysis of data from the three major RCTs in symptomatic patients, CEA compared with medical therapy reduced the end point of stroke or operative death at 5 years in patients with carotid stenoses of 50% or greater, as assessed by carotid angiography using the NASCET criteria (Fig. 46-6).[13] This benefit was more pronounced in patients with stenoses of 70% to 99% (absolute risk reduction [ARR], 15.3%; 95% confidence interval [CI], 9.8% to 20.7%) than in those with stenoses of 50% to 69% (ARR, 7.8%; 95% CI, 3.1% to 12.5%). In addition, the crossover of the event-free curves occurred very early in the patient cohort with 70% to 99% stenoses (1 to 2 months) compared with the patient cohort with 50% to 69% stenosis (1 year). The incidence of perioperative stroke and/or death in these studies was uniformly less than 6%; the benefits derived from CEA are predicated on the maintenance of similar procedural outcomes. No significant benefit was observed in patients with near-occlusion of the carotid artery (ARR, 0.1%; 95% CI, −10.3 to 10.2), likely related to the lower risk of recurrent stroke with medical therapy in this group. These studies were performed in the late 1980s and early to mid-1990s; therefore the only stipulated medical therapy in the nonsurgical arm was aspirin. Contemporary medical therapy would likely attenuate the observed benefit associated with CEA. However, given the magnitude of the observed benefit associated with CEA in symptomatic patients, investigators have been reluctant to repeat randomized studies using contemporary medical therapy alone as a treatment arm.

Compared with medical therapy, CEA has also been shown to significantly reduce the incidence of stroke or operative death at 5-year follow-up in asymptomatic patients with carotid stenoses of 60% or greater, as assessed by carotid ultrasound (11.8% versus 6.4%; ARR; 5.4%; 95% CI, 3% to 7.8%).[6] It is important to emphasize that in this asymptomatic population, the early hazard associated with revascularization persists up to 2 years from the time of CEA. If the life expectancy of the patient is less than 5 years, then significant benefit should not be anticipated. In addition, participation in these trials involving patients with asymptomatic carotid stenoses required documentation of a perioperative stroke and death rate of less than 3% at the investigation site, and the generalization of these findings is predicated on reproducing similar procedural outcomes.

Percutaneous Carotid Revascularization

Initial animal experimentation with percutaneous carotid revascularization began in the late 1970s and was followed by the first clinical reports of carotid angioplasty in the early 1980s. The first rigorous

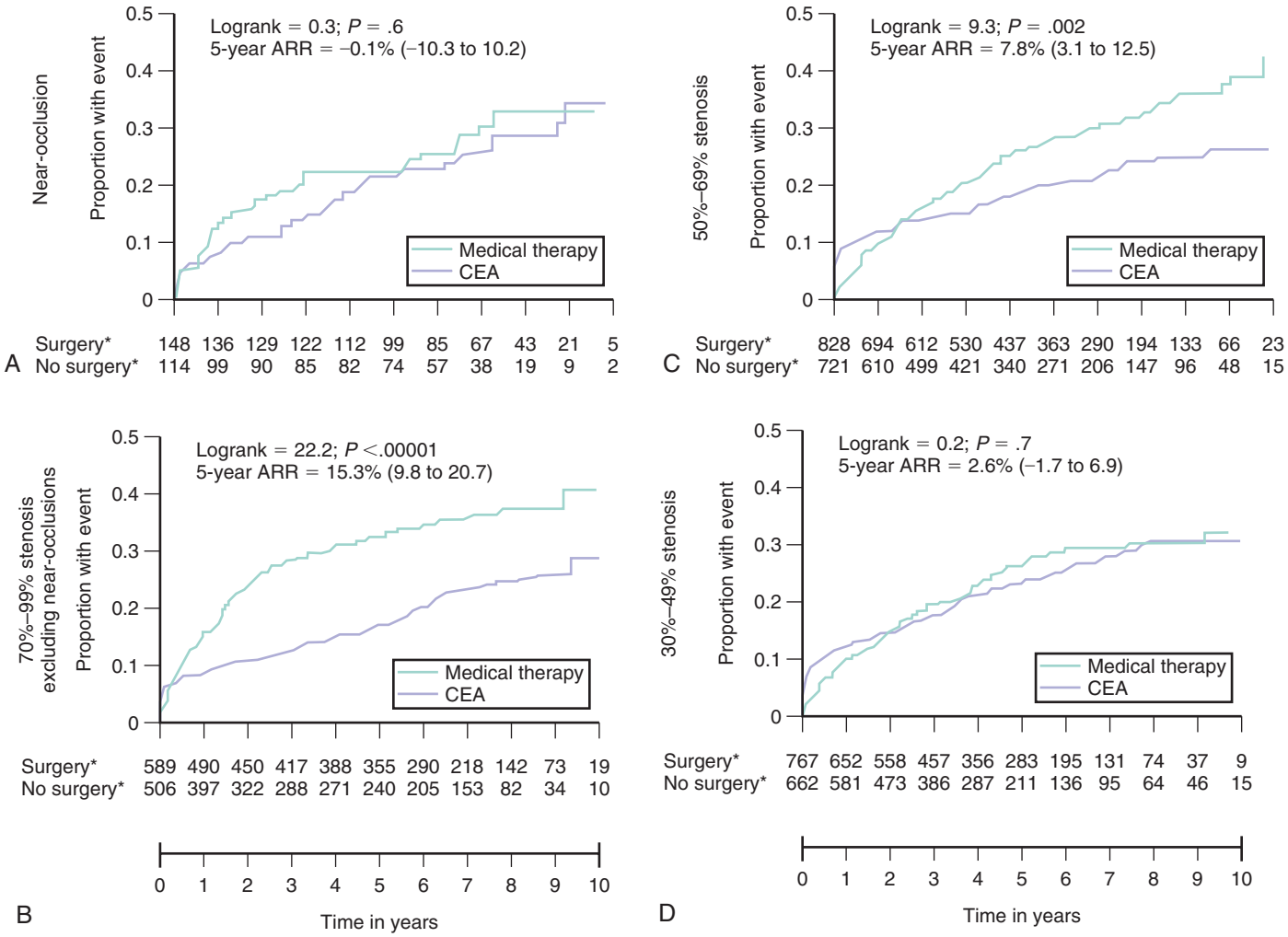

FIGURE 46-6 Risk of any stroke or operative death in medically treated *(green line)* and surgically treated *(purple line)* symptomatic patients with varying degrees of carotid artery stenosis. **A,** Near-occlusion. **B,** 70% to 99%. **C,** 50% to 69%. **D,** 30% to 49%. (Adapted from Rothwell PM, Eliasziw M, Gutnikov SA, et al: Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 361:107-116, 2003.)[13]

clinical testing of percutaneous carotid revascularization began in the mid-1990s. Although these studies demonstrated feasibility, two subsequent pivotal developments allowed percutaneous carotid revascularization to emerge as a viable alternative to CEA in the treatment of carotid disease: the ability to provide protection from distal embolization at the time of intervention, using a variety of embolic protection devices (EPDs), and the use of self-expanding stents. Carotid artery stenting (CAS) using self-expanding stents in combination with embolic protection represents the contemporary approach to carotid revascularization.

Carotid Artery Stenting: The Procedure

Preprocedural Assessment

Before any CAS procedure is undertaken, clinical assessment of the patient and anatomic assessment of the aortic arch and carotid/cerebral vasculature are essential.[14] Advanced age (>80 years) has been associated with significantly worse outcomes with CAS and should be carefully considered for the appropriateness of intervention.[15,16] Decreased cerebral reserve, manifested by the presence of dementia or cognitive impairment, and a history of prior strokes or lacunar infarcts increases the likelihood that distal embolization will be clinically manifested and is a relative contraindication for the procedure.[17] Anatomic assessments usually can be made based on noninvasive studies, notably computed tomography (CT) angiography and magnetic resonance (MR) angiography. CT angiography offers higher spatial resolution and superior visualization of the aortic arch compared with MR angiography, and it allows an assessment of the degree of calcification of the aortic arch and carotid bifurcation lesion that is not possible with MR angiography. Table 46-1 lists the anatomic features that should be reviewed and highlights the importance of each. Overall, these anatomic features allow the operator to more accurately determine the procedural risk and facilitate the planning of appropriate technique for procedural success.

Baseline Angiography

In most circumstances, CAS procedures are performed with the use of femoral artery access. Although the extent of baseline angiography varies depending on the preprocedural noninvasive assessment, high-quality angiography of the carotid bifurcation, the ipsilateral ICA, and intracranial anterior circulation is essential. We administer a heparin bolus of 25 mg/kg before any diagnostic cerebrovascular procedure in an effort to minimize the risk of thrombotic complications. A variety of catheter types are used to perform angiography, depending on the personal preference of the operator and the anatomy of the aortic arch and great vessels. For patients with uncomplicated anatomy (i.e., type

TABLE 46-1 Anatomic Assessments Recommended Before Carotid Artery Stenting and Their Impacts on Interventional Planning

Angiographic Assessment	Impact on Interventional Procedure
Arch Anatomy	
Type I, II, or III arch Anomalies of origin of great vessels Tortuosity of proximal portion of great vessels	Predict difficulty of percutaneous approach and influence strategy for delivery of guide or sheath to CCA
Lesion Characteristics	
Precise location of lesion, with definition of proximal and distal extent of lesion Lesion length Complex lesion ulceration Severity of stenosis Severity of lesion calcification Diameter of vessel(s) proximal and distal to lesion	Influence planned location for stent placement and stent length Influence strategy for delivery of guide or sheath to distal CCA Influence choice of stent length Predict difficulty of crossing lesion with filter device or wire Predict need for predilation of lesion before filter delivery Influence choice of stent diameter
ICA Distal to Lesion	
Assess cervical portion of ICA for presence of disease and tortuosity Diameter of cervical ICA	Influence choice of landing zone for filter or proximal occlusion EPD Increased tortuosity favors use of guide to provide support for delivery of filter Influence choice of diameter of filter-type or proximal occlusion EPD
Patency of External Carotid Artery	Influences strategy for delivery of guide or sheath to distal CCA

CCA, Common carotid artery; *EPD,* embolic protection device; *ICA,* internal carotid artery.

I aortic arch, no tortuosity of the great vessels), a Bernstein catheter functions well. For more complicated anatomies (e.g., type II or III arch, tortuosity of the great vessels, bovine origin of the left common carotid artery [CCA]), a Vitek or Simmons catheter is usually required.

Interventional Technique

The technique for CAS placement follows a number of well-defined steps. Before CAS placement, all patients should receive aspirin. In addition, it is our practice to administer clopidogrel for at least 3 days before the procedure. During the procedure, anticoagulation using unfractionated heparin to achieve an activated clotting time (ACT) of 275 to 300 seconds is standard.[18] For patients with a contraindication to heparin, a direct thrombin inhibitor such as bivalirudin has been shown to be safe.[19] In a cohort of 3555 patients from the Carotid Artery Revascularization and Endarterectomy (CARE) registry, bivalirudin was associated with less need for transfusion (0.9% versus 1.5%; $P = .01$) and no difference in myocardial infarction (MI), stroke, and death at 30 days, compared with unfractionated heparin in a propensity score analysis.[20] Most operators perform the procedure without the administration of sedatives, which enhances the ability to screen for any neurologic change during the procedure.

Delivery of Sheath or Guide to the Common Carotid Artery

In order to deliver the range of contemporary equipment required for CAS, a 6-Fr sheath or 8-Fr guide must be placed in the distal CCA. In patients with difficult aortic arch anatomy, bovine origin of the left CCA, occlusion of the external carotid artery (ECA), distal CCA lesions, or significant tortuosity of the great vessels, this can be one of the most technically challenging parts of the procedure. This portion of the procedure is "unprotected" in that there is no distal EPD to protect against distal embolization, so the safety of this step is heavily operator dependent.

TABLE 46-2 Filter-Type Embolic Protection Devices Used During Carotid Intervention

Filter	Manufacturer	Diameter (mm)	Pore Size (μm)
Interceptor	Medtronic	4.5, 5.5, 6.5	100
FilterWire EZ	Boston Scientific	3.5-5.5	80
Angioguard XP Angioguard RX	Cordis	4, 5, 6, 7, 8	100
EmboShield NAV[6]	Abbott Laboratories	2.5-4.8, 4-7	140
Spider	ev3	3, 4, 5, 6, 7	50-200
Accunet OTW Accunet RX	Abbott Laboratories	4.5, 5.5, 6.5, 7.5	120
FiberNet	Medtronic	3.5-5, 5-6, 6-7	40

OTW, Over the wire; *RX,* monorail.

The standard procedure for delivery of a 6-Fr sheath in the CCA is as follows. The CCA of interest is engaged with a diagnostic catheter. A stiff-angled glidewire is advanced into the ECA, and the diagnostic catheter is advanced over it. The glidewire is exchanged for a superstiff Amplatz or SupraCore wire, and then the diagnostic catheter is removed. The 6-Fr sheath and its dilator are delivered over the stiff wire to the distal CCA, after which the dilator is removed.

Although this standard approach is sufficient for approximately 70% of cases, a number of variations to the technique may be necessary, depending on the specific anatomic features of the individual patient. Much of the learning curve in CAS involves achieving experience with these variations and learning how to predict which variation is appropriate for an individual patient's anatomy. One of the pivotal dogmas in CAS is that guidewires and catheters should never be placed across the carotid lesion in order to deliver the sheath or guide to the CCA. It is preferable to refer the patient for CEA than to persist in risky attempts to deliver the guide or sheath.

Delivery of Embolic Protection Device

The use of EPDs is now considered the standard of care during CAS. Compelling observational data support this recommendation. Several studies have demonstrated that distal embolization is ubiquitous during CAS,[21,22] and observational series have shown a significant association between decreased periprocedural rates of stroke and death and the use of EPDs.[16,23] Over the last decade, three different device systems that provide protection from distal embolization at the time of carotid intervention have been developed.[24,25] In clinical practice, the most popular and most user friendly of these systems is the filter-type EPD (Table 46-2). These systems allow continued antegrade flow during carotid intervention—an important consideration for patients with compromised collateral flow to the ipsilateral carotid territory (e.g., patients with contralateral carotid artery disease or occlusion).

Because filter-type EPDs have been used in most contemporary CAS registries and RCTs, more data exist to support their use in carotid intervention compared with other EPDs. Based on the submission of these data to the U.S. Food and Drug Administration (FDA), multiple filter-type EPDs have received FDA approval, including Accunet, EmboShield, Spider, Angioguard, FilterWire, and FiberNet devices (Fig. 46-7; see Table 46-2). Although there is some variation in the individual design of these devices, they typically contain a polyurethane membrane with pores of fixed size (ranging from 80 to 140 μm in different devices), supported by a nitinol frame. The Spider and Interceptor EPDs are unique in that the filter pores are formed by a nitinol mesh. Each filter is integrated with a 0.014-inch guidewire with a 3- to 4-cm shapeable floppy tip. With the exception of the EmboShield and Spider devices, the filter is fixed to the wire.

The technique for delivery of a filter-type EPD varies according to the design of the system. In systems such as the Accunet, FilterWire

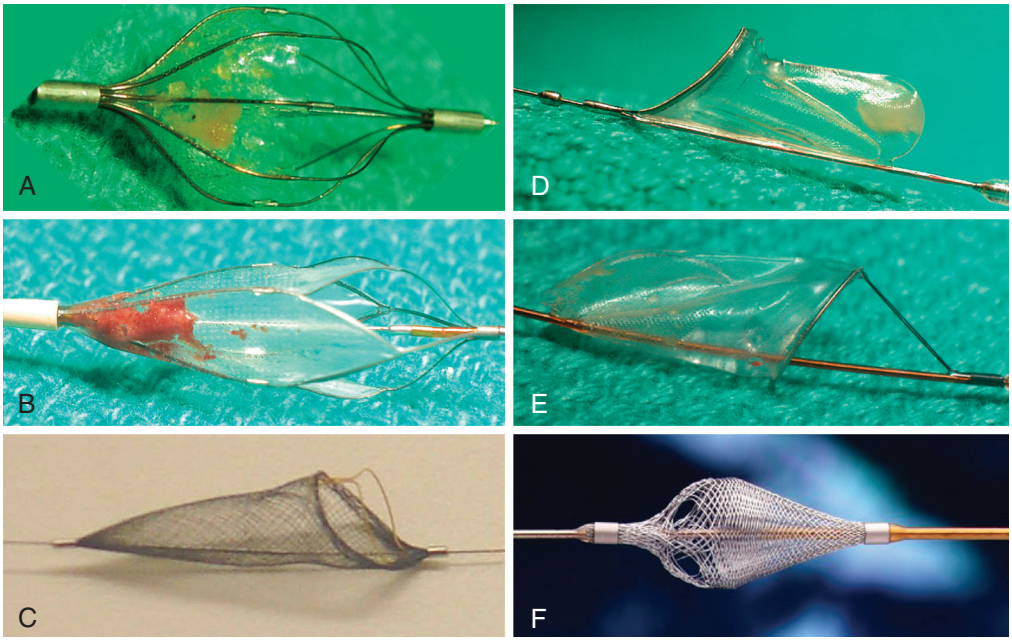

FIGURE 46-7 Examples of filter-type embolic protection devices used during carotid intervention. **A,** Angioguard XP (Cordis, Warren, NJ). **B,** Accunet (Abbott Vascular, Abbott Park, IL). **C,** Spider (ev3, Plymouth, MN). **D,** FilterWire EX (Boston Scientific, Natick, MA). **E,** FilterWire EZ (Boston Scientific). **F,** Interceptor (Medtronic, Minneapolis, MN). (From Casserly IP, Sachar R, Yadav JS: *Manual of peripheral vascular intervention,* Philadelphia, 2005, Lippincott Williams & Wilkins.)

EZ, or Angioguard, the filter is delivered in a collapsed form across the carotid lesion on the attached guidewire. With the EmboShield system, a unique 0.014-inch wire (BareWire) is used to cross the lesion first; the filter is then delivered in a collapsed form over this wire and deployed over the distal portion of the wire. The Spider system allows the lesion to be crossed using any 0.014-inch wire followed by a 2.9-Fr delivery catheter. It allows delivery of the Spider filter, which is integrated with a dedicated 0.014-inch wire that allows a small range of independent motion of the wire and filter. Predilation of the carotid lesion before delivery of the filter-type EPD is required in fewer than 1% to 2% of cases. If it is required, a small-caliber coronary balloon (i.e., 2.0 mm diameter) that minimizes the risk of distal embolization should be used. Regardless of the filter-type EPD that is used, the filter should ideally be deployed in a straight and nondiseased portion of the cervical ICA, which is typically in the distal cervical portion of the vessel. The presence of tortuosity or disease in the cervical portion of the ICA may necessitate an alternative placement, but there must be at least 3 to 4 cm of distance between the proximal margin of the filter and the distal margin of the ICA lesion to allow subsequent delivery of interventional equipment.

Distal occlusion balloon EPDs were the first type of EPD used during a carotid intervention (circa 1998). The only remaining example of this type of system is the Percusurge GuardWire device (Medtronic Vascular, Minneapolis, MN), which consists of an 0.014-inch angioplasty wire with a hollow nitinol hypotube and a distal compliant balloon that is inflated and deflated through the hypotube. The GuardWire is advanced across the carotid lesion with the balloon deflated. Complete interruption of antegrade flow is then achieved by inflating the balloon. After treatment of the carotid lesion, a monorail Export catheter is used to aspirate the column of blood proximal to the balloon, thus removing any debris that may have embolized from the treatment site. The balloon is then deflated and the GuardWire removed. There are no randomized comparisons of carotid intervention using filter-type or distal occlusion EPDs. A retrospective comparison of outcomes from a large CAS registry showed no significant difference in in-hospital death or stroke between these systems (2.3% for distal occlusion EPDs versus 1.8% for filter-type EPDs; $P = .96$).[26]

The most recent group of EPDs developed for carotid intervention are the proximal occlusion devices (e.g., the Parodi Anti-embolism System from Gore Medical, Flagstaff, AZ, and the MO.MA System from Medtronic). These systems attempt to protect the brain from distal embolization by eliminating antegrade flow in the ICA during the procedure, essentially generating an endovascular clamp.[27] Compliant balloons are inflated in the distal CCA and ECA, interrupting antegrade carotid flow and theoretically eliminating the risk of distal embolization from debris liberated during angioplasty and stenting. The success of such systems is predicated on adequate collateral circulation from the circle of Willis to maintain cerebral perfusion. With the Parodi device (not currently available in the United States), retrograde flow is generated in the ICA by connecting the lumen of the catheter, whose tip is in the CCA and distal to the occlusive balloon, to a catheter in the femoral vein. Blood flows down its pressure gradient from the CCA, through the blood return system, and to the femoral vein. In contrast, the MO.MA device simply creates a static column of blood in the ICA without continuous flow reversal, and removal of this unfiltered column of blood is achieved by aspiration with a syringe. Proximal EPDs appear to be particularly useful for cases in which tortuosity or disease distal to the carotid bifurcation lesion precludes the use of filter-type or distal balloon-occlusion EPDs.

Data with proximal EPDs are more limited than those for distal EPDs, but they are emerging. The Proximal Flow Blockage Cerebral Protection During Carotid Stenting (PRIAMUS) study,[27a] an initial large registry using a proximal balloon-occlusion system, enrolled 416 "real world" patients with carotid disease and reported a high rate of technical success (~99%) and acceptable clinical outcomes (4.5% incidence of in-hospital stroke, death, or MI). Two prospective registries using the MO.MA system have also been reported. In the Proximal Protection with the MO.MA Device During Carotid Stenting (ARMOUR) study, 262 high-risk patients undergoing CAS with embolic protection were enrolled, with a reported 30-day rate of stroke, death, or MI of 2.7%.[28] In a larger, single-center registry of 1300

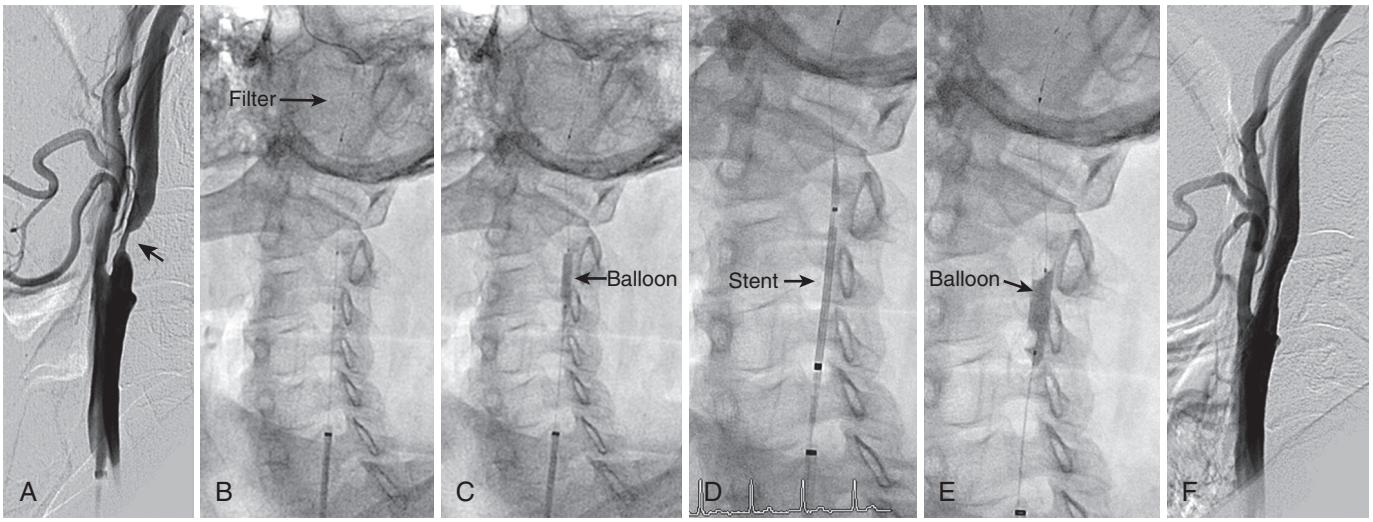

FIGURE 46-8 Angiographic images from a carotid artery stent procedure. **A,** Baseline angiographic image shows severe internal carotid artery stenosis *(arrow)*. **B,** Placement of filter-type embolic protection device (5.5-mm-diameter Accunet filter, Abbott Vascular, Abbott Park, IL). **C,** Predilation (4.0- by 20-mm Maverick balloon, Boston Scientific, Natick, MA). **D,** Placement of tapered 6- to 8-mm-diameter by 30-mm long self-expanding nitinol stent (Acculink, Abbott Vascular). **E,** Postdilation with 5.0- by 20-mm Aviator balloon (Cordis, Warren, NJ). **F,** Final angiographic appearance after removal of filter.

TABLE 46-3 Self-Expanding Carotid Artery Stents

Stent	Manufacturer	Metal Composition	Design	Tapered Version Available	FDA-Approved
Carotid WALLSTENT	Boston Scientific, Natick, MA	Cobalt chromium	Closed-cell	No	Yes
Exponent	Medtronic, Minneapolis, MN	Nitinol	Open-cell	No	Yes
Precise	Cordis, Warren, NJ	Nitinol	Open-cell	No	Yes
Protégé	ev3, Plymouth, MN	Nitinol	Open-cell	No	Yes
AccuLink	Abbott, Abbott Park, IL	Nitinol	Open-cell	Yes	Yes
X-Act	Abbott, Abbott Park, IL	Nitinol	Closed-cell	Yes	Yes
Zilver	Cook, Bloomington, IN	Nitinol	Open-cell	No	No
Cristallo Ideale	Invatec, Roncadelle, Italy	Nitinol	Hybrid	Yes	No

patients who underwent CAS with embolic protection from the MO.MA device, the 30-day rate of stroke or death was a remarkable 1.4%, and the procedural success rate was 99.7%.[29] Finally, in a meta-analysis of four studies including 2397 patients (mix of normal and high surgical risk and symptomatic and asymptomatic status) undergoing CAS, the 30-day stroke rate was an impressive 1.7%.[30] A small randomized trial examining the incidence of diffusion-weighted MR imaging defects also showed that there was clearly less distal embolization with proximal EPDs compared with distal EPDs,[31] but a significant effect on clinical outcome has yet to be demonstrated. Although these results are encouraging, a direct comparison of proximal versus distal embolic protection in a randomized trial with hard clinical outcomes is needed.

Angioplasty and Stenting

Figure 46-8 shows angiographic images from a carotid artery stent procedure.

Predilation

After placement of the EPD system, the lesion is usually predilated to facilitate stent delivery. Low-profile coronary balloons with diameters of 3.0 to 4.0 mm are used. Attempts to deliver the stent without predilation have been associated with a greater amount of atheroembolism, likely related to increased trauma to the lesion with forcible passage of the stent across a tight stenosis.[17]

Stent Selection and Placement

As in other vascular territories, the ability to stent carotid lesions has allowed operators to achieve a predictable angiographic result, deal with procedural complications such as dissection and abrupt vessel closure, and improve long-term patency by eliminating vessel recoil. Initial attempts at carotid stenting using relatively inflexible stainless steel balloon-expandable stents (e.g., Palmaz stent, Cordis, Warren, NJ) were associated with acute technical success. However, their use was abandoned owing to the subsequent development of stent crushing, likely related to compression of the superficially located carotid stent from neck movements.[32] This complication led to the development and use of flexible self-expanding stents that could conform to the tortuous anatomy of the carotid bifurcation and changes in vessel shape associated with neck movements (Table 46-3). The functional properties of these stents are defined by their metal composition and design.[33] Nitinol, a nickel-titanium alloy, is the most widely used material for carotid self-expanding stents; because of its large elastic range, it confers an ability to withstand significant deformations. A variety of nitinol stents with either a closed- or an open-cell design is available. The closed-cell design offers superior scaffolding at the cost of reduced flexibility. A single cobalt-based alloy stent with a closed-cell design is currently available (e.g., WALLSTENT, Boston Scientific, Natick, MA). Both the metal composition and the design of this stent result in a more rigid stent with excellent scaffolding properties.

Carotid stents come in a variety of sizes that match the typical diameter of the ICA and CCA (5 to 10 mm), and they are typically 20

to 40 mm long. The nominal diameter of the stent used should be 1 to 2 mm larger than the diameter of the largest treated vessel (usually the CCA). Stent lengths are chosen to provide complete lesion coverage. Initially, all carotid stents were cylindrical. However, tapered stents that conform to the size mismatch between the ICA and the CCA and facilitate treatment across the carotid bifurcation are now commonly used. The tapered stents used are usually 6 to 8 mm or 7 to 9 mm in diameter and either 30 or 40 mm long. The cylindrical stents used are usually 8 mm in diameter and of similar length (i.e., 30 to 40 mm). For most cases, any of the available carotid stents will achieve similar technical success and clinical outcomes. In the remaining cases (~25%), assuming that all stents are available to the operator, the choice of stent should be individualized and is largely influenced by arterial anatomy and lesion morphology.[34] For example, stents with the greatest degree of flexibility—that is, open-cell-design nitinol stents with large open-cell areas and highly flexible interconnecting bridges (e.g., Precise stent, Cordis; Zilver stent, Cook, Bloomington, IN)—may be optimal for treating lesions in tortuous locations. Calcified lesions should be treated with stents that have a high radial force and a moderate outward expansive force, such as nitinol stents with a closed-cell design (e.g., Xact stent, Abbott). Finally, lesions with the greatest risk for distal embolism should be treated with stents that provide greater vessel scaffolding (closed-cell nitinol or cobalt alloy stents; e.g., WALLSTENT, Xact).

Postdilation

Postdilation of the self-expanding stent is typically performed with the use of a 4.5- to 5.5-mm diameter noncompliant balloon (e.g., Aviator, Cordis; Sterling, Boston Scientific). There is general agreement that postdilation is associated with the greatest propensity for plaque embolization; therefore experienced operators advocate a conservative approach to postdilation balloon sizing. A residual stenosis of less than 20% is usually accepted.

After predilation, stent deployment, and postdilation, contrast angiography is performed to assess the angiographic result and detect any potential complications. When filter-type EPDs are being used, this practice allows the detection of "slow flow," which is an important finding that requires special management.[35] Slow flow is manifested by delayed antegrade flow in the ICA and may vary from complete cessation of antegrade flow to mild delay of ICA flow compared with the ECA (Fig. 46-9). Most likely, this phenomenon is caused by excessive distal embolization of plaque elements that occlude the filter pores, compromising antegrade flow through the filter (Fig. 46-10). The phenomenon is frequent, occurring in 8% to 10% of cases,[35,36] and is most commonly observed after postdilation of the stent (75% of cases) or after stent deployment (25% of cases). Predictors of this event include treatment of symptomatic lesions, increased patient age, and increased stent diameter.[35] In patients with slow flow, the column of blood proximal to the filter has not been appropriately cleared of debris embolized from the treatment site by the filter EPD. In an effort to prevent distal embolization of this debris at the time of filter retrieval, use of an Export catheter to aspirate 40 to 60 mL of blood from the column of blood proximal to the filter before retrieval of the filter EPD is recommended. If slow flow is observed after stent deployment, poststent dilation is discouraged, because it will probably exacerbate the degree of embolization from the treatment site.

Removal of the Embolic Protection Device and Final Angiography

Removal of filter-type EPD devices is achieved by advancing a retrieval sheath over the interventional wire and collapsing the filter. The collapsed filter is then withdrawn carefully across the stent and removed. Most retrieval sheaths are available in a straight or angled shape to allow them to be advanced past the stent. Rarely, the patient may have to turn his or her head or external compression may have to be applied to the carotid to facilitate this maneuver. Final angiography at the treatment site, the EPD landing zone, and the ipsilateral anterior cerebral circulation is performed to assess the procedural outcome and detect any procedural complication (e.g., distal embolization, spasm at the filter site).

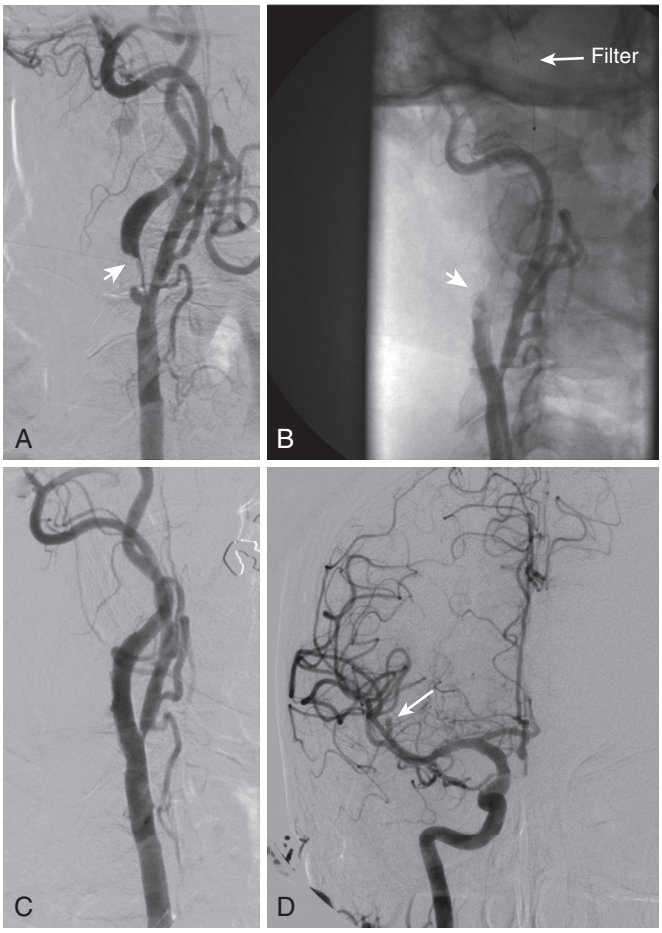

FIGURE 46-9 Angiographic appearance and complication of slow flow during carotid intervention. **A,** Baseline angiogram shows critical bulky stenosis at the origin of the right internal carotid artery (ICA) in a symptomatic patient. **B,** Angiographic appearance after poststent dilation shows cessation of flow in the ICA *(arrow)*. Notice the complete filling of the external carotid artery. **C,** Angiographic appearance after aspiration of the column of blood proximal to the filter and subsequent retrieval of the filter. **D,** Angiogram of the middle cerebral artery after retrieval of the filter shows occlusion of one of its branches *(arrow)*.

Postprocedural Care and Follow-Up

At most centers, patients are admitted overnight to a step-down telemetry floor and typically discharged the next day. Neurologic and hemodynamic monitoring are the most important components of care. All patients should receive lifelong aspirin therapy unless contraindicated, and clopidogrel is recommended for a minimum of 4 weeks after the procedure. Patients are seen at 1 month and 12 months after the procedure for clinical assessment and a carotid ultrasound study to screen for in-stent stenosis. Thereafter, yearly carotid ultrasound examination is recommended.[37]

COMPLICATIONS OF CAROTID INTERVENTION

Stroke

Stroke is the most important complication of CAS. Regardless of whether the patient is deemed to be at high or normal risk for CEA, the risk of periprocedural stroke is most strongly related to the patient's symptomatic status.[29] In studies of high-risk patients, most were asymptomatic. The 30-day incidence of stroke after CAS in multiple

observational studies of high-risk patients has ranged from 2.3% to 6.9%[28,36,38-43] with a majority of high-risk registry studies in recent years reporting stroke rates of 2.3% to 4.4%.[28,36,38,40,41,43] These rates are comparable to the 30-day stroke rate of 3.1% that was observed in the sole randomized trial of high-risk patients.[44] Approximately 80% of these reported strokes were ipsilateral to the treatment site; of these, 25% to 33% were classified as major strokes (i.e., persistence of neurologic deficit beyond 30 days based on a National Institutes of Health [NIH] Stroke Scale score >3). The 30-day rate of stroke in the four contemporary trials of normal-risk, symptomatic patients ranged from 5% to 9% (Table 46-4).[45-48] A lower 30-day stroke rate of 2.5% was also reported in an asymptomatic subgroup from one trial of normal-risk patients.[45]

Although it has been poorly documented in most studies, our experience is that the majority of strokes occur at the time of the CAS procedure. This impression is corroborated by data from the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), in which 16 of 22 ischemic strokes in the 30-day period after carotid intervention occurred within the first 24 hours after the procedure.[49] Beyond 30 days, the risk of ipsilateral stroke with CAS is extremely low. In the Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, there were only two additional strokes (both minor) in the period between 30 days and 1 year after CAS among 167 patients, emphasizing the long-term safety of the procedure.[44] Most procedure-related strokes (>80%) are ischemic in nature, with the dominant mechanism being distal embolization of plaque due to manipulation of catheters and wires in the aortic arch and CCA and embolization of plaque elements associated with angioplasty and stent placement at the treatment site. Hemorrhagic strokes accounted for 15% to 20% of all strokes in larger high-risk stent registries.[42,43] The timing of these strokes is slightly later than that of ischemic strokes, and the dominant mechanism is probably related to cerebral hyperperfusion after CAS.

Neurologic deficits during the CAS procedure should be assumed to be ischemic in nature, and immediate cerebral angiography should be performed. A normal angiogram is associated with an excellent clinical outcome, and no further treatment should be instituted. In contrast, occlusion of a large artery (≥2-2.5 mm diameter) is associated with a poor neurologic outcome, and attempted recanalization using a combination of mechanical (i.e., angioplasty) and pharmacologic (i.e., thrombolytics, glycoprotein IIb/IIIa inhibitors) therapies by qualified interventionalists with experience in intracranial intervention is reasonable.[50] Even in skilled hands, however, the outcome of such rescue maneuvers is unpredictable, because conventional therapies have largely been designed to treat thrombus, and the occlusive emboli in the setting of CAS are composed of atheromatous debris.

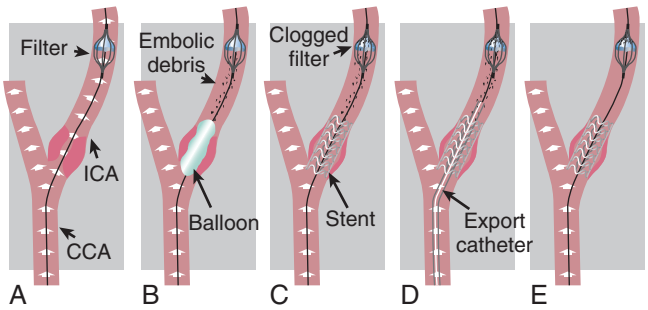

FIGURE 46-10 Schematic diagram of proposed mechanism of slow flow and rationale for aspiration. **A,** Carotid bifurcation lesion with filter placed distally. **B** and **C,** Balloon angioplasty and stenting result in embolization of debris from atherosclerotic plaque toward the filter, causing occlusion of filter pores and accumulation of debris in the column of blood proximal to the filter. **D** and **E,** Aspiration proximal to the filter removes debris from the column of blood without affecting the debris causing occlusion of the filter. (From Casserly IP, Abou-Chebl A, Fathi R: Slow-flow phenomenon during carotid artery intervention with embolic protection devices: predictors and clinical outcome. *J Am Coll Cardiol* 46[8]:1466-1472, 2005.)

Hemodynamic Depression

Baroreceptors located in the adventitia of the carotid sinus form part of the rapidly acting pressure control mechanism of the body and are activated by increases in blood pressure. Signals from these receptors are transmitted through the glossopharyngeal nerve (cranial nerve IX) toward the vasomotor center in the medulla, which in turn activates the vagus nerve (cranial nerve X) and reticulospinal tract, resulting in peripheral vasodilation, bradycardia, and decreased cardiac contractility (Fig. 46-11). Transient pressure from angioplasty and more prolonged pressure from self-expanding stents activates these baroreceptors, causing the hypotension and bradycardia that is frequently associated with CAS. In general, these hemodynamic effects are seen immediately at the time of intervention; in some patients, they persist into the postprocedural period for 24 to 48 hours.[51-53] It is uncommon for significant effects to be seen beyond 48 to 72 hours, because the baroreceptors gradually adapt to the pressure from the self-expanding stent.

In a retrospective analysis of 500 consecutive CAS cases from a single center, the frequency of procedural hemodynamic depression—defined as a systolic blood pressure lower than 90 mm Hg or bradycardia of less than 60 beats/min—was 42%, with persistent hemodynamic depression after the procedure in 17% of cases.[51] Not surprisingly, the location of the lesion at the carotid bulb was a predictor of the event. Prior endarterectomy was associated with a reduced incidence of hemodynamic depression, most likely because of denervation of the carotid sinus.

The management of hemodynamic depression is usually straightforward. Prophylactic measures include withholding antihypertensive medications on the morning of the procedure and ensuring adequate

TABLE 46-4 Thirty-Day Outcomes from Randomized Trials of CAS and CEA in Normal-Risk Patients

	STROKE (%)			MYOCARDIAL INFARCTION (%)			DEATH (%)		
Trial	CAS	CEA	*P* Value	CAS	CEA	*P* Value	CAS	CEA	*P* Value
CREST									
Total	4.1	2.3	0.01	1.1	2.3	0.03	0.7	0.3	0.18
Symptomatic	5.5	3.2	0.04	1.0	2.3	0.08	3	0	NR
Asymptomatic	2.5	1.4	0.15	1.2	2.2	0.2	0	0	NA
ICSS	7.0	3.3	<0.01	0.4	0.5	NR	1.3	0.5	0.07
EVA-3S	8.8	2.7	<0.01	0.4	0.8	0.62	0.8	1.2	0.68
SPACE	7.5	6.2	NS	NR	NR	NR	0.7	0.9	NS

CAS, Carotid artery stenting; *CEA,* carotid endarterectomy; *CREST,* Carotid Revascularization Endarterectomy Versus Stenting Trial; *EVA-3S,* Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; *ICCS,* International Carotid Stenting Study; *NA,* not applicable; *NR,* not reported; *NS,* not statistically significant but specific *P* values not reported; *SPACE,* Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy trial.

hydration with intravenous fluids before and during the procedure. Some operators routinely administer atropine (0.25 to 0.5 mg IV) before the angioplasty and stenting portion of the procedure, whereas others restrict its use to patients who have critical aortic stenosis or critical coronary artery disease or who demonstrate an exaggerated hemodynamic response to angioplasty or stent deployment. In the presence of severe asymptomatic (i.e., systolic blood pressure <75 mm Hg) or any symptomatic hemodynamic depression, the use of intravenous pressors (e.g., phenylephrine, dopamine, epinephrine) is indicated. For less severe asymptomatic hemodynamic depression, oral pseudoephedrine (40-60 mg every 4-6 hours) may be used in an effort to avoid intravenous pressors. For patients with persistent postprocedural hemodynamic depression, it is important to withhold routine antihypertensive medications and to carefully titrate these medications as the patient's blood pressure returns to baseline. Providing the patient with an automated blood pressure cuff and ensuring daily contact between the patient and the health care provider is advisable to optimize this management after hospital discharge.

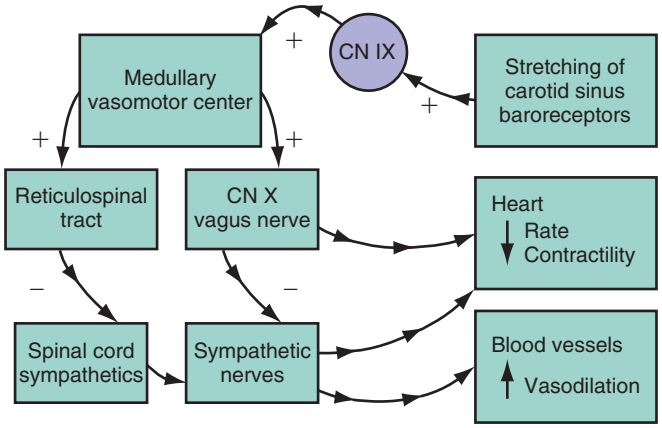

FIGURE 46-11 Diagrammatic representation of the effect of activation of mechanoreceptors in the carotid sinus during carotid intervention. *CN,* Cranial nerve.

Hyperperfusion Syndrome

Cerebral hyperperfusion syndrome is a rare but potentially life-threatening complication of carotid and vertebral revascularization procedures that improve flow to a chronically ischemic cerebral territory.[54] The syndrome is thought to be caused by significant increases in cerebral blood flow (>100% of baseline) after revascularization,[55] which in combination with impaired cerebral autoregulation results in transudation of fluid into the brain's interstitium and cerebral edema (Fig. 46-12). Although hypertension is always present in these patients, it is not a universal finding. Clinically, patients typically complain of a throbbing headache that is ipsilateral to the revascularization site, although the headache may be diffuse. Associated symptoms include nausea, vomiting, confusion, and visual disturbances. In the most severe cases, patients develop focal neurologic deficits and seizures.

The feared complication of the hyperperfusion syndrome is intracerebral or subarachnoid hemorrhage, which is associated with a high mortality rate (40% to 60%) and severe morbidity among survivors. In 12 observational studies published since 2003 reporting rates of hyperperfusion syndrome after carotid stenting, the incidence of hyperperfusion syndrome was 1.3% (73 of 5431 cases).[56-59] There is some variation in the timing of the syndrome, but most cases manifested within 24 hours after the procedure, and cases beyond 2 to 4 days were rare. Based on data in patients undergoing carotid revascularization with CEA, an increased risk of the syndrome likely persists up to 28 days after CAS. The rate of hemorrhagic complications of the syndrome after CAS appears to be high, with 25% to 60% of cases being complicated by intraparenchymal or subarachnoid hemorrhage.[58,60,61]

The low event rates for hyperperfusion syndrome in these reports preclude multivariate analyses of predictors of the syndrome after CAS. Several risk factors have been reported in the CEA literature, and these probably also apply in patients undergoing CAS. They include preexisting hypertension, postprocedural hypertension, contralateral carotid occlusion, critical ipsilateral carotid stenosis, and incomplete circle of Willis.[54] These risk factors permit the identification of patients who are at high risk for cerebral hyperperfusion after CAS. However, aggressive control of blood pressure after CAS is recommended in all patients to prevent it. One study reported an incidence of hyperperfusion syndrome of 3 (0.5%) among a cohort of 570 patients with the implementation of an aggressive blood pressure-lowering algorithm after carotid stenting.[62]

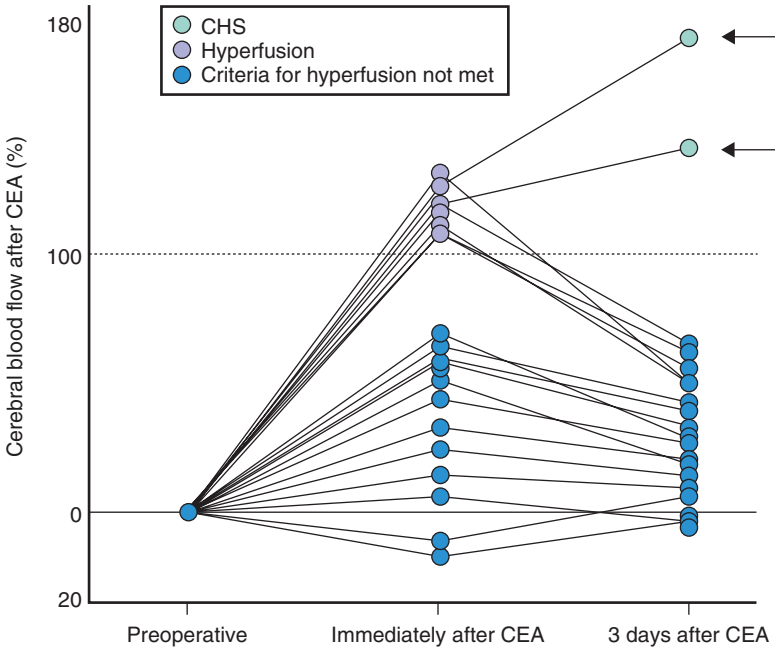

FIGURE 46-12 Graph showing the increase in cerebral blood flow (CBF) after carotid endarterectomy. Increase in CBF >100% from baseline defines the patient group with cerebral hyperperfusion *(purple circles)*. Within this group, two patients *(arrows)* developed clinical signs and symptoms consistent with cerebral hyperperfusion syndrome (CHS). *CEA,* Carotid endarterectomy. (From van Mook WN, Rennenberg RJ, Schurink GW, et al: Cerebral hyperferfusion syndrome, *Lancet* 4:877-888, 2005.)

The cornerstones of management of hyperperfusion syndrome are prompt diagnosis and emergent institution of therapy. The diagnosis is initially a clinical one, based on the patient's symptoms. Although confirmatory studies are helpful, the clinical diagnosis of hyperperfusion syndrome mandates immediate medical therapy. Because blood flow is pressure dependent in patients with cerebral hyperperfusion syndrome, the major focus of therapy is a reduction in systemic arterial pressure.[54] Several antihypertensive agents are contraindicated because they are associated with increased cerebral blood flow, including glycerol trinitrate, nitroprusside, calcium channel antagonists, and angiotensin-converting enzyme inhibitors. Recommended agents include beta-blockers, labetalol (mixed alpha- and beta-adrenergic antagonist), and clonidine (central alpha$_2$-adrenergic antagonist), which have favorable effects on cerebral blood flow and cerebral perfusion pressure in this clinical situation. Patients should be cared for in an intensive care setting that facilitates meticulous control of systemic arterial pressure. After institution of treatment, imaging studies (i.e., CT and MR imaging) are helpful to screen for hemorrhagic complications and assess for the presence of cerebral edema. In addition, transcranial Doppler ultrasonography documenting a significant increase in flow velocity (>150% to 300% compared with baseline) in the ipsilateral middle cerebral artery is useful in confirming the diagnosis.

Adverse Cardiac Events

MI has not been included in the outcome analysis of all RCTs of normal-risk patients. However, the importance of MI as a component of the primary composite end point is underscored by the increased risk of death among patients who suffer MI in the perioperative period after vascular surgery (Fig. 46-13).[64,65] For this reason, the incidence of MI, as determined by preprocedural and postprocedural electrocardiograms and serial measurements of creatine kinase (CK) and CK-MB fraction, has been included in the end point of most high-risk CAS registries and trials. In this patient cohort, the 30-day incidence of MI has been in the range of 0% to 2.4%.[28,36,38-44] More than 80% of these MIs were non-Q-wave in type. When CAS was compared with CEA in high-risk patients in the SAPPHIRE trial, there appeared to be a significant and consistent reduction in MI with CAS (2.4% versus 6.1%; $P = .04$).[44] The risk of MI among normal-risk patients undergoing CAS is likely to be lower, a contention supported by data from the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), which reported 30-day MI rates of 1.1% in the CAS arm and 2.3% in the CEA group ($P = .03$) (see Table 46-4).[45]

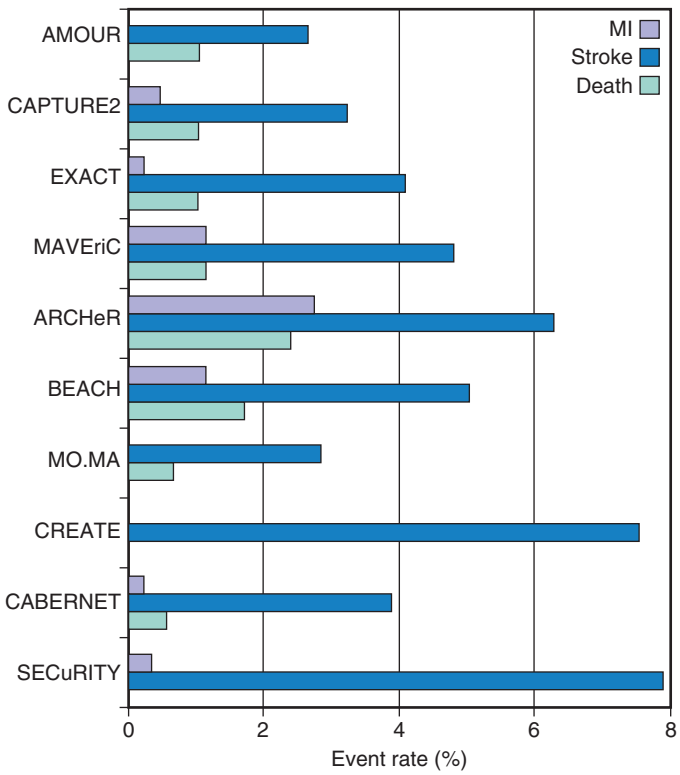

FIGURE 46-13 Incidence of death, stroke, and myocardial infarction (MI) at 30 days in high-risk carotid artery stent registries. The registries are ordered, with the most recently published at the top and the earliest published at the bottom.[28,36,38-43,63]

Restenosis

In-stent restenosis (ISR) is an important late complication of CAS. Because of its acceptable sensitivity, safety, and accessibility, duplex ultrasound screening for carotid ISR[66] has largely been used for frequency estimates. Based on this method, the incidence of severe ISR (≥80%) is 3% to 4% at approximately 18 months of follow-up.[67,68] The rate of ISR at 2 years in a randomized trial of CAS and CEA was higher (11.1%) when a lower cutoff value (i.e., ≥70%) was used to define it.[69] However, for less severe degrees of ISR, conventional ultrasound criteria for determination of the degree of stenosis in a nonstented carotid artery may overestimate stenosis after CAS because of alterations in the compliance of the stented artery.[70] Nonetheless, data suggest that ISR is associated with low rates of clinical events. In two large series, only 1 of 12 patients with severe ISR (>80%) was symptomatic,[67,68] and only 2 of 54 patients with ISR greater than 70% were symptomatic.[69] Additionally, the rate of clinically driven target vessel revascularization was only 2.4% at 3 years in a randomized trial of high-risk patients.[44]

A serial intravenous ultrasound (IVUS) study demonstrated that the immediate postprocedural minimal carotid stent area is negatively correlated with the percentage of restenotic area at follow-up.[71] Before this study, it was thought that such a relationship would not exist owing to the large caliber of the carotid artery. This finding emphasizes the need to balance the short-term procedural risk of distal embolization and stroke from aggressive poststent dilation against the long-term risk of ISR. As in the case of restenosis after CEA, the clinical benefits of revascularization for ISR after CAS have not been demonstrated. Both of these pathologies appear to be associated with a relatively benign clinical outcome,[71] suggesting that a conservative approach is appropriate. Repeat revascularization is usually limited to patients with severe ISR and may be influenced by other considerations, such as the presence of contralateral disease or occlusion. A variety of interventional techniques have been reported for treatment of carotid ISR, including angioplasty, cutting-balloon angioplasty, repeat stenting, and brachytherapy, with recurrence rates ranging from 0% to 50%.[67,68,72,73]

CAROTID ARTERY STENTING—CLINICAL DATA

Although the benefits of CEA compared with medical therapy have been clearly demonstrated in RCTs, these trials systematically excluded patients with certain baseline comorbidities or high-risk anatomic features (Table 46-5). Subsequent "real world" assessments of clinical outcomes with CEA have suggested that the conclusions of these trials might not be broadly applicable in clinical practice. For example, Wennberg and colleagues[74] analyzed outcomes in 113,000 Medicare patients undergoing CEA between 1992 and 1993 and reported mortality rates at least three times greater than those reported in prior RCTs. A single-center CEA registry of more than 3000 patients demonstrated that comorbidities such as severe coronary artery disease, chronic obstructive pulmonary disease, and renal insufficiency were associated with a 7.4% incidence of perioperative death, stroke, or MI, compared with 2.9% in a low-risk cohort of patients without these comorbidities.[75] Based on such data, initial attempts to demonstrate

equipoise between contemporary percutaneous carotid revascularization and CEA focused on a high-risk patient cohort as the study population of interest. Accepting that carotid revascularization has not been proven in RCTs to be more efficacious than medical therapy in this study population, surgical CEA has been widely employed by vascular surgeons on the basis that a beneficial effect in high-risk patients could be extrapolated from trial data in normal-risk study populations.

TABLE 46-5 Criteria Used to Define a High-Risk Population in Studies of Carotid Artery Stenting

Clinical Criteria
Age > 75-80 yr
Congestive heart failure (class III/IV)
Known severe left ventricular dysfunction (LVEF <30%-35%)
Planned CABG or heart valve surgery
Recent MI (>24 hr and <4-6 wk)
Unstable angina (CCS class III/IV)
Severe pulmonary disease*
Contralateral cranial nerve injury
Anatomic Criteria
Previous CEA with recurrent stenosis
Surgically inaccessible lesion
High cervical lesion (at or above C2)
Below the clavicle
Contralateral carotid occlusion
Radiation therapy to neck
Prior radical neck surgery
Severe tandem lesions
Spinal immobility of the neck

CABG, Coronary artery bypass surgery; *CEA,* carotid endarterectomy; *CCS,* Canadian Cardiovascular Society; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction.
*Defined as need for home oxygen, partial pressure of oxygen (Po_2) <60 mm Hg on room air, forced expiratory volume in 1 second (FEV_1) <30% to 50% of predicted.

Carotid Artery Stenting in High-Risk Patients

Among high-risk patients, outcomes of CAS using contemporary techniques have been reported in the form of case series, industry-sponsored registries, and a single RCT. In general, studies of high-risk patients have grouped symptomatic and asymptomatic patients together, with most patients (~75%) being asymptomatic. The enrollment criteria have relied heavily on data from prior RCTs in normal-risk patients; symptomatic patients with 50% or greater carotid stenosis and asymptomatic patients with 70% to 80% carotid stenosis being eligible for inclusion. Case series were particularly helpful in the early stages of the development of CAS but in general have suffered from a lack of stringent oversight. A large number of multicenter, industry-sponsored registries with stricter oversight have been performed (Table 46-6, see Fig. 46-13).

The largest and most recently published of these registries are the EmboShield and Xact Post Approval Carotid Stent Trial (EXACT; $N = 2145$) and the Carotid RX ACCULINK/RX ACCUNET Post-Approval Trial to Uncover Unanticipated or Rare Events study (CAPTURE2; $N = 4175$). In both of these studies, there was independent adjudication of neurologic outcomes. At 30 days, the rate of death was 0.9% in both trials; the rate of stroke was 3.6% in EXACT and 2.8% in CAPTURE2.[38] These event rates are somewhat lower than what was reported in smaller, earlier published registries of carotid stenting with distal EPD, in which the study populations ranged from approximately 200 to 500 participants and the stroke rates were 3.4% to 6.9% (see Table 46-6 and Fig. 46-13).[39,41-43] This temporal trend suggests that increased operator experience has played a role in reducing adverse outcomes.

Emerging data on the use of proximal EPDs also suggest that these devices may be associated with reduced rates of stroke. In a European multicenter registry of 157 high-risk patients treated with CAS and proximal embolic protection with MO.MA, the 30-day rate of stroke was 2.5%. Similarly, in another multicenter registry of 263 subjects treated with CAS and MO.MA, the stroke rate was 2.3% (see Table 46-6 and Fig. 46-13).[28,36] The SAPPHIRE trial is the sole randomized trial comparing CEA with CAS in high-risk patients.[44] Enrollment in this

TABLE 46-6 "High-Risk" Registries of Carotid Artery Stenting With Embolic Protection

Study	Sponsor	Sample Size	Stent	Embolic Protection Device	Status
SAPPHIRE (CAS registry)	Cordis	409	Precise	Angioguard	3-yr outcomes published
ARCHeR 2, 3	Guidant	ARCHeR 2—278 ARCHeR 3—145	Acculink (OTW & RX)	Accunet	2-yr outcomes published
SECuRITY	Abbott Vascular Devices	320	MedNova Xact	MedNova NeuroShield/ EmboShield	1-yr outcomes presented
BEACH	Boston Scientifc	480	WALLSTENT	FilterWire EX and EZ	1-yr outcomes published
CABERNET	EndoTex	380	NexStent	FilterWire EX	3-yr outcomes published
MAVErIC International	Medtronic	51	Exponent	Interceptor	1-yr outcomes published
MAVErIC II	Medtronic	Phase I—99 Phase II—399	Exponent	GuardWire	1-yr outcomes published
PASCAL	Medtronic	115	Exponent	Any CE mark–approved device	30-day outcomes presented
CREATE	ev3	400	Protégé	Spider	30-day outcomes published
MO.MA*	Invatec	157	Any carotid stent	MO.MA	30-day outcomes published
CAPTURE2	Abbott	4175	Acculink	Accunet	30-day outcomes published
EXACT	Abbott	2145	Xact	EmboShield	30-day outcomes published
ARMOUR	Invatec	262	Any carotid stent	MO.MA	30-day outcomes published

ARCHeR, Acculink for Revascularization of Carotids in High-Risk Patients; *BEACH,* The Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients; *CABERNET,* Carotid Artery Revascularization Using the Boston Scientific EPI FilteRwire EX/EZ and the EndoTex NexStent; *CAPTURE2,* Carotid RX ACCULINK/RX ACCUNET Post-Approval Trial to Uncover Unanticipated or Rare Events; *CAS,* carotid artery stent; *CREATE,* The Carotid Revascularization With ev3 Arterial Technology Evolution trial; *EXACT,* EmboShield and Xact Post Approval Carotid Stent Trial; *MAVErIC,* Evaluation of the Medtronic AVE Self-Expanding Carotid Stent System With Distal Protection in the Treatment of Carotid Stenosis; *MO.MA,* a prospective multicenter clinical registry for carotid stenting with a new neuro-protection device based on endovascular clamping; *OTW,* over-the-wire; *PASCAL,* Performance and Safety of the Medtronic AVE Self-Expandable Stent in Treatment of Carotid Artery Lesions; *Rx,* monorail; *SAPPHIRE,* Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy Endarterectomy; *SECuRITY,* a registry study to evaluate the NeuroShield bare wire cerebral protection system and Xact stent in patients at high risk for carotid endarterterectomy.
*75% of patients were considered high-risk.

TABLE 46-7 Outcomes in the SAPPHIRE Trial (Based on Intention-to-Treat Analysis)

	RANDOMIZED TRIAL	
	CAS (%)	CEA (%)
30-Day Outcomes		
Death	0.6	2.0
Stroke	3.1	3.3
MI	1.9	6.6
Death/stroke/MI	4.4	9.9
1-Year Outcomes		
Death	7.4	13.5
Stroke	6.2	7.9
MI	3.0	7.5
30-day death/stroke/MI plus death and ipsilateral stroke between 31 days and 1 yr	12.2	20.1
3-Year Outcomes		
Death	18.6	21.0
Stroke	9.0	9.0
MI	5.4	8.4
30-day death/stroke/MI plus death and ipsilateral stroke between 1 and 3 yr	24.6	26.9

CAS, Carotid artery stenting; *CEA,* carotid endarterectomy; *MI,* myocardial infarction; *SAPPHIRE,* Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy.

study differed from the multicenter industry-sponsored registries in one important respect: The carotid lesion had to be deemed amenable to revascularization by both surgical and percutaneous methods. As a result, the overall risk of the cohort in the randomized portion of this trial was likely somewhat less than in registry-type studies.

Given its randomized design, the SAPPHIRE trial has provided the most robust data supporting the role of CAS with filter-type EPDs compared with CEA in high-risk patients. At 30-day and 1-year follow-up, there was a trend toward a reduction in the incidence of death in the CAS group, a significant reduction in the incidence of MI in the CAS arm, but no significant difference in stoke rate (Table 46-7). Target lesion revascularization (0.7% versus 4.6%; $P = .04$) and cranial nerve palsies (0% versus 5.3%; $P = .003$) were also significantly reduced in the CAS arm. At 3 years' follow-up in this RCT, event rates were comparable between CAS and CEA patients: Death occurred in 19% of patients in the CEA arm and 21% of patients in the CAS arm ($P = .68$), and stroke occurred in 9% of patients in each arms. Overall, these data support the conclusion that CAS with embolic protection is not inferior to CEA in high-risk patients and provides equivalent long-term protection from stroke events.[73]

Carotid Artery Stenting in Normal-Risk Patients

Carotid intervention remains investigational in normal-risk patients. In contrast to high-risk CAS trials, studies in normal-risk patients have typically included symptomatic and asymptomatic patients seen in isolation, according to the clearly established differences in their natural history based on symptomatic status. Additionally, most major normal-risk studies have had a randomized design and in general have compared CAS with CEA. A total of five randomized trials of carotid intervention in normal-risk patients have been completed (Table 46-8; see Table 46-4).

The CAVATAS trial was the first of these and included a largely symptomatic patient cohort with carotid disease.[49] However, because this study enrolled patients between 1992 and 1997, the endovascular arm largely employed a strategy of angioplasty alone—EPDs were not available, and carotid stents became available only toward the end of the trial. Despite the lack of a contemporary CAS technique, the 30-day incidence of death or disabling stroke was identical in each arm (6%; P = Not Significant). Not surprisingly, the low rate of stent usage was associated with a high rate of restenosis in the endovascular arm. Given the absence of EPD and carotid stent use in this trial, the relevance of the CAVATAS data to contemporary practice is limited.

The Stent-Protected Percutaneous Angioplasty of the Carotid Versus Endarterectomy (SPACE) trial and the Endarterectomy Versus Angioplasty in patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial were the first two RCTs comparing contemporary CAS technique (i.e., EPD and carotid stent use) with CEA.[47,76] Both were performed in Europe, and the 30-day and long-term (2- to 4-year) outcomes have been published. In the EVA-3S trial, the 30-day incidence of stroke or death was 9.6% in the CAS arm versus 3.9% in the CEA arm ($P = .01$).[47] The SPACE trial reported the incidence of ipsilateral stroke and death at 30 days in the CAS arm as 6.8% versus 6.3% in the CEA arm.[76] Based on predefined statistical rules to prove the equivalence of CAS versus CEA, the SPACE investigators concluded that CAS failed to demonstrate equivalence. Because enrollment would have had to be doubled to provide enough power to prove equivalence, they stopped further patient recruitment into the trial.

For proponents of CAS, these results were disappointing and certainly raised concern regarding the safety of CAS in this patient subset. However, the results of both of these studies need to be interpreted in the context of several factors that challenge the validity of the findings. Neither study had a roll-in phase to ensure that operators were completely familiar with the equipment for CAS and to audit their clinical outcomes. This limitation was compounded by the fact that the threshold carotid interventional experience required for operators in both of these studies was suboptimal. For example, in the EVA-3S trial, an operator who had performed only five prior CAS procedures was eligible to treat randomized patients. Similarly, in the SPACE trial, eligible operators for the CAS arm need not have ever performed carotid stenting; rather, eligibility was set by a threshold of having performed 25 successful angioplasty procedures in any vascular bed. There were additional issues with regard to the interventional technique used in these studies. Despite the availability of EPDs, the EVA-3S study did not initially mandate their use. Only after an interim analysis demonstrated an increased incidence of stroke among patients in whom EPDs were not used was the protocol amended to mandate their use. In the SPACE trial, the use of EPDs was left to the discretion of the operator, and they were ultimately used in only 27% of all patients. Predilation before stenting was performed in only 17% of patients in the EVA-3S trial, which is a definite deviation from accepted CAS technique in the United States. In a further deviation from accepted U.S. practice, 15% of patients in EVA-3S were not administered dual antiplatelet therapy after carotid stent placement. In summary, the data provided by the EVA-3S and SPACE trials did not support equivalency of CAS versus CEA in symptomatic patients at normal risk for CEA, but deficiencies in trial design and execution are believed by proponents of CAS to explain the signal of harm associated with CAS in these trials.

The remaining two RCTs of CAS versus CEA in normal-risk symptomatic patients were the International Carotid Stenting Study (ICSS) and the CREST trial.[45,46] More than 1700 patients from Europe, Australia, New Zealand, and Canada were enrolled in the ICSS. Unfortunately, this study did not have a roll-in phase, and the minimum training requirement for CAS operators was set at 50 total stenting procedures, of which only 10 had to be in the carotid territory. In addition, the use of EPDs was not mandated; they appear to have been used in approximately 80% of cases. Considerable controversy has been generated by the finding that there was an increased incidence of new ischemic lesions on diffusion-weighted MR imaging in patients treated at centers in which EPDs were used versus centers in which EPDs were not used. It is unclear whether this finding represents real harm due to EPD use or whether operators were inexperienced with their use. Accepting these limitations, the major finding of ICSS was that the incidence of stroke at 30 days was significantly lower with CEA than with CAS (3.9% versus 7.6%). This difference was driven largely by an excess of nondisabling strokes in the CAS group. At 120 days' follow-up,

TABLE 46-8 "Normal-Risk" Carotid Artery Stent Trials

Trial	Planned Sample Size	Sites of Enrollment	Funding	Clinical Enrollment Criteria	Lesion Enrollment Criteria	Endovascular Strategy	Primary End Points	Status of Trial
ICSS (CAVATAS-2)	1500	Europe Australia Canada	Stroke Association Sanofi Synthelabo European Commission	TIA/stroke within 12 mo	>50% by NASCET method or noninvasive equivalent	CAS + EPD	30-day death/stroke/MI 3-yr death/disabling stroke	120-day outcomes published
EVA-3S	900	France	National Research Organization	TIA/stroke within 4 mo	>60% by NASCET or noninvasive equivalent	CAS + EPD	30-day death/stroke 30-day death/stroke + ipsilateral stroke at 2-4 yr	4-yr outcomes published
SPACE	1900	Germany Austria Switzerland	Federal Ministry of Education and Research German Research Foundation Industry Funding	TIA/stroke within 6 mo	>50% by NASCET or 70% by Doppler	CAS ± EPD	30-day death/ipsilateral stroke	2-yr outcomes published
CREST	2500	North America Europe	National Institute of Neurological Disorders and Stroke—NIH Guidant Corporation	Symptomatic Asymptomatic	>50% by NASCET >70% by ultrasound >60% by NASCET >70% by ultrasound	CAS + EPD	30-day death/stroke/MI Ipsilateral stroke after 30 days	30-day outcomes published
ACT I	1540	North America	Abbott Vascular	Asymptomatic		CAS + EPD	Stroke/death/MI within 30 days + ipsilateral stroke at 30-365 days	Enrollment began April 2005
TACIT	3700	North America Europe	NIH, Pharma, Device Industry	Asymptomatic	>60% by ultrasound	CAS + EPD	Stroke/death at 3- to 5-yr follow-up	Held due to lack of funding
SPACE2	3523	Germany Austria Switzerland	Federal Ministry of Education and Research German Research Foundation Industry Funding	Asymptomatic	>50% by ultrasound	CAS + EPD	30-day stroke/death Ipsilateral stroke at 5 yr	Enrolling study participants

ACT I, Asymptomatic Carotid Stenosis, Stenting Versus Endarterectomy Trial; *CAS,* carotid artery stenting; *CAVATAS,* Carotid and Vertebral Artery Transluminal Angioplasty Study; *CREST,* Carotid Revascularization Endarterectomy Versus Stent Trial; *EPD,* embolic protection device; *EVA-3S,* Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis; *ICCS,* International Carotid Stenting Study; *MI,* myocardial infarction; *NASCET,* North American Symptomatic Carotid Endarterectomy Trial; *NIH,* National Institutes of Health; *SPACE,* Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy Trial; *TACIT,* Transatlantic Asymptomatic Carotid Intervention Trial; *TIA,* transient ischemic attack.

the rates of death and stroke were significantly lower with CEA than with CAS (0.8% versus 2.3%, and 4.1% versus 7.7%, respectively). There was an extremely low rate of MI in both arms (0.4% for CAS and 0.5% for CEA).[46]

The CREST trial was a U.S.-based trial sponsored by the NIH that enrolled more than 2500 patients. Unlike other RCTs in normal-risk populations, both symptomatic (53%) and asymptomatic patients were included, a decision that was driven by initial problems with patient recruitment. In contrast to other trials of normal-risk patients, there was a stringent lead-in phase to ensure that operators were familiar with the single carotid stent and filter system used in the study and to audit clinical outcomes before approval for recruitment of patients into the randomized portion of the trial. The primary end point of the trial (periprocedural death, stroke, or MI plus ipsilateral stroke up to 4 years after carotid revascularization) occurred in 7.2% of the CAS group compared with 6.8% of the CEA group ($P = .51$). There was an increased incidence of stroke at 30 days in the CAS group (4.1% versus 2.3%; $P = .01$), driven by an increased incidence of minor rather than major stroke. There was a lower rate of periprocedural MI in the CAS group (1.1% versus 2.3%; $P = .03$), and, not surprisingly, cranial nerve palsies were more frequent in the CEA group (4.8% versus 0.3%; $P < .01$).[45] Proponents of CAS are likely to promote CREST as an example of a well-designed and executed U.S.-based trial in which stroke rates with CAS were lower than in earlier, non–U.S.-based trials with recognized limitations. Although debate is likely to continue, CREST appears to have restored confidence among the interventional community that CAS will ultimately become a viable option for normal-risk symptomatic (and asymptomatic) patients.

In summary, results from trials of CEA versus CAS in normal-risk symptomatic patients are mixed. The optimal method of carotid revascularization may depend on patient age, operator experience, and patient preference regarding the risks of periprocedural MI (higher with CEA), periprocedural stroke (higher with CAS, particularly if operators are inexperienced), and cranial nerve palsy (higher with

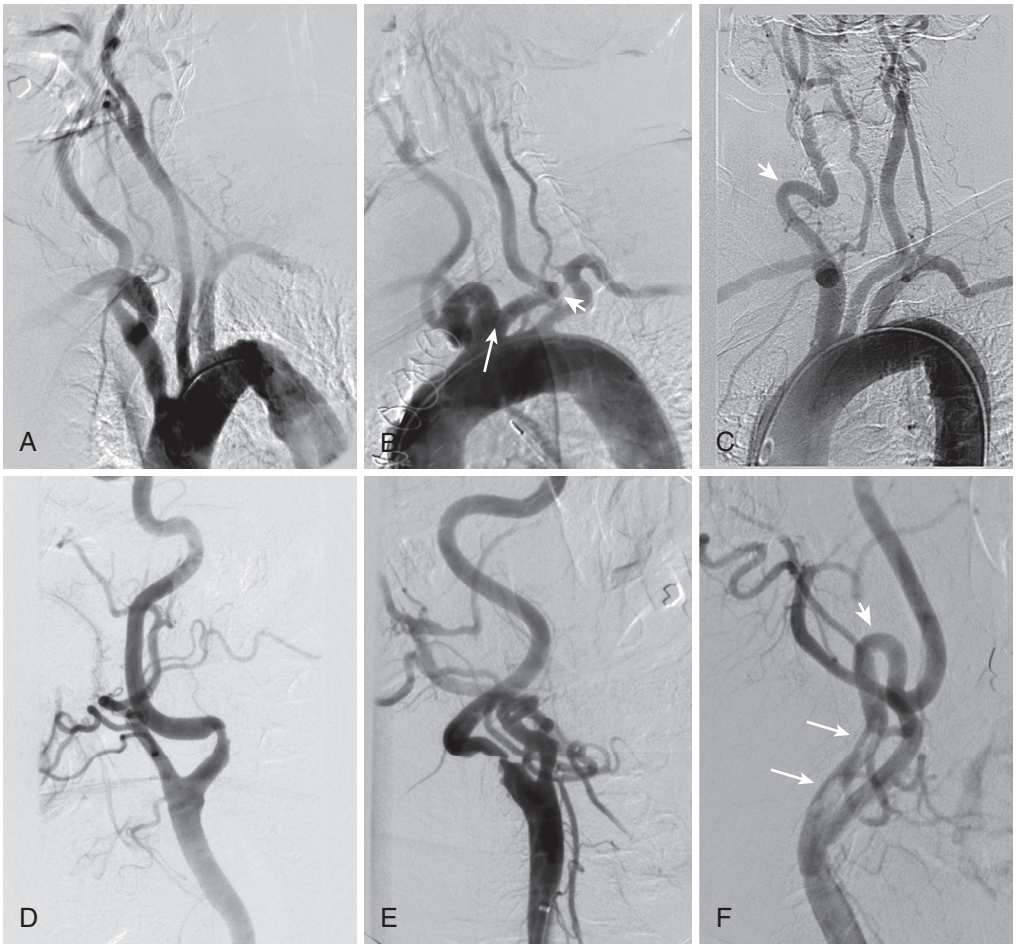

FIGURE 46-14 Examples of anatomic variations that increase procedural risk during carotid artery stenting. **A,** Type III aortic arch. **B,** Bovine origin of the left common carotid artery (CCA) *(long arrow)* and severe tortuosity in the left CCA *(short arrow)*. **C,** Severe tortuosity in the right CCA *(arrow)*. **D,** Marked angulation in the internal carotid artery (ICA) at the site of stenosis. **E,** Tandem areas of angulation distal to stenosis of the ICA. **F,** Dense circumferential calcification at lesion site *(long arrows)* and severe tortuosity distal to the ICA stenosis *(short arrow)*.

CEA). Regarding asymptomatic patients at normal risk for CEA, further dissection of the data from the asymptomatic arm of the CREST trial is required. Currently, results from CREST 2 are eagerly awaited. CREST 2 is a randomized trial comparing CEA, CAS, and optimal medical therapy in symptomatic and asymptomatic patients with carotid artery disease. Completion of this trial is expected in 2016. Disappointingly, two planned trials intended to compare medical therapy with carotid revascularization in asymptomatic patients will not be completed because of enrollment and funding issues (Asymptomatic Carotid Trial [ACT] and Transatlantic Asymptomatic Carotid Intervention Trial [TACIT]).[19]

CAROTID ARTERY STENTING—FUTURE PERSPECTIVE

Realizing the potential of CAS will require further refinements in interventional tools and technique. Perhaps more dramatic may be a reevaluation of the current paradigm for choosing patients for carotid revascularization. We need to move beyond using symptomatic status and percent carotid stenosis as the sole determinants of need for revascularization. Combining more sophisticated prediction models that incorporate multiple clinical variables with advanced imaging studies of carotid plaque (e.g., tissue characterization with MR imaging or ultrasound) that allow a more accurate estimation of an individual's risk of recurrent neurologic events is necessary. Additionally considering the individual's estimated procedural risk (for either CEA or CAS), based on clinical and anatomic assessments, will allow physicians to make a more valid judgment regarding the risk-benefit ratio for the individual patient (Fig. 46-14).

Further, the current culture of viewing CAS and CEA as competitive strategies for carotid revascularization is counterproductive and reminiscent of the debate on percutaneous coronary intervention versus coronary artery bypass surgery. Instead, these strategies should be viewed as complementary. The mode of revascularization that is most likely to achieve the safest procedural outcome for an individual patient should be chosen. Close examination of outcomes from CAS versus CEA trials should help elucidate those variables that favor one mode of revascularization over the other.

PROXIMAL VERTEBRAL ARTERY INTERVENTION

Atherosclerotic disease of the VA is most commonly located at the origin and proximal V1 extracranial segment of the vessel. Typically, disease at this location represents extension of plaque from the subclavian artery into the proximal VA. In a large prospective New England registry of patients with symptomatic ischemia of the posterior circulation, proximal VA disease was deemed the primary mechanism of stroke in 9%, underscoring the importance of atherosclerotic disease at this site.[77] The mechanism of stroke was attributed predominantly to either hemodynamic compromise or artery-to-artery embolism (i.e., VA to distal posterior circulation).

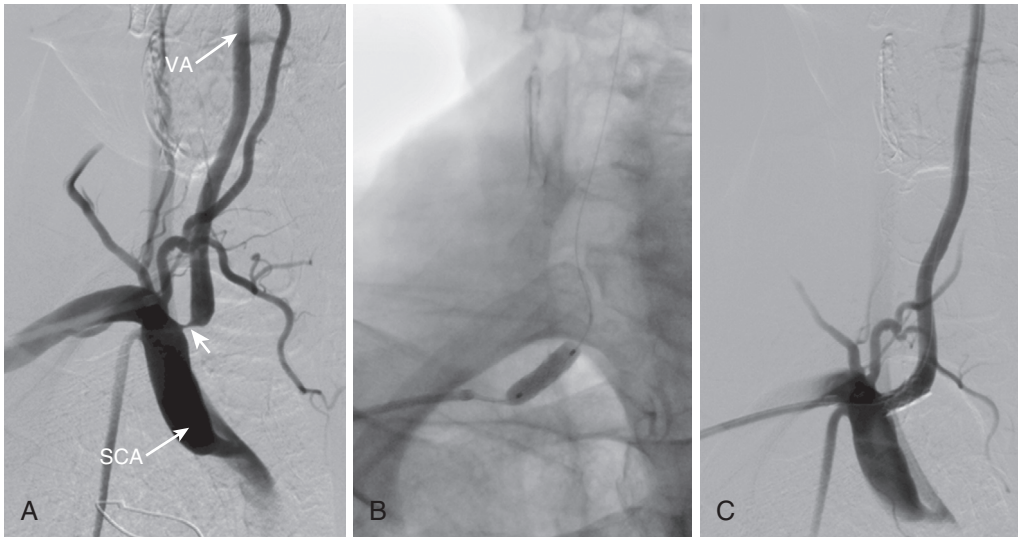

FIGURE 46-15 Vertebral artery intervention. **A,** Right subclavian artery (SCA) angiography shows severe stenosis *(arrow)* at the origin of right vertebral artery (VA). Because of the takeoff angle of the right VA, it was decided to approach the lesion from the right brachial artery. **B,** Inflation of a 5.0- by 12-mm Palmaz Blue balloon-expandable cobalt-chromium stent (Cordis, Warren, NJ) at the ostium of the right VA. **C,** Final angiographic appearance.

Contemporary surgical revascularization of proximal VA disease typically involves transposition of the VA to the ipsilateral CCA or ICA. Other surgical options include VA endarterectomy and vein patch angioplasty.[78] Although some centers have reported excellent procedural and long-term results,[79] these surgical techniques have now been almost completely replaced by endovascular therapies. However, lack of RCT data demonstrating a benefit of revascularization over medical therapy alone in patients with proximal VA disease makes clinical decision making problematic. Moreover, there is almost a complete absence of data regarding the natural history of asymptomatic patients with proximal VA disease and a relative paucity of data regarding the natural history in symptomatic patients. Given these uncertainties, most operators restrict endovascular revascularization to symptomatic patients, especially those for whom medical therapy has failed. Intervention in asymptomatic patients should be strictly limited to those deemed at high risk based on the appearance of the lesion, the presence of poor collateral flow from the carotid circulation, and the existence of contralateral VA disease.

Technique

Most proximal VA interventions are performed using femoral artery access, but the ipsilateral brachial artery may also be used, particularly if the VA origin has a retroflexed takeoff from the subclavian artery[80] (Fig. 46-15). Radial access has also been described as a feasible alternative.[81] A 6-Fr guide or 8-Fr sheath is delivered to the proximal subclavian artery, and the lesion is crossed using a soft-tipped 0.014-inch coronary wire. This wire is advanced to the distal V2 segment of the VA to provide support for device delivery. Predilation with a coronary balloon is routinely performed to facilitate stent delivery. Stenting with a balloon-expandable stent is recommended to provide radial strength and reduce restenosis. For smaller-sized VAs (i.e., diameter <3.75 mm), we typically use a coronary stainless steel drug-eluting or bare-metal stent. For larger-sized VAs (>4 mm diameter), stainless steel or cobalt-chromium peripheral balloon-expandable stents may be used. There is a lack of consensus regarding the need for EPDs during proximal VA intervention. If the V2 segment of the vessel is sufficiently large to accommodate current-generation filter-type EPDs (i.e., ≥4 mm) and the ostial lesion has a high-risk appearance (e.g., ulceration), the use of such devices is recommended.

Endovascular Outcomes

Data regarding the endovascular treatment of proximal VA disease are largely derived from a number of single-institution case series treating a symptomatic patient population.[80] With the use of contemporary stenting techniques, procedural success approaches 100% and periprocedural neurologic complications are rare (Table 46-9). The high restenosis rates associated with angioplasty alone have been significantly improved with stenting, with most series reporting ISR in 3% to 10% of patients. As expected, lesion length has been identified as an independent predictor of ISR, and this may have implications for the selection of drug-eluting rather than bare-metal stents for longer lesions.[82] Long-term follow-up shows a late stroke rate of less than 1%, reinforcing the overall safety of the procedure.

Coward and colleagues reported an analysis of a small subset of patients from the CAVATAS trial with proximal VA disease (mean stenosis, approximately 75%).[83] From a cohort of 16 patients, 8 patients received endovascular therapy (angioplasty in 6, stenting in 2), and 8 patients received medical therapy. There were two procedure-related posterior circulation TIAs in the endovascular therapy group and no neurologic events in the medically treated group. Although this trial subgroup involved a small number of patients and does not reflect contemporary endovascular techniques, it does reinforce the need for dedicated trials of endovascular revascularization versus medical therapy in patients with proximal VA disease to help define the benefit, if any, of endovascular revascularization in this patient cohort. Currently, the Vertebral Artery Stenting Trial (VAST) is comparing medical therapy with VA stenting for recently symptomatic VA stenoses greater than 50%.[84]

INTRACRANIAL INTERVENTION

Intracranial large vessel atherosclerosis is estimated to account for 5% to 10% of all ischemic strokes in the United States. In Asian, Hispanic, and black populations, the incidence of intracranial atherosclerosis is significantly greater and accounts for a greater proportion of all ischemic strokes.[1,85] As in the extracranial circulation, atherosclerosis of the intracranial circulation has a predilection for specific anatomic sites, In the anterior cerebral circulation, these include the petrous, cavernous, and supraclinoid (Fig. 46-16) portions of the ICA and the

TABLE 46-9 Clinical Outcomes in Selected Series of Proximal Vertebral Artery Stenting

Study	*N*	Technical Success (%)	Procedural Complications	Improvement in Symptoms	Mean Follow-Up (Months)	Late Stroke	Restenosis
Mukherjee et al	12	100	None	12/12	6.4	0	1/12
Malek et al	13	100	1 TIA	11/13	20.7	0	N/A
Jenkins et al	32	100	1 TIA	31/32	10.6	0	1/32
Chastain et al	50	98	None	48/50	25	1	5/50
Qureshi et al	12	92*	None	N/R	1	0	N/R
Ogilvy et al	50	100	None	41/43	21	0	11/36
Jenkins et al	105†	100	1 TIA 1 dissection	95/105	29	5	14/105‡
Parkhutik et al	29	100	1 stroke	N/A	32	1	1/29

N/A, Not available; *TIA,* transient ischemic attack.
*Technical success defined as successful deployment of distal protection device and final residual stenosis of <30%.
†97 cases involved proximal vertebral artery.
‡Target vessel revascularization.

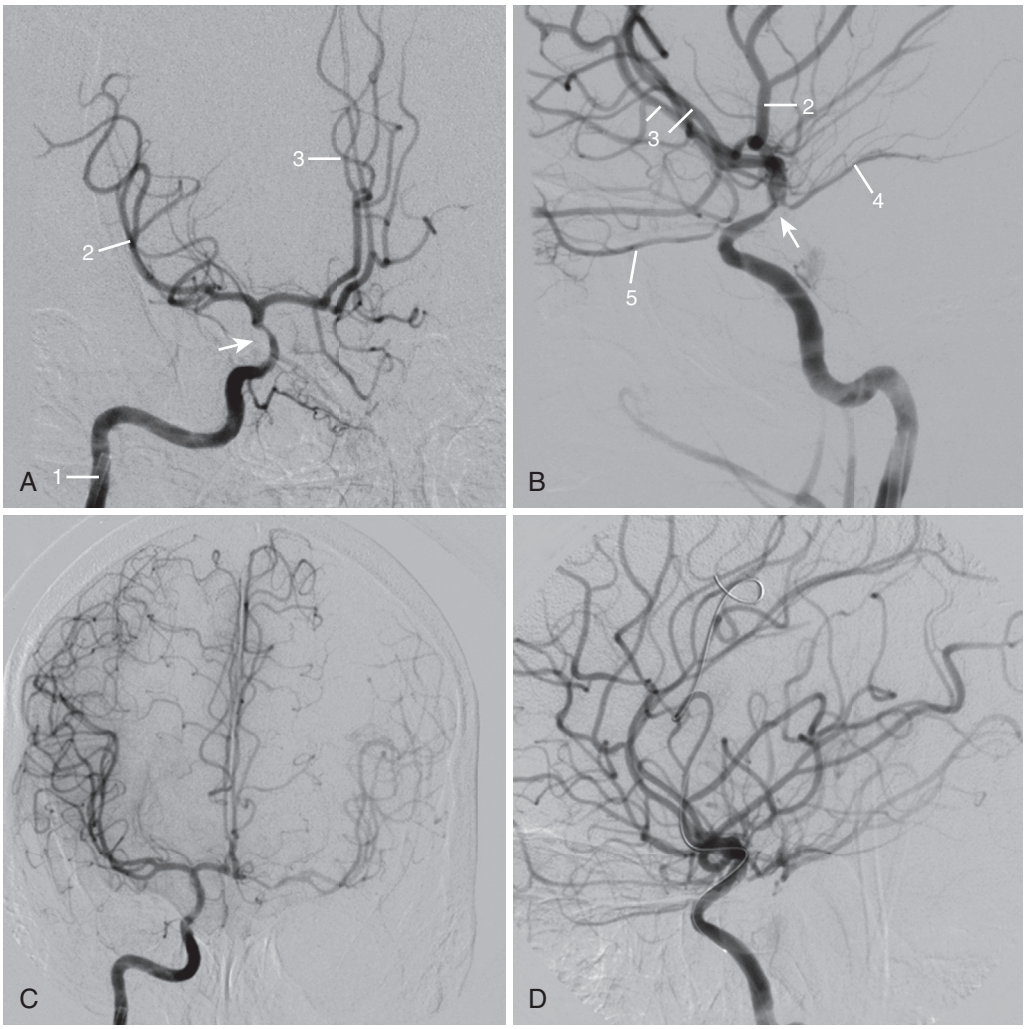

FIGURE 46-16 Intracranial intervention. **A** and **B,** Baseline cerebral angiography in posteroanterior (PA) cranial and lateral projections, respectively, show severe stenosis in the supraclinoid portion of the internal carotid artery *(arrows).* **C** and **D,** Cerebral angiography in PA cranial and lateral projections, respectively, after placement of 3.0- by 8-mm balloon-expandable Multilink Vision stent (Guidant Corporation, Indianapolis, IN). *1,* Internal carotid artery; *2,* middle cerebral artery; *3,* anterior cerebral artery; *4,* anterior choroidal branch; *5,* ophthalmic branch.

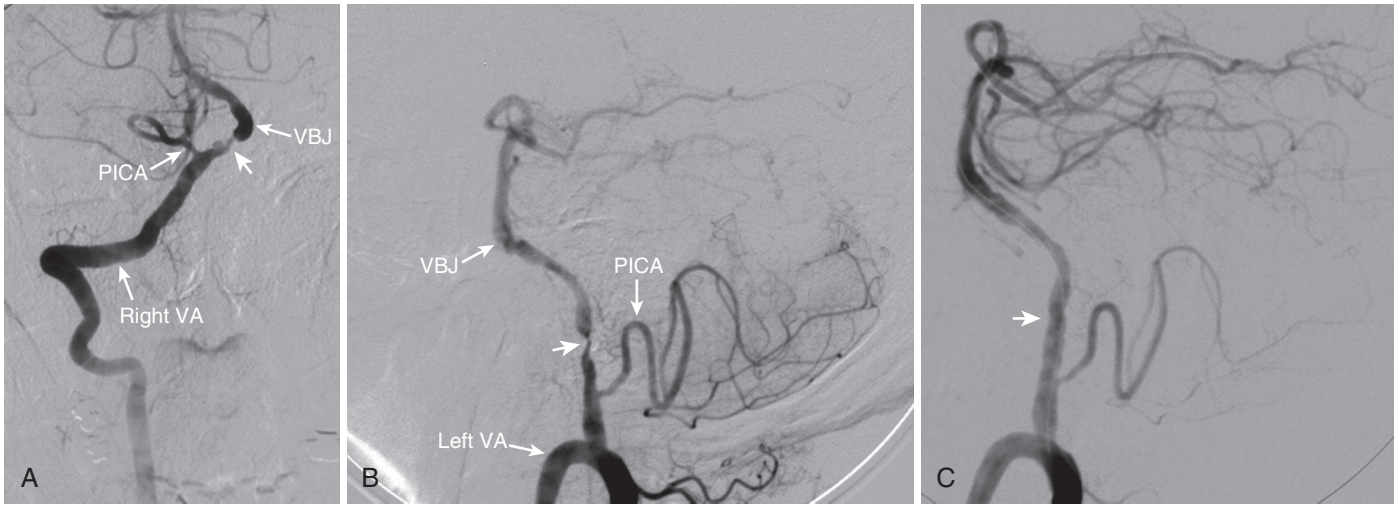

FIGURE 46-17 Intracranial intervention. **A** and **B,** Baseline angiography of right vertebral artery (VA) demonstrates severe stenosis *(arrows)* in intracranial portion of vessel between the origin of the posterior inferior cerebellar artery (PICA) and the vertebrobasilar junction (VBJ). **C,** Vertebral artery angiography after placement *(arrow)* of 3.0- by 12-mm Multilink Vision stent (Abbott Vascular, Abbott Park, IL).

main trunk of the MCA; in the posterior cerebral circulation, the distal VA (Fig. 46-17), vertebrobasilar junction, and midportion of the basilar artery are most commonly affected.

Intracranial atherosclerosis can cause ischemic stroke by a variety of mechanisms including hypoperfusion, thrombotic occlusion at the site of disease, distal embolization from the site of disease, and occlusion of small penetrating arteries due to plaque extension. In identifying those patients most likely to benefit from revascularization therapy, it is important to develop an understanding of the likely mechanism of stroke in each patient based on clinical evaluation, noninvasive imaging, and contrast angiography.

The natural history of asymptomatic intracranial atherosclerosis is largely unknown, but limited data suggest a benign course.[86] By contrast, the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial provided a reasonable estimate of the high risk of recurrent events in patients with a recent TIA or stroke due to angiographically verified 50% to 99% stenosis of a major intracranial vessel.[87] In this cohort, the 1-year risk of an ischemic stroke in the distribution of the diseased intracranial artery in medically treated patients was approximately 12%. Additional retrospective studies have suggested a variety of clinical and angiographic variables to further risk-stratify patients with symptomatic intracranial atherosclerosis, including recurrent symptoms despite medical therapy,[88] lesion location (e.g., vertebral and ICA lesions proximal to major points of collateral supply have a lower risk than lesions involving the basilar artery or MCA), and severity of stenosis.[89]

Surgical revascularization of intracranial ICA and MCA disease was first performed in 1967 and subsequently tested in a large RCT of almost 1400 patients, which was reported in 1985.[90] Patients were randomly assigned to surgical revascularization (by anastomosis of branches of the ECA to the cortical branches of the MCA) or to medical therapy with aspirin (325 mg four times daily). Surgical therapy was associated with a 14% increase in the relative risk of nonfatal and fatal stroke, and this approach was subsequently abandoned as a therapy for the treatment of intracranial carotid disease. Despite this finding, initial attempts at percutaneous revascularization of intracranial disease were made in the 1980s. The initial experience was disappointing, with limited technical success and prohibitively high complication rates. However, by the mid-1990s, a variety of technological advances, borrowed from the coronary intervention field, and improved operator expertise resulted in a renewed enthusiasm for the technique. Technological advances included the availability of 0.014-inch wires that could negotiate the tortuous intracranial anatomy and low-profile, flexible balloon dilation catheters.

As in other vascular territories, stents were used to address some of the shortcomings associated with angioplasty of intracranial vessels (i.e., vessel recoil, abrupt vessel closure, and restenosis). However, the tortuosity of the intracranial circulation presented a significantly greater challenge for stent delivery than that encountered in the coronary circulation, so it was not until the availability of third- and fourth-generation coronary stents with improved flexibility and lower crossing profiles that stenting of intracranial disease became more widespread. Today, a number of stents designed specifically for use in intracranial intervention, most notably the nitinol self-expanding Wingspan Stent (Boston Scientific), the balloon-expandable stainless steel Apollo stent (MicroPort Medical, Shanghai, China), and the balloon-expandable Pharos device (Micrus Endovascular, Sunnyvale, CA) have been developed and tested in prospective studies.[91,92]

Although stenting offers an effective treatment for arterial dissection and vessel recoil and improves restenosis rates, the use of stents in intracranial vessels raises a number of unique concerns. Intracranial arteries are particularly fragile because of the sparse adventitia and elastic layers of the media and hence are prone to perforation. Depending on the lesion location, such perforations result in either subarachnoid or intraparenchymal hemorrhages, which are associated with high morbidity and mortality.[93] Given this consideration, intracranial stents are typically undersized and inflated to lower pressures (4 to 8 atm). However, several studies of stenting in the coronary circulation have shown that the use of stents that are appropriately sized to the reference vessel diameter and inflated to high pressures (14 to 16 atm) is required for optimal stent deployment and apposition of stent struts to the vessel wall. The latter considerations are believed to minimize the risk of stent thrombosis and to reduce the rate of restenosis.

As described, potentially serious consequences are associated with the current practice of intracranial stenting. Moreover, stenting is associated with significantly more plaque shifting than angioplasty alone. Although the occlusion of small side branches in the coronary circulation is usually a benign event, compromise of critical side branches from intracranial vessels (e.g., lenticulostriate branches of the MCA and perforating branches of the basilar artery) can have severe neurologic consequences.[94] Finally, significant complications (e.g., stent dislodgement, vessel dissection, distal embolization of plaque) may occur with attempts to deliver stents through the technically challenging vascular terrain of the intracranial circulation.

Technique

Intracranial intervention is almost universally performed with the use of femoral arterial access. Most operators use general anesthesia, in contrast to other cerebrovascular interventions, but conscious sedation has been shown to be a viable alternative.[95] Preprocedural antiplatelet and procedural anticoagulation regimens mirror those practiced during carotid bifurcation intervention. The first task during anterior or posterior circulation intracranial intervention is the delivery of a guide or sheath to the distal CCA or the proximal subclavian artery, respectively. Sheaths are most commonly used (e.g., Shuttle sheath, Cook), and the inner luminal diameter of a 6-Fr sheath is adequate for delivery of standard interventional equipment. For normal-sized individuals, a 70-cm length sheath is optimal; longer sheath lengths may restrict the ability to treat distal intracranial lesions owing to limitations in the length of current balloon and stent delivery systems. Through this sheath, a 6-Fr Envoy guide is advanced over an 0.035-inch wire to the level of the distal cervical ICA for anterior circulation intracranial intervention, or the distal V2 segment of the VA for posterior circulation intracranial intervention. Having achieved this platform, a variety of 0.010- to 0.014-inch wires (e.g., Synchro, Boston Scientific) may be used to cross the intracranial lesion. In order to provide sufficient support for device delivery, the wire is usually advanced to the second- or third-order branches of the middle or posterior cerebral artery for anterior or posterior circulation interventions, respectively.

Angioplasty is performed with the use of coronary balloons (e.g., Maverick, Boston Scientific), and the angioplasty technique is modified to minimize the risk of vessel perforation. These modifications include using balloon diameters that are 70% to 80% of the vessel diameter and performing slow, prolonged inflation of the balloon to less than nominal pressures (4 to 8 atm), followed by slow deflation. In addition, the minimal balloon length required to treat the lesion is chosen to minimize the risk of compromising flow in side or perforating branches. Whereas some operators adopt a strategy of "provisional" stenting (i.e., stenting only if the angioplasty result is suboptimal), an increasing number practice primary stenting (stent placement regardless of the initial angioplasty result). Currently, the most popular stents used for intracranial intervention are the recent generation of cobalt-chromium balloon-expandable coronary stents (e.g., Multilink Vision, Abbott; Driver, Medtronic), which have superior deliverability compared with stainless steel coronary stents. Balloon-expandable stents are sized 0.5 mm smaller than the estimated vessel diameter and are inflated to moderate pressures (6 to 8 atm). The minimal stent length is used to attenuate the risk of plaque shift into critical side or perforating branches. Final angiography of the lesion site and distal cerebral circulation is performed, and patients recover in a neurointensive care setting.

Clinical Outcomes

The initial data regarding intracranial intervention were derived mostly from retrospective observational case series at a small number of institutions with highly experienced operators; as such, they had significant limitations in applicability to broad clinical settings. Case series from the late 1990s and early 2000s reported the experience with intracranial angioplasty. However, the availability of balloon-expandable coronary stents appears to have improved the technical success rate to greater than 90% without a significant increase in periprocedural complications. A systematic review of 31 studies, many of which were early case series, reported results from 1177 intracranial stenting procedures. The median rate of technical success was 96% (interquartile range, 90% to 100%), whereas the median rate of stroke and death was 7.7% (interquartile range, 4.4% to 14.3%).[96] A number of multicenter prospective studies of intracranial stenting for symptomatic atherosclerotic lesions have been performed in the past decade.[97-101] Each of these studies reported procedural success rates of 90% or better, and four of the five studies reported procedural success of 95% or better.

Early complications rates have ranged from 2% to 7% for ischemic stroke, 1% to 3% for intracerebral hemorrhage, and 0% to 5% for death (Table 46-10). The evidence for long-term complication rates (e.g., restenosis) are less robust because there are fewer data, varying definitions of restenosis, and differing strategies for patient surveillance. Nonetheless, in the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) trial, between 30 days and 1 year of follow-up, there were two strokes, giving a cumulative 1-year stroke incidence of 14%. Repeat angiography at 6 months documented a restenosis rate of 32% in the intracranial cohort. In the overall group (intracranial and extracranial procedures), 39% of patients with restenosis were symptomatic (i.e., with TIAs or strokes).[98] In contrast to the SSYLVIA study, all patients in the Wingspan study with restenosis were asymptomatic. In this latter registry, the restenosis rate (>50% by angiography) at 6 months was 7.5%, and the incidence of ipsilateral stroke or death was 7.0%.[97] These prospective studies underscore the technical success of intracranial procedures, mirroring the rates reported in other observational series. However, the 6-month and 1-year rates of death and stroke in prospective cohort studies appear to be greater than in retrospective longitudinal studies, highlighting potential publication bias in the latter type of study design. Indeed, the 14% rate of stroke at 1 year in the SSYLVIA study is remarkably similar to the 1-year risk of stroke reported in the WASID trial in medically treated patients.[87,98]

The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke (SAMMPRIS) trial compared intracranial stenting with the Wingspan system plus optimal medical therapy versus optimal medical therapy alone in patients with symptomatic, severe intracranial arterial stenosis.[102] The primary end point was stroke or death at

TABLE 46-10 Multicenter Prospective Observational Studies of Intracranial Stenting

				LESION LOCATION			ADVERSE OUTCOMES			
Study	Year	*N*	Lesions	Anterior	Posterior	Technical Success (%)	Follow-Up	Ischemic Stroke	Intracerebral Hemorrhage	Death
SSYLVIA	2004	61*	61	20	23	95	30 days	3 (5%)	1 (2%)	0
WINGSPAN	2007	45	45	23	22	100	30 days	1 (2%)	1 (2%)	0
Fiorella et al	2007	78	82	54	28	99	Periprocedural	4 (5%)	1 (1%)	4† (5%)
Zaidat et al	2008	129	129	76	53	97	30 days	6 (5%)	3 (2%)	4‡ (3%)
INTRASTENT§	2010	372	388	223	165	90	Periprocedural	28 (7%)	12 (3%)	8 (2%)

*43 lesions were intracranial.
†Deaths were due to the 4 ischemic strokes.
‡3 deaths were due to either ischemic or hemorrhagic strokes.
§149 patients were enrolled prospectively. A study center could enter consecutive patients retrospectively if done completely ($n = 239$).

30 days. The trial was stopped early after results from the first 451 of a planned 764 enrolled patients were obtained because of higher event rates in the intervention arm. At 30 days, stroke and death had occurred in 14.7% of the stenting and medical therapy group, compared with only 5.8% of the medical therapy alone group ($P = .002$). The disparity in outcome rates was driven primarily by intraprocedural complications, indicating that technical advances could potentially improve outcomes for intracranial intervention. Nonetheless, results from SAMMPRIS have dampened enthusiasm for endovascular therapy for obstructive intracranial arterial disease.

CONCLUSIONS

Cerebrovascular intervention has evolved dramatically over the last decade. It is clear that these procedures are feasible and—when performed by experienced endovascular specialists using contemporary interventional equipment and techniques—are safe. The challenge for the future is to advance understanding of the natural history of cerebrovascular atherosclerosis, more accurately predict those patients who will develop recurrent events, and refine the patient populations in whom endovascular revascularization provides meaningful clinical benefit.

REFERENCES

1. White H, Boden-Albala B, Wang C, et al: Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. *Circulation* 111(10):1327–1331, 2005.
2. Golledge J, Greenhalgh RM, Davies AH: The symptomatic carotid plaque. *Stroke* 31(3):774–781, 2000.
3. Redgrave JN, Lovett JK, Gallagher PJ, Rothwell PM: Histological assessment of 526 symptomatic carotid plaques in relation to the nature and timing of ischemic symptoms: the Oxford plaque study. *Circulation* 113(19):2320–2328, 2006.
4. North American Symptomatic Carotid Endarterectomy Trial Collaborators: Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 325(7):445–453, 1991.
5. Barnett HJ, Taylor DW, Eliasziw M, et al: Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 339(20):1415–1425, 1998.
6. Halliday A, Mansfield A, Marro J, et al: Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 363(9420):1491–1502, 2004.
7. Naylor AR: ICSS and EXACT/CAPTURE: more questions than answers. *Eur J Vasc Endovasc Surg* 38(4):397–401, 2009.
8. Cuffe RL, Rothwell PM: Effect of nonoptimal imaging on the relationship between the measured degree of symptomatic carotid stenosis and risk of ischemic stroke. *Stroke* 37(7):1785–1791, 2006.
9. Fox AJ, Eliasziw M, Rothwell PM, et al: Identification, prognosis, and management of patients with carotid artery near occlusion. *AJNR Am J Neuroradiol* 26(8):2086–2094, 2005.
10. Inzitari D, Eliasziw M, Gates P, et al: The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 342(23):1693–1700, 2000.
11. Rothwell PM: Prediction and prevention of stroke in patients with symptomatic carotid stenosis: the high-risk period and the high-risk patient. *Eur J Vasc Endovasc Surg* 35(3):255–263, 2008.
12. Rothwell PM, Mehta Z, Howard SC, et al: Treating individuals 3: from subgroups to individuals—general principles and the example of carotid endarterectomy. *Lancet* 365(9455):256–265, 2005.
13. Rothwell PM, Eliasziw M, Gutnikov SA, et al: Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 361(9352):107–116, 2003.
14. Casserly IP, Sachar R, Yadav JS: *Manual of peripheral vascular intervention*, Philadelphia, 2005, Lippincott Williams & Wilkins.
15. Hobson RW, 2nd, Howard VJ, Roubin GS, et al: Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST lead-in phase. *J Vasc Surg* 40(6):1106–1111, 2004.
16. Roubin GS, New G, Iyer SS, et al: Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis: a 5-year prospective analysis. *Circulation* 103(4):532–537, 2001.
17. Roubin GS, Iyer S, Halkin A, et al: Realizing the potential of carotid artery stenting: proposed paradigms for patient selection and procedural technique. *Circulation* 113(16):2021–2030, 2006.
18. Saw J, Bajzer C, Casserly IP, et al: Evaluating the optimal activated clotting time during carotid artery stenting. *Am J Cardiol* 97(11):1657–1660, 2006.
19. Katzen BT, Ardid MI, MacLean AA, et al: Bivalirudin as an anticoagulation agent: safety and efficacy in peripheral interventions. *J Vasc Interv Radiol* 16(9):1183–1187, quiz 1187, 2005.
20. Wayangankar SA, Abu-Fadel MS, Aronow HD, et al: Hemorrhagic and ischemic outcomes after bivalirudin versus unfractionated heparin during carotid artery stenting: a propensity score analysis from the NCDR. *Circ Cardiovasc Interv* 6(2):131–138, 2013.
21. Al-Mubarak N, Roubin GS, Vitek JJ, Iyer SS: Microembolization during carotid stenting with the distal-balloon antiemboli system. *Int Angiol* 21(4):344–348, 2002.
22. Angelini A, Reimers B, Della Barbera M, et al: Cerebral protection during carotid artery stenting: collection and histopathologic analysis of embolized debris. *Stroke* 33(2):456–461, 2002.
23. Zahn R, Mark B, Niedermaier N, et al: Embolic protection devices for carotid artery stenting: better results than stenting without protection? *Eur Heart J* 25(17):1550–1558, 2004.
24. Gruberg L, Beyar R: Cerebral embolic protection devices and percutaneous carotid artery stenting. *Int J Cardiovasc Intervent* 7(3):117–121, 2005.
25. Kasirajan K, Schneider PA, Kent KC: Filter devices for cerebral protection during carotid angioplasty and stenting. *J Endovasc Ther* 10(6):1039–1045, 2003.
26. Zahn R, Ischinger T, Mark B, et al: Embolic protection devices for carotid artery stenting: is there a difference between filter and distal occlusive devices? *J Am Coll Cardiol* 45(11):1769–1774, 2005.
27. Bates MC, Dorros G, Parodi J, Ohki T: Reversal of the direction of internal carotid artery blood flow by occlusion of the common and external carotid arteries in a swine model. *Catheter Cardiovasc Interv* 60(2):270–275, 2003.

27a. Coppi G, Moratto R, Silingardi R, et al: PRIAMUS–proximal flow blockage cerebral protectIon during carotid stenting: results from a multicenter Italian registry. *J Cardiovasc Surg (Torino)* 46(3):219–227, 2005.

28. Ansel GM, Hopkins LN, Jaff MR, et al: Safety and effectiveness of the INVATEC MO.MA proximal cerebral protection device during carotid artery stenting: results from the ARMOUR pivotal trial. *Catheter Cardiovasc Interv* 76(1):1–8, 2010.
29. Stabile E, Salemme L, Sorropago G, et al: Proximal endovascular occlusion for carotid artery stenting: results from a prospective registry of 1,300 patients. *J Am Coll Cardiol* 55(16):1661–1667, 2010.
30. Bersin RM, Stabile E, Ansel GM, et al: A meta-analysis of proximal occlusion device outcomes in carotid artery stenting. *Catheter Cardiovasc Interv* 80(7):1072–1078, 2012.
31. Bijuklic K, Wandler A, Hazizi F, Schofer J: The PROFI study (Prevention of Cerebral Embolization by Proximal Balloon Occlusion Compared to Filter Protection During Carotid Artery Stenting): a prospective randomized trial. *J Am Coll Cardiol* 59(15):1383–1389, 2012.
32. Mathur A, Dorros G, Iyer SS, et al: Palmaz stent compression in patients following carotid artery stenting. *Cathet Cardiovasc Diagn* 41(2):137–140, 1997.
33. Stoeckel D, Bonsignore C, Duda S: A survey of stent designs. *Minim Invasive Ther Allied Technol* 11:137–147, 2002.
34. Bosiers M, Deloose K, Verbist J, Peeters P: Carotid artery stenting: which stent for which lesion? *Vascular* 13(4):205–210, 2005.
35. Casserly IP, Abou-Chebl A, Fathi RB, et al: Slow-flow phenomenon during carotid artery intervention with embolic protection devices: predictors and clinical outcome. *J Am Coll Cardiol* 46(8):1466–1472, 2005.
36. Reimers B, Sievert H, Schuler GC, et al: Proximal endovascular flow blockage for cerebral protection during carotid artery stenting: results from a prospective multicenter registry. *J Endovasc Ther* 12(2):156–165, 2005.
37. Bates ER, Babb JD, Casey DE, Jr, et al: ACCF/SCAI/SVMB/SIR/ASITN 2007 Clinical Expert Consensus Document on carotid stenting. *Vasc Med* 12(1):35–83, 2007.
38. Gray WA, Chaturvedi S, Verta P: Thirty-day outcomes for carotid artery stenting in 6320 patients from 2 prospective, multicenter, high-surgical-risk registries. *Circ Cardiovasc Interv* 2(3):159–166, 2009.
39. Gray WA, Hopkins LN, Yadav S, et al: Protected carotid stenting in high-surgical-risk patients: the ARCHeR results. *J Vasc Surg* 44(2):258–268, 2006.
40. Higashida RT, Popma JJ, Apruzzese P: Zimetbaum P: Evaluation of the Medtronic Exponent self-expanding carotid stent system with the Medtronic guardwire temporary occlusion and aspiration system in the treatment of carotid stenosis: combined from the MAVErIC (Medtronic AVE Self-expanding CaRotid Stent System with distal protection In the treatment of Carotid stenosis) I and MAVErIC II trials. *Stroke* 41(2):e102–e109, 2010.
41. Hopkins LN, Myla S, Grube E, et al: Carotid artery revascularization in high surgical risk patients with the NexStent and the Filterwire EX/EZ: 1-year results in the CABERNET trial. *Catheter Cardiovasc Interv* 71(7):950–960, 2008.
42. Safian RD, Bresnahan JF, Jaff MR, et al: Protected carotid stenting in high-risk patients with severe carotid artery stenosis. *J Am Coll Cardiol* 47(12):2384–2389, 2006.
43. White CJ, Iyer SS, Hopkins LN, et al: Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30 day results. *Catheter Cardiovasc Interv* 67(4):503–512, 2006.
44. Yadav JS, Wholey MH, Kuntz RE, et al: Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 351(15):1493–1501, 2004.
45. Brott TG, Hobson RW, 2nd, Howard G, et al: Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 363(1):11–23, 2010.
46. International Carotid Stenting Study Investigators, Ederle J, Dobson J, et al: Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet* 375(9719):985–997, 2010.
47. Mas JL, Chatellier G, Beyssen B, et al: Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med* 355(16):1660–1671, 2006.
48. Group SC, Ringleb PA, Allenberg J, et al: 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 368(9543):1239–1247, 2006.
49. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* 357(9270):1729–1737, 2001.
50. Wholey MH, Tan WA, Toursarkissian B, et al: Management of neurological complications of carotid artery stenting. *J Endovasc Ther* 8(4):341–353, 2001.
51. Gupta R, Abou-Chebl A, Bajzer CT, et al: Rate, predictors, and consequences of hemodynamic depression after carotid artery stenting. *J Am Coll Cardiol* 47(8):1538–1543, 2006.
52. Trocciola SM, Chaer RA, Lin SC, et al: Analysis of parameters associated with hypotension requiring vasopressor support after carotid angioplasty and stenting. *J Vasc Surg* 43(4):714–720, 2006.
53. Qureshi AI, Luft AR, Sharma M, et al: Frequency and determinants of postprocedural hemodynamic instability after carotid angioplasty and stenting. *Stroke* 30(10):2086–2093, 1999.
54. van Mook WN, Rennenberg RJ, Schurink GW, et al: Cerebral hyperperfusion syndrome. *Lancet Neurol* 4(12):877–888, 2005.
55. Ogasawara K, Yukawa H, Kobayashi M, et al: Prediction and monitoring of cerebral hyperperfusion after carotid endarterectomy by using single-photon emission computerized tomography scanning. *J Neurosurg* 99(3):504–510, 2003.
56. Brantley HP, Kiessling JL, Milteer HB, Jr, Mendelsohn FO: Hyperperfusion syndrome following carotid artery stenting: the largest single-operator series to date. *J Invasive Cardiol* 21(1):27–30, 2009.
57. Karkos CD, Karamanos DG, Papazoglou KO, et al: Thirty-day outcome following carotid artery stenting: a 10-year experience from a single center. *Cardiovasc Intervent Radiol* 33(1):34–40, 2010.
58. Moulakakis KG, Mylonas SN, Sfyroeras GS, Andrikopoulos V: Hyperperfusion syndrome after carotid revascularization. *J Vasc Surg* 49(4):1060–1068, 2009.
59. Tan GS, Phatouros CC: Cerebral hyperperfusion syndrome post-carotid artery stenting. *J Med Imaging Radiat Oncol* 53(1):81–86, 2009.
60. Abou-Chebl A, Yadav JS, Reginelli JP, et al: Intracranial hemorrhage and hyperperfusion syndrome following carotid artery stenting: risk factors, prevention, and treatment. *J Am Coll Cardiol* 43(9):1596–1601, 2004.
61. Meyers PM, Higashida RT, Phatouros CC, et al: Cerebral hyperperfusion syndrome after percutaneous transluminal stenting of the craniocervical arteries. *Neurosurgery* 47(2):335–343, discussion 343-345, 2000.
62. Abou-Chebl A, Reginelli J, Bajzer CT, Yadav JS: Intensive treatment of hypertension decreases the risk of hyperperfusion and intracerebral hemorrhage following carotid artery stenting. *Catheter Cardiovasc Interv* 69(5):690–696, 2007.
63. Iyer SS, White CJ, Hopkins LN, et al: Carotid artery revascularization in high-surgical-risk patients using the Carotid WALLSTENT and FilterWire EX/EZ: 1-year outcomes in the BEACH Pivotal Group. *J Am Coll Cardiol* 51(4):427–434, 2008.
64. Kim LJ, Martinez EA, Faraday N, et al: Cardiac troponin I predicts short-term mortality in vascular surgery patients. *Circulation* 106(18):2366–2371, 2002.
65. Lopez-Jimenez F, Goldman L, Sacks DB, et al: Prognostic value of cardiac troponin T after noncardiac surgery: 6-month follow-up datac. *J Am Coll Cardiol* 29(6):1241–1245, 1997.

66. Goldman CK, Morshedi-Meibodi A, White CJ, Jaff MR: Surveillance imaging for carotid in-stent restenosis. *Catheter Cardiovasc Interv* 67(2):302–308, 2006.
67. Lal BK, Hobson RW, 2nd, Goldstein J, et al: In-stent recurrent stenosis after carotid artery stenting: life table analysis and clinical relevance. *J Vasc Surg* 38(6):1162–1168, discussion 1169, 2003.
68. Zhou W, Lin PH, Bush RL, et al: Management of in-sent restenosis after carotid artery stenting in high-risk patients. *J Vasc Surg* 43(2):305–312, 2006.
69. Eckstein HH, Ringleb P, Allenberg JR, et al: Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol* 7(10):893–902, 2008.
70. Lal BK, Hobson RW, 2nd, Goldstein J, et al: Carotid artery stenting: is there a need to revise ultrasound velocity criteria? *J Vasc Surg* 39(1):58–66, 2004.
71. Clark DJ, Lessio S, O'Donoghue M, et al: Mechanisms and predictors of carotid artery stent restenosis: a serial intravascular ultrasound study. *J Am Coll Cardiol* 47(12):2390–2396, 2006.
72. Chan AW, Roffi M, Mukherjee D, et al: Carotid brachytherapy for in-stent restenosis. *Catheter Cardiovasc Interv* 58(1):86–92, 2003.
73. Setacci C, de Donato G, Setacci F, et al: In-stent restenosis after carotid angioplasty and stenting: a challenge for the vascular surgeon. *Eur J Vasc Endovasc Surg* 29(6):601–607, 2005.
74. Wennberg DE, Lucas FL, Birkmeyer JD, et al: Variation in carotid endarterectomy mortality in the Medicare population: trial hospitals, volume, and patient characteristics. *JAMA* 279(16):1278–1281, 1998.
75. Ouriel K, Hertzer NR, Beven EG, et al: Preprocedural risk stratification: identifying an appropriate population for carotid stenting. *J Vasc Surg* 33(4):728–732, 2001.
76. Hacke W, Brown MM, Mas JL: Carotid endarterectomy versus stenting: an international perspective. *Stroke* 37(2):344, author reply 344, 2006.
77. Wityk RJ, Chang HM, Rosengart A, et al: Proximal extracranial vertebral artery disease in the New England Medical Center Posterior Circulation Registry. *Arch Neurol* 55(4):470–478, 1998.
78. Jenkins JS, Patel SN, White CJ, et al: Endovascular stenting for vertebral artery stenosis. *J Am Coll Cardiol* 55(6):538–542, 2010.
79. Berguer R, Flynn LM, Kline RA, Caplan L: Surgical reconstruction of the extracranial vertebral artery: management and outcome. *J Vasc Surg* 31(1 Pt 1):9–18, 2000.
80. Mukherjee D, Rosenfield K: Vertebral artery disease. In Casserly I, Sachar R, Yadav J, editors: *Manual of peripheral vascular intervention*, Philadelphia, 2005, Lippincott Williams & Wilkins, pp 110–119.
81. Patel T, Shah S, Malhotra H, et al: Transradial approach for stenting of vertebrobasilar stenosis: a feasibility study. *Catheter Cardiovasc Interv* 74(6):925–931, 2009.
82. Lin YH, Liu YC, Tseng WY, et al: The impact of lesion length on angiographic restenosis after vertebral artery origin stenting. *Eur J Vasc Endovasc Surg* 32(4):379–385, 2006.
83. Coward LJ, Featherstone RL, Brown MM: Percutaneous transluminal angioplasty and stenting for vertebral artery stenosis. *Cochrane Database Syst Rev* (2):CD000516, 2005.
84. Compter A, van der Worp HB, Schonewille WJ, et al: VAST: Vertebral Artery Stenting Trial—protocol for a randomised safety and feasibility trial. *Trials* 9:65, 2008.
85. Wong KS, Huang YN, Gao S, et al: Intracranial stenosis in Chinese patients with acute stroke. *Neurology* 50(3):812–813, 1998.
86. Kremer C, Schaettin T, Georgiadis D, Baumgartner RW: Prognosis of asymptomatic stenosis of the middle cerebral artery. *J Neurol Neurosurg Psychiatry* 75(9):1300–1303, 2004.
87. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al: Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med* 352(13):1305–1316, 2005.
88. Thijs VN, Albers GW: Symptomatic intracranial atherosclerosis: outcome of patients who fail antithrombotic therapy. *Neurology* 55(4):490–497, 2000.
89. Prognosis of patients with symptomatic vertebral or basilar artery stenosis. The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study Group. *Stroke* 29(7):1389–1392, 1998.
90. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke: results of an international randomized trial. The EC/IC Bypass Study Group. *N Engl J Med* 313(19):1191–1200, 1985.
91. Jiang WJ, Xu XT, Jin M, et al: Apollo stent for symptomatic atherosclerotic intracranial stenosis: study results. *AJNR Am J Neuroradiol* 28(5):830–834, 2007.
92. Kurre W, Berkefeld J, Sitzer M, et al: Treatment of symptomatic high-grade intracranial stenoses with the balloon-expandable Pharos stent: initial experience. *Neuroradiology* 50(8):701–708, 2008.
93. Terada T, Tsuura M, Matsumoto H, et al: Hemorrhagic complications after endovascular therapy for atherosclerotic intracranial arterial stenoses. *Neurosurgery* 59(2):310–318, discussion 318, 2006.
94. Levy EI, Chaturvedi S: Perforator stroke following intracranial stenting: a sacrifice for the greater good? *Neurology* 66(12):1803–1804, 2006.
95. Abou-Chebl A, Krieger DW, Bajzer CT, Yadav JS: Intracranial angioplasty and stenting in the awake patient. *J Neuroimaging* 16(3):216–223, 2006.
96. Groschel K, Schnaudigel S, Pilgram SM, et al: A systematic review on outcome after stenting for intracranial atherosclerosis. *Stroke* 40(5):e340–e347, 2009.
97. Bose A, Hartmann M, Henkes H, et al: A novel, self-expanding, nitinol stent in medically refractory intracranial atherosclerotic stenoses: the Wingspan study. *Stroke* 38(5):1531–1537, 2007.
98. SSYLVIA Study Investigators: Stenting of symptomatic atherosclerotic lesions in the vertebral or intracranial arteries (SSYLVIA): study results. *Stroke* 35(6):1388–1392, 2004.
99. Fiorella D, Levy EI, Turk AS, et al: US multicenter experience with the wingspan stent system for the treatment of intracranial atheromatous disease: periprocedural results. *Stroke* 38(3):881–887, 2007.
100. Kurre W, Berkefeld J, Brassel F, et al: In-hospital complication rates after stent treatment of 388 symptomatic intracranial stenoses: results from the INTRASTENT multicentric registry. *Stroke* 41(3):494–498, 2010.
101. Zaidat OO, Klucznik R, Alexander MJ, et al: The NIH registry on use of the Wingspan stent for symptomatic 70-99% intracranial arterial stenosis. *Neurology* 70(17):1518–1524, 2008.
102. Derdeyn CP, Chimowitz MI, Lynn MJ, et al: Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. *Lancet* 383(9914):333–341, 2014.

Stroke Centers and Interventional Cardiology

47

CHRISTOPHER J. WHITE

KEY POINTS

- The three broad categories of stroke are hemorrhagic, thrombotic, and embolic (i.e., artery to artery and chamber to artery).
- Carotid plaque, unlike coronary lesions, most often causes symptoms due to atheroembolization rather than thrombotic occlusion.
- The size of a brain infarction is determined by the time it takes for reperfusion to occur, the patency of the circle of Willis as a collateral source, and the viability of the surrounding penumbra of ischemic tissue.
- The only approved treatment for acute ischemic stroke is intravenous thrombolysis for patients within 3 to 4.5 hours of the onset and without contraindications.
- The risk of intracranial hemorrhage complicating intravenous thrombolytic therapy for stroke is increased in direct relation to the size of the stroke, time to treatment (>3 hours), patient age (>85 years), and uncontrolled hypertension.
- Catheter-based therapy for stroke is reasonable in patients in whom systemic thrombolysis is contraindicated and at risk for larger strokes and greater disabilities.
- Catheter-based therapy for stroke is different from catheter-based therapy for myocardial infarction in that the occlusion is often embolic in origin and the thrombus may be older, more organized, and more resistant to thrombolysis.
- Interventional cardiologists with carotid stent and angiography experience make excellent additions to a multidisciplinary stroke team to provide around-the-clock interventional treatment of stroke patients who are not candidates for intravenous thrombolysis.

Stroke affects approximately 750,000 Americans each year, resulting in almost 150,000 deaths.[1] Stroke is the third leading cause of death in the United States after heart disease and cancer. It is the number one cause of disability and the number one reason for rehabilitation. There are more than 3 million stroke survivors in the United States, and one third of them are young adults with long-term disabilities.[2]

The causes of stroke include hemorrhage, thrombus, and embolus. Embolic strokes may extend artery to artery or from a heart chamber (left atrium or ventricle) to an artery, particularly in patients with atrial fibrillation. A major tenet of treatment of ischemic stroke is that *time is brain*.

The extent of ischemic brain injury is determined by the time from the onset of symptoms to reperfusion; the collateral circulation, including an intact circle of Willis; and the penumbra of viability surrounding the infarcted brain tissue. The penumbra is the region of brain surrounding the infarct area where the blood supply is significantly reduced but energy metabolism is maintained due to collateral flow. The viability of this area depends on the severity and duration of ischemia. If blood flow is rapidly restored, some ischemic brain tissue can be saved. For ischemic and hemorrhagic strokes, there are opportunities to minimize injury early after the onset of the stroke. This puts a premium on the rapid assessment of patients with stroke (Table 47-1).[3]

The goals of treatment include preventing or limiting the mortality and morbidity of the acute event and preventing recurrent events. More than 80% of strokes are ischemic.[4] Ischemic stroke therapy, designed to achieve reperfusion as quickly as possible and minimize further damage, consists of intravenous thrombolysis or catheter-based reperfusion therapy, which can include intraarterial thrombolysis, mechanical thrombectomy, or balloon angioplasty with or without stent placement.

Although rapid initiation of intravenous recombinant tissue-type plasminogen activator (rtPA) with a door-to-needle time of less than 60 minutes is important for a good outcome, the American Heart Association's Get With the Guidelines–Stroke national registry reported that fewer than one in three stroke patients are treated in less than 60 minutes of arrival at the hospital.[5] Although a national heart attack quality initiative has enabled interventional cardiologists to achieve dramatic reductions in door-to-balloon times,[6] acute stroke therapy languishes without a mandate to provide early reperfusion. As of 2013, a goal for door-to-treatment time was not standard of care for stroke therapy as it was for heart attacks.[7] In the United States, most patients with acute ischemic stroke do not receive any form of reperfusion therapy, neither thrombolysis nor catheter-based therapy.[8-10]

NEW IMAGING STRATEGIES

The American Heart Association/American Stroke Association (AHA/ASA) has a class I recommendation to perform noncontrast computed tomography (CT) or magnetic resonance imaging (MRI) for patients who are evaluated within 3 hours of stroke symptom onset to exclude intracranial bleeding.[2] Imaging is the cornerstone for triaging candidates for stroke therapy. The purpose of the baseline CT is to detect conditions that make the patient ineligible for thrombolysis, such as subdural, subarachnoid, or parenchymal intracranial hemorrhage (ICH). CT may also detect mass lesions or hemorrhagic infarctions.

Brain imaging in the setting of an acute stroke has four major goals. First, ICH must be excluded. The patient with ICH has a neurosurgical emergency, and the neurosurgeon needs to be involved immediately. Second, CT and MRI can be used to noninvasively identify intravascular thrombus. Data regarding the geographic distribution and the size of the thrombus burden can assist in deciding on intravenous thrombolysis, intraarterial thrombolysis, or endovascular thrombectomy. Third, the volume of the nonviable, irreversibly infarcted brain predicts the patient's potential for recovery. Fourth, the size of the penumbra, the periinfarct zone of viable but ischemic brain tissue, can be assessed and compared with the volume of infracted brain tissue.

MANAGEMENT OF PHYSIOLOGIC VARIABLES

A cornerstone of managing acute stroke is reducing the risk of recurrent events and minimizing the disability due to the established stroke. Acute therapy involves management of physiologic variables, reperfusion of ischemic tissue, and reduction of the risk of ICH. The patient's level of consciousness, airway status, and oxygenation need to be determined immediately. An electrocardiogram is needed to rule out a concomitant myocardial infarction.

Hypertension

Most patients with stroke have arterial hypertension, which is associated with a poorer outcome, but lower blood pressure may decrease perfusion to the ischemic penumbra, extending the size of the

infarction. The best approach to treatment of hypertension during acute stroke is uncertain. Current recommendations include lowering systolic blood pressure to 220 mm Hg or less and diastolic pressure to 120 mm Hg or less.[11]

Hypoglycemia

Severe hypoglycemia may mimic a stroke and can be detected by a finger-stick glucose determination. Immediate reversal is warranted with intravenous or oral glucose solutions, or both.

Hyperglycemia

Elevated blood glucose levels are associated with worse outcomes for acute stroke patients. This may be related to increased lactate production, which increases infarct size, reduces the effectiveness of thrombolytic therapy, and may increase the risk of hemorrhagic transformation of infarcted brain tissue. Hyperglycemia can increase the extent of infarction in cerebral ischemia, and a blood glucose level above 200 should be controlled to as close to the normal range as possible, using insulin if necessary.

Fever

Fever is associated with poorer stroke outcomes, possibly because of a detrimental effect on brain metabolism, increased free radical production, or deterioration of the blood-brain barrier function. If bacterial endocarditis is suspected, samples for blood cultures should be drawn, and an echocardiogram should be obtained before interventional management. Current recommendations are to use antipyretics to maintain normothermia.

REPERFUSION STRATEGIES

Intravenous Thrombolysis

Intravenous administration of the thrombolytic agent rtPA is the only U.S. Food and Drug Administration (FDA)–approved therapy for acute ischemic stroke (Table 47-2).[12] Intravenous rtPA was shown to be an effective therapy for stroke in a metaanalysis of 2775 patients treated within 6 hours of onset.[13] Patients treated within 90 minutes of onset had almost a threefold increase in good outcomes, a rate that dropped to a 1.6-fold increase if they were treated between 91 and 180 minutes. For those treated between 180 and 270 minutes, the odds ratio for benefit was 1.4 times greater than for placebo. The risk of ICH was greater for the thrombolytic group (5.9%) compared with the placebo group (1.1%).

Intravenous rtPA has limited effectiveness in recanalizing stroke-related arteries with a large clot burden. Recanalization rates range from less than 10% for internal carotid artery occlusions to approximately 50% for middle cerebral artery distal branch occlusions.[14,15] Many experts suggest that when pretreatment computed tomography angiography demonstrates proximal cerebral artery occlusion, endovascular therapy should be offered to improve outcomes.[16]

The risk-to-benefit ratio for intravenous thrombolysis in ischemic stroke is narrow. About 11% more patients benefit at 3 months from intravenous lysis, whereas 6.4% develop ICH. Unfortunately, less than 10% of eligible acute ischemic stroke patients receive reperfusion treatment in the United States.[17] Seven stroke patients must be treated with intravenous lysis to achieve an excellent outcome and avoid one stroke death or disability. For every 100 stroke patients treated with intravenous thrombolysis within 3 hours, 32 have a better outcome despite the 3 who suffer significant ICH. At 1 year after treatment, those treated with intravenous lysis have a 30% increased likelihood of minimal or no disability compared with placebo, but there were no differences in the rates of mortality and recurrent strokes.[18] The risk of hemorrhage is increased for older adult patients and those with larger strokes, diabetes mellitus, a history of stroke, or thrombocytopenia.

The European Cooperative Acute Stroke Study III (ECASS III) tested the efficacy of extending the treatment window for intravenous thrombolysis to between 3 and 4.5 hours after stroke symptom onset. Favorable outcomes occurred for 52.4% of patients assigned to rtPA and for 45.2% of the placebo group (odds ratio [OR] = 1.34; 95% CI, 1.02 to 1.76; $P = .04$). However, the incidence of ICH was higher in the rtPA group (27%) compared with placebo (17.6%, $P = .001$). There was no difference in mortality rates between the two groups.

Important exclusion criteria in this trial included a history of stroke and diabetes mellitus, oral anticoagulation therapy regardless of international normalized ratio (INR), a National Institutes of Health Stroke Scale (NIHSS) score greater than 25, and age greater than 80 years.[19] The AHA/ASA published a science advisory with a class I, level of evidence B recommendation for the administration of rtPA to ischemic stroke patients who are admitted within 3 to 4.5 hours of symptom onset and meet the ECASS III inclusion criteria (Table 47-3).[20]

Treatment of the stroke patient with intravenous thrombolysis includes admission to an intensive care unit with frequent monitoring of vital signs and neurologic status. Arterial, central venous, and

TABLE 47-1 Seven *D*s of Stroke Care

- Detection
- Dispatch
- Delivery
- Door-to-treatment time
- Data
- Decision
- Drug and device administration

TABLE 47-2 Randomized Trials of Thrombolytic Therapy for Acute Ischemic Stroke

Study	Treatment Window	Medications Tested	Delivery	Dose of Agent	No. of Patients
NINDS tPA Stroke Trial (parts 1 and 2)	3 hr (½ 90 min)	tPA	IV	0.9 mg/kg over 1 hr	624
ECASS I	6 hr	tPA	IV	1.1 mg/kg over 1 hr	620
ECASS II	6 hr	tPA	IV	0.9 mg/kg over 1 hr	800
Atlantis A	6 hr	tPA	IV	0.9 mg/kg over 1 hr	142
Atlantis B	0 to 5 hr	tPA	IV	0.9 mg/kg over 1 hr	613
ASK	4 hr	Streptokinase	IV	1.5 million units over 1 hr	340
MAST-I	6 hr	Streptokinase	IV	1.5 million units over 1 hr	622
MAST-E	6 hr	Streptokinase	IV	1.5 million units over 1 hr	310
PROACT II	6 hr	Prourokinase plus IV heparin	IA	9 mg over 2 hr	180

ASK, Australian streptokinase trial; *ECASS,* European Cooperative Acute Stroke Study; *IA,* intraarterial; *IV,* intravenous; *MAST-E,* Multicentre Acute Stroke Trial–Europe; *MAST-I,* Multicentre Acute Stroke Trial–Italy; *NINDS,* National Institute of Neurologic Disorders and Stroke; *PROACT II,* Prolyse in Acute Cerebral Thromboembolism II; *tPA,* tissue plasminogen activator.

bladder catheters should not be placed until at least 2 hours after completion of the thrombolytic agent infusion. An elevated blood pressure may be lowered very cautiously. Head CT should be done if ICH is suspected. All anticoagulants (i.e., antithrombotic and antiplatelet therapy) should be held for at least 24 hours.

Intraarterial Thrombolysis

Intraarterial thrombolysis involves selective placement of a catheter into the cerebral vessels and is analogous in many ways to the treatment of an acute myocardial infarction. There are also major differences between the catheter-based treatment of acute stroke and acute myocardial infarction. The benefit of catheter-based intracranial therapy is the ability to use smaller doses of lytic agents and to employ mechanical clot disruption and extraction with guidewires, balloons, and thrombectomy devices.

The effectiveness of intraarterial thrombolysis has been established in several trials. The Prolyse in Acute Cerebral Thromboembolism II (PROACT II) trial randomized patients admitted within 6 hours with stroke and angiographically documented occlusion of the middle cerebral artery to 9 mg of intraarterial prourokinase plus unfractionated heparin or to unfractionated heparin alone.[21] Successful reperfusion was achieved in 66% of the intraarterial prourokinase group compared with only 18% of the control group ($P < .001$). Forty percent of the prourokinase group had slight or no neurologic disability (modified Rankin Scale score ≤2) at 90 days compared with only 25% of the control group ($P = .04$).

There were more symptomatic cases of ICH in the thrombolytic group compared with controls (11% vs. 3%, $P = .03$). The number needed to treat to make one patient independent was seven. This trial extended the efficacy for stroke treatment to 6 hours from onset of symptoms, but only 2% of all screened patients were enrolled. Contraindications to catheter-directed thrombolysis include recent brain surgery, unknown time of onset of the deficit, uncontrolled hypertension, and CT evidence of hemorrhage or tumor.

Mechanical Thrombectomy

An alternative strategy for reperfusion in stroke patients who are not candidates for thrombolysis is mechanical clot removal, or thrombectomy (Figs. 47-1 through 47-5). There are two approved devices (Merci Retriever, Concentric Medical, Mountain View, CA; Penumbra Stroke System, Penumbra Inc., San Leandro, CA) for mechanical thrombectomy during acute stroke intervention. Both devices have demonstrated superior outcomes compared with historical controls for intracranial thrombus removal.[22,23]

New mechanical thrombectomy devices (Solitaire FR, Covidien, Mansfield, MA; Trevo Proview Retriever, Stryker Neurovascular, Mountain View, CA) are self-expanding, stentlike devices (Fig. 47-6) that offer improved deliverability compared with conventional

TABLE 47-3 Eligibility for Thrombolysis for Stroke

Indication: ischemic stroke within 3 hours of onset of symptoms

Clinical contraindications
- History of intracranial hemorrhage (ICH)
- Systolic blood pressure >185, diastolic blood pressure >110 mm Hg
- Rapid improvement in neurologic status
- Mild neurologic impairment
- Symptoms of subarachnoid bleeding
- Stroke or head trauma within the last 3 months
- Gastrointestinal or genitourinary hemorrhage within 3 weeks
- Major surgery within 3 weeks
- Recent heart attack
- Seizure with stroke
- Taking oral anticoagulants
- Received heparin within 48 hours

Radiologic contraindications
- Evidence of ICH

Laboratory contraindications
- International normalized ratio >1.7
- Platelet count <100,000
- Elevated activated partial thromboplastin time
- Blood glucose <50 mg/dL

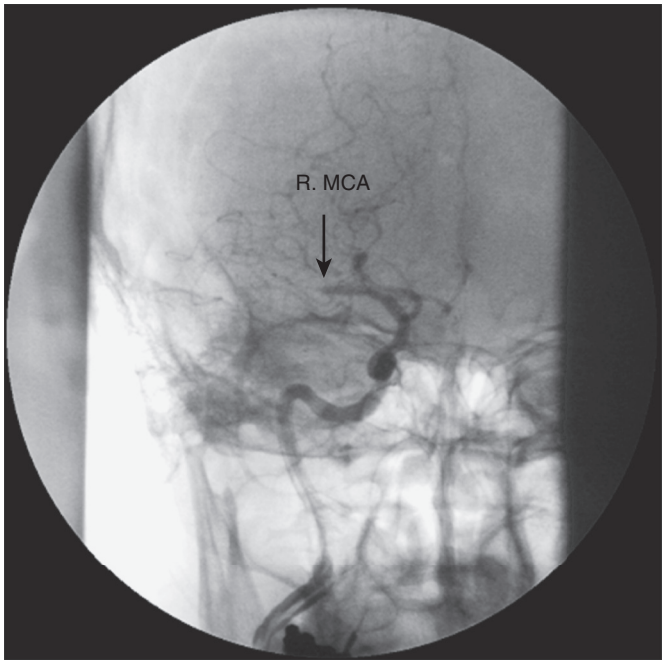

FIGURE 47-1 Patient with atrial fibrillation had an acute right middle cerebral artery occlusion.

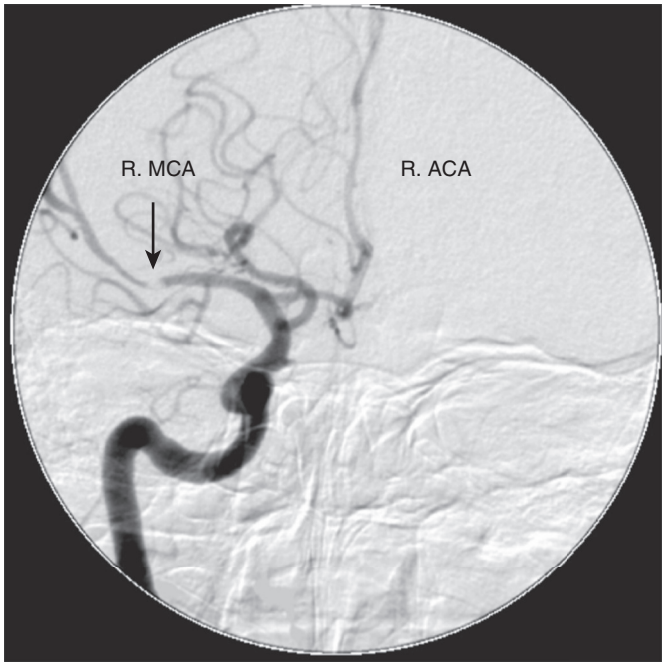

FIGURE 47-2 Intracranial administration of 2 mg of recombinant tissue-type plasminogen activator produced partial recanalization *(arrow)* of the right middle cerebral artery (MCA). *ACA,* Anterior cerebral artery.

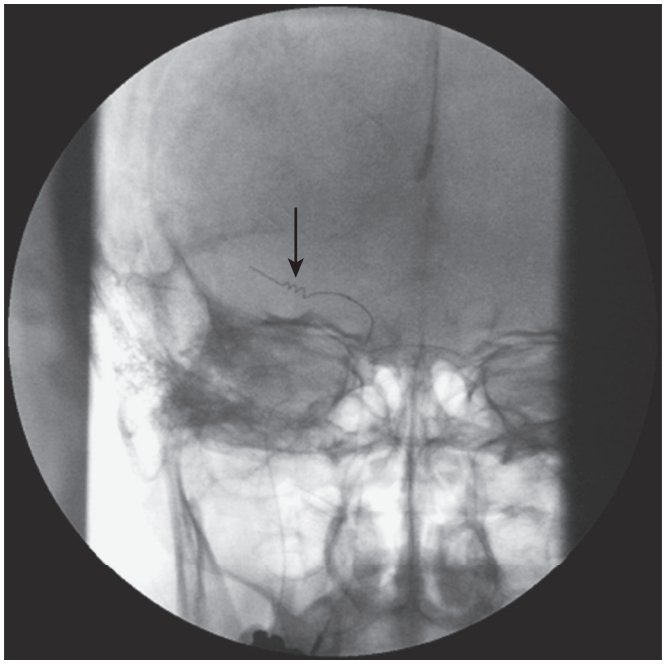

FIGURE 47-3 Placement of the MERCI thrombectomy catheter *(arrow)* in the right middle cerebral artery.

FIGURE 47-5 Result after recanalization of the right middle cerebral artery.

FIGURE 47-4 Retrieval of fibrous clot with the MERCI device. The imprint from the left atrial appendage can be seen.

mechanical thrombectomy catheters (i.e., Merci and Penumbra), which tend to be bulky and can be difficult to manipulate in the tortuous intracranial vessels that are encased in skull bone.[24,25]

For patients admitted within 4.5 hours of stroke onset with occlusion of a large intracranial vessel, one of the highest reperfusion rates (95%) for stroke thrombectomy was reported with a mean door-to-device time of 95 ± 33 minutes.[26] This result is consistent with results of randomized trial that demonstrated the superiority of the Solitaire FR device compared with the Merci Retriever.[27] Almost two thirds of these high-risk patients had a favorable clinical outcome (modified Rankin Scale score ≤2) at 3 months, a very low risk of ICH (2.5%), and an acceptable mortality rate (12.5%).

Angioplasty and Stent Placement

Balloon angioplasty is commonly performed for residual stenoses after intraarterial lysis or mechanical thrombectomy. Balloons are commonly undersized to avoid arterial dissection and perforation. Often, lesions manifest acute recoil or flow-limiting dissections necessitating the use of off-label stents. There is interest in a strategy of immediate stent placement, similar to how acute myocardial infarction is treated. Immediate direct stenting of the culprit lesion can minimize the time for reperfusion of the infarct zone.[28-35] Three stent systems are FDA approved for intracranial use (but not for acute stroke) in the United States: Neuroform (Boston Scientific, Natick, MA), Wingspan (Boston Scientific, Natick, MA), and Enterprise (Codman Neurovascular, Raynham, MA). These devices are self-expanding stents with extremely deliverable catheters to navigate the tortuous intracranial circulation.

The Stent-Assisted Recanalization in Acute Ischemic Stroke (SARIS) trial was a prospective, FDA-approved, single-site registry designed to test the efficacy of direct stent placement in acute stroke. Twenty patients were enrolled with severe impairment (NIHSS score = 14 ± 3.8) with a duration of 313 ± 114 minutes from symptom onset to intervention. On baseline angiography, 17 patients had Thrombolysis in Myocardial Infarction (TIMI) 0 flow, and 3 patients had TIMI 1 flow. All patients were successfully recanalized (TIMI 3, 60%; TIMI 2, 40%). Serious complications included ICH in three patients, one of whom was symptomatic. The 1-month mortality rate was 25%. This rapid reperfusion strategy demonstrated marked improvement in the discharge NIHSS score (7.4), and at 1 month, almost one half of the patients were independently functioning with a modified Rankin Scale score of 1.[36] These registry data suggest a potential role for early endovascular therapy in selected stroke patients, but larger randomized trials are needed to quantify the risk-benefit ratio and to define better patient selection criteria.

Data strongly support the linkage between early restoration of blood flow and good clinical outcomes. A 30-minute delay in onset to

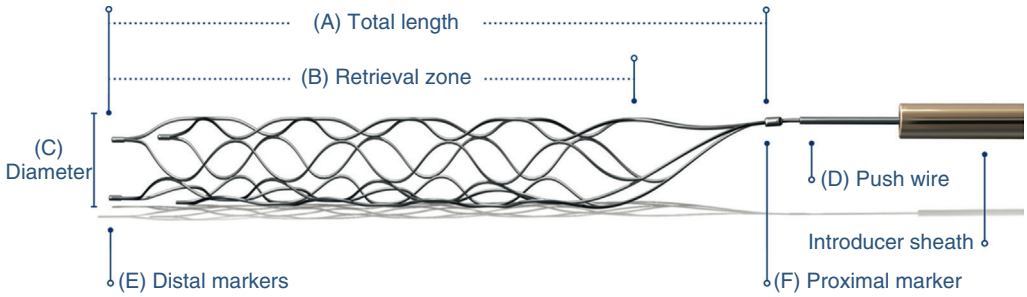

FIGURE 47-6 Components of the Solitaire catheter (Courtesy Covidien, Plymouth, NH).

TABLE 47-4 Comparison of Catheter-Based Therapy in the Ochsner Clinic Series With Intravenous and Intraarterial Thrombolysis in Stroke Treatment Trials

Study	Patients (*N*)	Age, % Males	NIHSS Baseline	Symptomatic ICH	Mortality at Follow-Up	Good Outcome at Follow-up
NINDS	168	69 yr, 57%	14	6.4%	17% at 3 mo	39%
STARS	389	69 yr, 55%	13	3.3%	13% at 1 mo	35%
PROACT II	121	64 yr, 58%	17	10%	25% at 3 mo	26%
Ochsner Clinic	42	64 yr; 44%	16	12%	9.5% at 1 mo	45%

ICH, Intracranial hemorrhage; *NIHSS,* National Institutes of Health Stroke Scale; *NINDS,* National Institute of Neurologic Disorders and Stroke; *PROACT II,* Prolyse in Acute Cerebral Thromboembolism II; *STARS,* Standard Treatment With Alteplase to Reverse Stroke Study.

reperfusion delay caused a 20% increase in mortality and ICH, and each 30-minute delay in onset to reperfusion delay resulted in a 20% reduction in good or excellent outcomes.[37]

The demonstration that early endovascular reperfusion is similar in principle to early intravenous thrombolysis reperfusion mandates a system change in hospital care. We must focus on a rapid transition from intravenous to endovascular therapies, minimizing time delays.

Neuroprotection

Although many drugs and devices are under investigation to prolong the life of the penumbra, maintain the blood-brain barrier, and reduce hemorrhage and reperfusion injury, none has been proved effective in humans. The latest AHA/ASA Guidelines for the Early Management of Adults With Ischemic Stroke, published in 2007, conclude that "no intervention with putative neuroprotective actions has been established as effective in improving outcomes after stroke, and therefore none currently can be recommended," assigning neuroprotection a class III recommendation.[2]

Despite this pessimism, there is enthusiasm among investigators for systemic hypothermia as an emerging therapy for stroke. Hypothermia provides neuroprotection by decreasing cellular metabolism, limiting cytotoxicity, reducing free radical formation, and preventing blood-brain barrier breakdown. Mechanisms of cooling include invasive central venous catheters and surface methods. Many data support the neuroprotective effects of hypothermia in animal models, but there are no comparative data for humans. The benefits of hypothermia are facilitated by early initiation.[38,39]

STROKE CENTERS

Stroke centers are a key component of building a successful stroke program. The concept of stroke centers was outlined by the Brain Attack Coalition (BAC) in 2000.[40] Stroke centers are modeled after streamlined trauma care and acute myocardial infarction care in that they require rapid identification and triage of patients to provide timely access to care.

This systems-based approach requires community-wide coordination and planning. It includes empowering ambulances to bypass hospitals to bring stroke patients to facilities with specialized treatment capabilities. Certified Primary Stroke Centers provide basic acute stroke care, including the initial assessment and treatment of stroke patients by stroke teams, stroke units, and 24-hour access to CT scans. Comprehensive Stroke Centers[41] are intended for complicated or high-risk stroke patients and offer specialized stroke personnel, including specialized neurologic intensive care unit; advanced neuroimaging capabilities; on-demand neurosurgical and endovascular interventional capabilities; and the infrastructure to support these activities.

The Comprehensive Stroke Center has an endovascular specialist and neurosurgeon available at all times for consultation and immediate procedural support, including aneurysm clipping, ventriculostomy placement, intracranial pressure transducer placement, and percutaneous, catheter-based therapy for stroke. Dedicated stroke units enable close monitoring of stroke patients by providers accustomed to treating stroke patients and familiar with their unique needs. Part of the infrastructure includes rigorous data collection and outcomes assessment for stroke patients to advance the field of stroke care. Community education about stroke risk factors and recognition and ambulance bypass systems are crucial components in building successful stroke treatment centers.

THE ROLE OF CARDIOLOGY IN A STROKE PROGRAM

There are similarities in the treatment of acute stroke and acute myocardial infarction. Both emphasize achieving early reperfusion driven by early patient recognition of symptoms, early hospital admission, and early treatment initiation. However, there are also significant differences. For example, stroke thrombi usually have an embolic origin, making them older, more organized, and more resistant to lysis. The volume of clot is larger in stroke patients, and cerebral vessel tortuosity can make clot-busting therapy more difficult than the treatment of acute myocardial infarction.

My colleagues and I have reported our experience with a multidisciplinary team that included interventional cardiologists and provided emergent endovascular therapy for patients with acute ischemic stroke who were ineligible for intravenous thrombolysis (Table 47-4).[42,43] A stroke neurologist in consultation with the interventional cardiologist and neuroradiologist is initially called to assess the patient and

determine the need for intervention. We considered stroke patients eligible for intervention if they were less than 8 hours from symptom onset. No specific cutoff or lower limit was used for their NIHSS score to exclude patients from intervention. Instead, patients were eligible if they had a serious deficit, even if the corresponding NIHSS score was comparatively low (e.g., monocular blindness).

In reviewing the most recent 124 consecutive stroke patients treated with catheter-based therapy, we found that successful revascularization led to good neurologic outcomes for selected patients. Medical comorbidities and increased age (>65 years) contributed to poor outcomes for stroke patients despite successful recanalization. There were no differences in outcomes based on the subspecialist treating the patient or the treatment device used. In support of broadening the number of physicians qualified to perform catheter-based stroke interventions, we demonstrated that interventional cardiologists participating in a stroke team achieved comparable outcomes for acute stroke patients to those of neurointerventionalists.

The most important problem facing stroke therapy is a lack of on-demand interventional therapy for most patients who are not candidates for lysis. Unlike the national standard of care for heart attacks, for which an army of interventional cardiologists have been mobilized behind a national effort to minimize door-to-balloon time for early reperfusion, endovascular therapy for stroke is uncommon because of the paucity of neurointerventional physicians to provide this service around the clock in most communities.[9] Relatively few neuroradiologists are available to provide coverage all times in every hospital that accepts stroke patients for treatment. One way to expand this service is to take advantage of the army of manpower available from interventional cardiology (Fig. 47-7).[44]

Interventional cardiologists are currently providing around-the-clock interventional responses for acute myocardial infarction. With training and formation of a multidisciplinary stroke treatment group that includes neurology, radiology, and surgical specialties, the treatment capabilities that are so badly needed in many communities could be extended. Many interventional cardiologists are currently performing carotid stent placement and intracerebral angiography. It is a reasonable and achievable step to enable competent carotid interventionalists who have cerebral angiography experience to perform acute stroke intervention (Table 47-5).

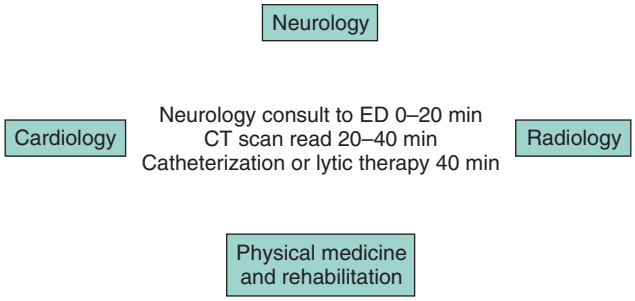

FIGURE 47-7 The Ochsner Health System acute stroke intervention service (OASIS) provides multidisciplinary services coordinated by the neurology department for rapid assessment and treatment of stroke.

TABLE 47-5 Strengths and Weaknesses of Cardiologists on the Stroke Intervention Team

Strengths
Excellent catheter skills
Experience with carotid stent placement and cerebral angiography
Management of atherosclerotic risk factors for stroke
Rapid response 24/7 to assist and relieve interventional neuroradiology
Management of coexistent cardiac disease (e.g., atrial fibrillation)
Weaknesses
Limited knowledge of
Cerebral anatomy
Computed tomography and magnetic resonance imaging interpretation
Localization of deficit
National Institutes of Health Stroke Scale and neurologic examination
Management of stroke complications (e.g., intracranial hemorrhage)

Interventional cardiologists are poised to fill the significant manpower shortage in treating acute stroke. As skilled angiographers, experienced interventionalists, and productive members of a multidisciplinary team, they can meet the challenge of providing reperfusion therapy for this devastating disease.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al: Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation* 127:e6–e245, 2013.
2. Adams HP, Jr, del Zoppo G, Alberts MJ, et al: Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Circulation* 115:e478–e534, 2007.
3. Adams HP, Jr, Adams RJ, Brott T, et al: Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke Council of the American Stroke Association. *Stroke* 34:1056–1083, 2003.
4. Pencina MJ, D'Agostino RB, Sr, Larson MG, et al: Predicting the 30-year risk of cardiovascular disease: the framingham heart study. *Circulation* 119:3078–3084, 2009.
5. Fonarow GC, Smith EE, Saver JL, et al: Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. *Circulation* 123:750–758, 2011.
6. Krumholz HM, Herrin J, Miller LE, et al: Improvements in door-to-balloon time in the United States, 2005 to 2010. *Circulation* 124:1038–1045, 2011.
7. Patel RD, Saver JL: Evolution of reperfusion therapies for acute brain and acute myocardial ischemia: a systematic, comparative analysis. *Stroke* 44:94–98, 2013.
8. Demaerschalk BM, Yip TR: Economic benefit of increasing utilization of intravenous tissue plasminogen activator for acute ischemic stroke in the United States. *Stroke* 36:2500–2503, 2005.
9. Suzuki S, Saver JL, Scott P, et al: Access to intra-arterial therapies for acute ischemic stroke: an analysis of the US population. *AJNR Am J Neuroradiol* 25:1802–1806, 2004.
10. Cloft HJ, Rabinstein A, Lanzino G, Kallmes DF: Intra-arterial stroke therapy: an assessment of demand and available work force. *AJNR Am J Neuroradiol* 30:453–458, 2009.
11. Dawson J, Walters M: New and emerging treatments for stroke. *Br Med Bull* 77-78:87–102, 2006.
12. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 333:1581–1587, 1995.
13. Hacke W, Donnan G, Fieschi C, et al: Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 363:768–774, 2004.
14. Wolpert SM, Bruckmann H, Greenlee R, et al: Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. The rt-PA Acute Stroke Study Group. *AJNR Am J Neuroradiol* 14:3–13, 1993.
15. Alexandrov AV, Grotta JC: Arterial reocclusion in stroke patients treated with intravenous tissue plasminogen activator. *Neurology* 59:862–867, 2002.
16. Papanagiotou P, Roth C, Walter S, et al: Carotid artery stenting in acute stroke. *J Am Coll Cardiol* 58:2363–2369, 2011.
17. Reeves MJ, Arora S, Broderick JP, et al: Acute stroke care in the US: results from 4 pilot prototypes of the Paul Coverdell National Acute Stroke Registry. *Stroke* 36:1232–1240, 2005.
18. Kwiatkowski TG, Libman RB, Frankel M, et al: Effects of tissue plasminogen activator for acute ischemic stroke at one year. National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. *N Engl J Med* 340:1781–1787, 1999.
19. Hacke W, Kaste M, Bluhmki E, et al: Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 359:1317–1329, 2008.
20. Del Zoppo GJ, Saver JL, Jauch EC, Adams HP, Jr: Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. *Stroke* 40:2945–2948, 2009.
21. Furlan A, Higashida R, Wechsler L, et al: Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. *JAMA* 282:2003–2011, 1999.
22. The Penumbra Pivotal Stroke Trial Investigators: The Penumbra Pivotal Stroke Trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke* 40(8):2761–2768, 2009.
23. Nogueira RG, Liebeskind DS, Sung G, et al: Predictors of good clinical outcomes, mortality, and successful revascularization in patients with acute ischemic stroke undergoing thrombectomy: pooled analysis of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI Trials. *Stroke* 40:3777–3783, 2009.
24. Nogueira RG, Lutsep HL, Gupta R, et al: Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. *Lancet* 380:1231–1240, 2012.
25. Roth C, Papanagiotou P, Behnke S, et al: Stent-assisted mechanical recanalization for treatment of acute intracerebral artery occlusions. *Stroke* 41:2559–2567, 2010.
26. Roth C, Reith W, Walter S, et al: Mechanical recanalization with flow restoration in acute ischemic stroke: the ReFlow (mechanical recanalization with flow restoration in acute ischemic stroke) study. *JACC Cardiovasc Interv* 6:386–391, 2013.
27. Saver JL, Jahan R, Levy EI, et al: Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet* 380:1241–1249, 2012.

28. Fiorella DJ, Levy EI, Turk AS, et al: Target lesion revascularization after wingspan: assessment of safety and durability. *Stroke* 40:106–110, 2009.
29. Levy EI, Mehta R, Gupta R, et al: Self-expanding stents for recanalization of acute cerebrovascular occlusions. *AJNR Am J Neuroradiol* 28:816–822, 2007.
30. Turk AS, Levy EI, Albuquerque FC, et al: Influence of patient age and stenosis location on wingspan in-stent restenosis. *AJNR Am J Neuroradiol* 29:23–27, 2008.
31. Brekenfeld C, Schroth G, Mattle HP, et al: Stent placement in acute cerebral artery occlusion: use of a self-expandable intracranial stent for acute stroke treatment. *Stroke* 40:847–852, 2009.
32. Levy EI, Turk AS, Albuquerque FC, et al: Wingspan in-stent restenosis and thrombosis: incidence, clinical presentation, and management. *Neurosurgery* 61:644–650, discussion 650-641, 2007.
33. Zaidat OO, Wolfe T, Hussain SI, et al: Interventional acute ischemic stroke therapy with intracranial self-expanding stent. *Stroke* 39:2392–2395, 2008.
34. Mocco J, Snyder KV, Albuquerque FC, et al: Treatment of intracranial aneurysms with the Enterprise stent: a multicenter registry. *J Neurosurg* 110:35–39, 2009.
35. Mathews MS, Sharma J, Snyder KV, et al: Safety, effectiveness, and practicality of endovascular therapy within the first 3 hours of acute ischemic stroke onset. *Neurosurgery* 65:860–865, discussion 865, 2009.
36. Levy EI, Siddiqui AH, Crumlish A, et al: First Food and Drug Administration-approved prospective trial of primary intracranial stenting for acute stroke: SARIS (stent-assisted recanalization in acute ischemic stroke). *Stroke* 40:3552–3556, 2009.
37. Mazighi M, Chaudhry SA, Ribo M, et al: Impact of onset-to-reperfusion time on stroke mortality: a collaborative pooled analysis. *Circulation* 127:1980–1985, 2013.
38. Berger C, Schramm P, Schwab S: Reduction of diffusion-weighted MRI lesion volume after early moderate hypothermia in ischemic stroke. *Stroke* 36:e56–e58, 2005.
39. Holzer M: Devices for rapid induction of hypothermia. *Eur J Anaesthesiol Suppl* 42:31–38, 2008.
40. Alberts MJ, Hademenos G, Latchaw RE, et al: Recommendations for the establishment of primary stroke centers. *JAMA* 283:3102–3109, 2000.
41. Alberts MJ, Latchaw RE, Selman WR, et al: Recommendations for comprehensive stroke centers: a consensus statement from the brain attack coalition. *Stroke* 36:1597–1616, 2005.
42. Ramee SR, Subramanian R, Felberg RA, et al: Catheter-based treatment for patients with acute ischemic stroke ineligible for intravenous thrombolysis. *Stroke* 35:e109–e111, 2004.
43. DeVries JT, White CJ, Collins TJ, et al: Acute stroke intervention by interventional cardiologists. *Catheter Cardiovasc Interv* 73:692–698, 2009.
44. White CJ, Cates CU, Cowley MJ, et al: Interventional stroke therapy: current state of the art and needs assessment. *Catheter Cardiovasc Interv* 70:471–476, 2007.

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48 Imaging for Intracardiac Interventions

FEMI PHILIP | MEHDI SHISHEHBOR | SAMIR R. KAPADIA

KEY POINTS

- Structural heart disease interventions require multimodality imaging in the cardiac catheterization laboratory, including fluoroscopy, ultrasound-based, and three-dimensional (3D) rotational imaging.
- Fluoroscopy allows real-time use of radiopaque devices, and intraprocedural ultrasound imaging shows non–radiopaque cardiac structures and helps with the safety and precision of the procedures.
- Fluoroscopy visualizes a large area of heart with excellent temporal and spatial resolution and projects 3D in two dimensions (2D). Therefore multiple projections (commonly biplane imaging) are needed to precisely locate devices and structures in 3D space.
- The ability to acquire a 3D dataset with rotational imaging in the cardiac catheterization laboratory has revolutionized imaging and fusion possibilities.
- 3D and biplane echocardiography help considerably to localize structures and devices. Live 3D color imaging and fusion imaging will further advance this field in the near future.
- Ultrasound-based imaging, either intracardiac echocardiography (ICE) or transesophageal echocardiography (TEE), is used to guide septal interventions (transseptal puncture, patent foramen ovale and atrial septal defect closures), left atrial appendage closure, and mitral valve interventions. It is increasingly being used during transcatheter valve implantations and for paravalvular leak closure.
- Synthesis of fluoroscopic, computed tomographic, and echocardiographic images in the catheterization laboratory is expanding the scope of structural heart interventions.

Intracardiac therapies for structural heart lesions continue to expand in scope and complexity due to advances in the imaging techniques. Structural heart interventions require an understanding of complex three-dimensional (3D) anatomic relationships, and soft tissue visualization requires the addition of ultrasound-based imaging modalities, computed tomography (CT), and/or cardiac magnetic resonance imaging. In this regard, imaging has become an integral part of these procedures, from preprocedural planning and patient selection to intraprocedural guidance, postprocedural assessment of results, and long-term follow-up care. These imaging modalities require expertise in multiple imaging modalities and real-time integration for a successful procedural outcome. This chapter first highlights the structural anatomy using each of these imaging modalities and then provides a guide to their use during intracardiac interventions.

FLUOROSCOPY AND ANGIOGRAPHY

Left-Sided Structures

Left Atrial Angiogram

A left atrial angiogram is rarely performed by direct injection, but the left atrium is frequently seen on the levophase of the right-sided angiogram or ventriculogram. Direct injection in the left atrial appendage (LAA) is performed to evaluate the anatomy before percutaneous closure (Fig. 48-1). Typically, the right anterior oblique (RAO) cranial view shows the LAA opening in the medial-lateral diameter and the RAO caudal view delineates the superior-inferior opening diameter (see Fig. 48-1). These views are also important to study the shape of the LAA, which is critical in percutaneous closure planning.[1]

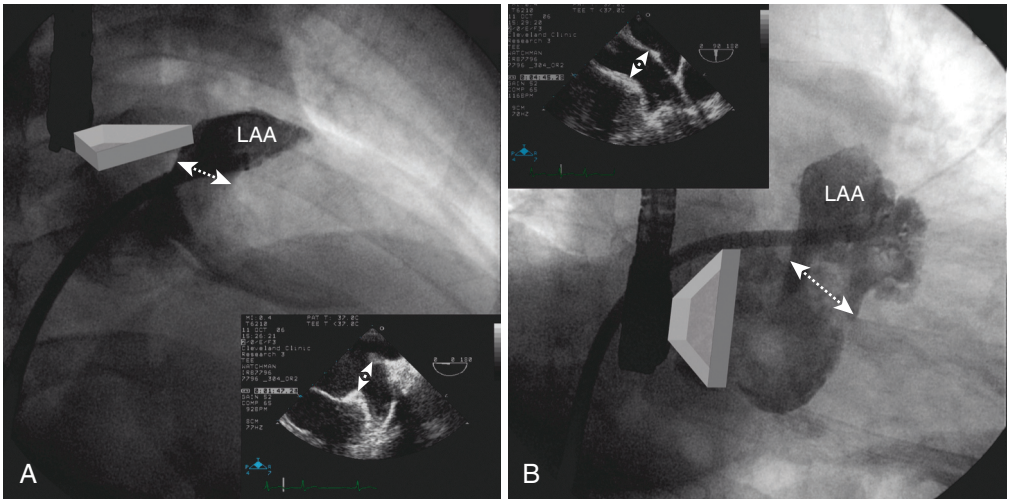


FIGURE 48-1 **A,** Right anterior oblique (RAO) cranial view of left atrial appendage (LAA) injection. The "width" of the LAA opening is shown by the *dotted arrows* and is also depicted in the horizontal view in transesophageal echocardiography (TEE) *(insert)*. **B,** RAO caudal view of the LAA in the same subject shows the "height" of the opening *(dotted arrows),* which corresponds to a vertical view by TEE *(insert)*.

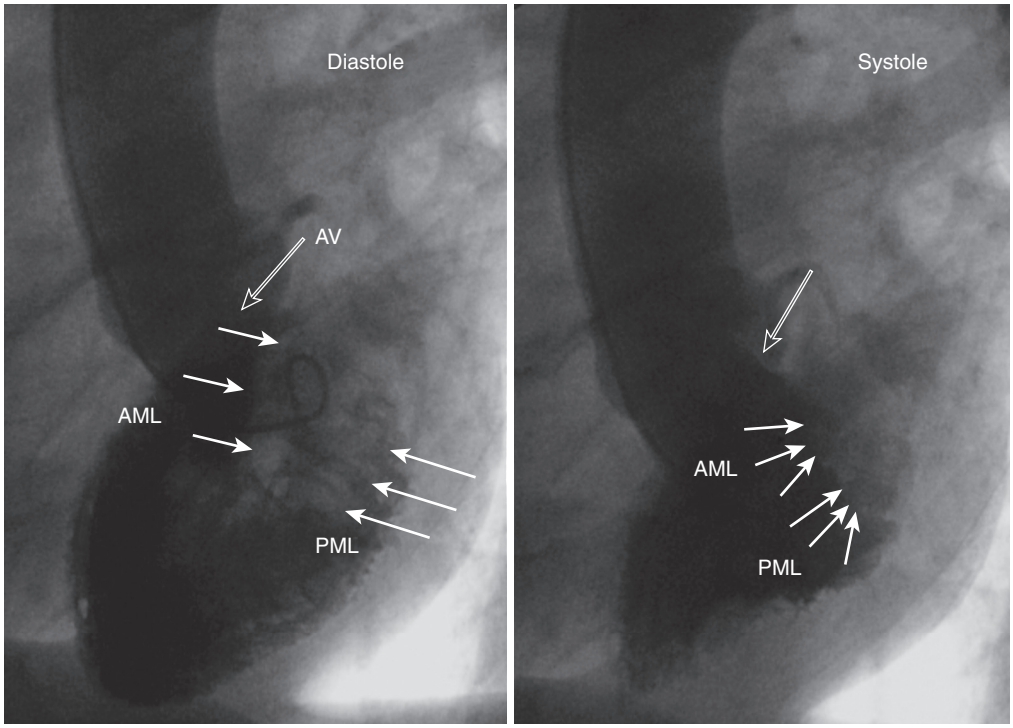


FIGURE 48-2 Right anterior oblique (RAO) 30-degree view of the left ventricle in diastole and systole. The aortic valve *(open arrow),* mitral valve *(solid white arrows),* and papillary muscles are shown. In diastole *(left panel),* the mitral valve is open and there is clearance of contrast as the blood enters the left ventricle from the left atrium. Anterior and posterior leaflets are separate in diastole. In systole *(right panel),* the mitral valve is closed and the aortic valve is open. In this view, the anterior, apex, and inferior walls can be assessed. *AML,* Anterior mitral leaflet; *AV,* aortic valve; *PML,* posterior mitral leaflet.

Left Ventriculogram

The left ventricle is typically divided into inflow and outflow segments.[2] The inflow consists of the mitral valve (MV) apparatus, and the outflow portion includes the apex, left ventricular outflow tract (LVOT), and aortic valve (Fig. 48-2). The angle between the inflow and outflow tract is approximately 30 degrees in young persons and increases with "unfolding of aorta." Because the interventricular septum maintains its position while the aorta is transposed anteriorly and more horizontally, there can be "bulging" of the septum.

A left ventriculogram is typically performed in the RAO 30-degree projection; however, different views should be considered depending on the purpose of the procedure. The RAO projection delineates the separation of atria from ventricles. Various structures seen on the RAO projection are shown in Figure 48-2. The anterior and inferior walls and the apex are seen without overlap in this view. The lateral wall and septum are overlapped, and their motion is perpendicular to the x-ray beam. Anterior and posterior MV leaflets are seen from the side in a longitudinal plane along with the inflow portion of the ventricle. It is critical to recognize this relationship when performing MV intervention and devices must be advanced coaxially in the inflow (e.g., Inoue-Balloon catheter [Toray Medical, Tokyo], MitraClip [Abbott Vascular, Abbott Park, IL]). Anterolateral and posteromedial commissures are superior and inferior in this view, and there is significant overlap between various segments of the anterior and posterior leaflets. The aortic valve and the coronary sinus can be appreciated in this view. The right coronary sinus and the noncoronary sinus are located on the right and left sides of the aortic root, respectively. The left coronary sinus is located between the right coronary sinus and the noncoronary sinus. In this view, the ostia of the right and left coronary arteries are located close to one another; this is useful for anterior/posterior localization in the aortic root.

The anatomic structures seen in the left anterior oblique (LAO) view are outlined in Figure 48-3. The LAO projection delineates the intraventricular groove and separates right ventricle from the left ventricle. In order to align mitral inflow to the apex of the ventricle, some caudal angulation can be added to the LAO projection. This allows one to see the left ventricle in end-on projection so that papillary muscles, as well as anterior and posterior leaflets, can be clearly identified. The inflow and outflow of the ventricle are typically well separated in this view. The left and the right coronary sinuses and coronary ostia are separated clearly, and the noncoronary sinus is overlapped by the right coronary cusp (albeit located lower in the aortic root).

Unconventional views allow better delineation of certain parts of the left ventricle. The LAO cranial projection is typically better for assessment of the LVOT. The purpose of this projection is to see the anterior leaflet of the MV in a longitudinal view when it does not overlap the interventicular septum. It is also the view of choice to see the interventricular septum in the muscular portion for assessment of a ventricular septal defect. The LAO caudal projection allows one to see the MV end-on and to place the anterolateral and posteromedial commissures in their proper contexts: the bifurcation of left main coronary artery into left anterior descending and left circumflex arteries and the posterior descending artery, respectively.

Aortogram

An ascending aortogram is performed to examine the aortic valve and root, aortic aneurysms, and, rarely, aortic dissections. The aortogram is performed in the RAO (30-degree) and LAO (40-degree) projections. A high rate of injection (20 mL/sec for 2-3 sec) and proper catheter positioning allows assessment of the different aortic cusps. The aortogram is usually performed with a multi-sidehole pigtail catheter positioned 2 to 3 cm above the sinus of Valsalva (Fig. 48-4). It is important to recognize various anatomic relationships on fluoroscopy, including the relation of the noncoronary cusp to the interatrial septum (IAS) for transseptal puncture, the superior vena cava (SVC) for ICE imaging, and the anterior leaflet of the MV for antegrade interventions.

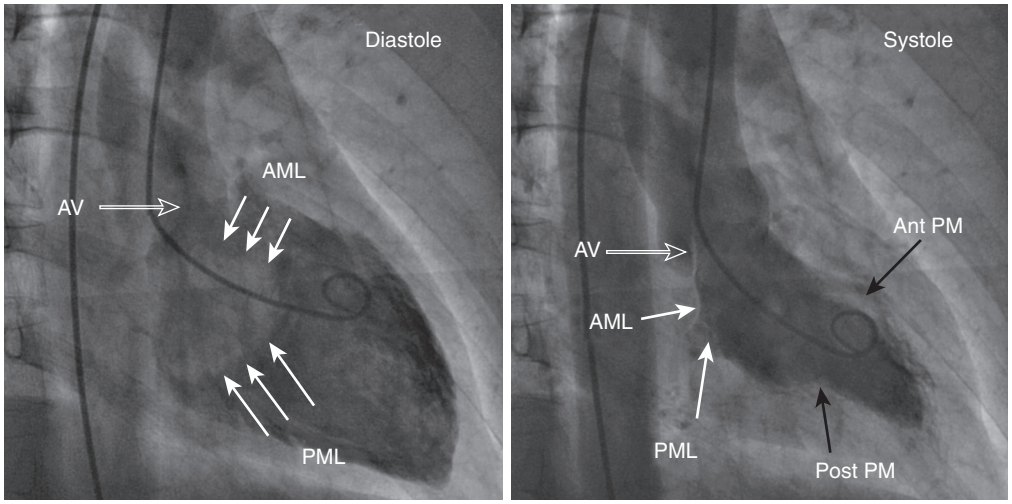


FIGURE 48-3 Left anterior oblique (LAO) 60-degree view of the left ventricle in diastole and systole. The aortic valve *(open arrow),* mitral valve *(solid white arrows),* and papillary muscles *(solid black arrows)* are shown. In diastole *(left panel),* the mitral valve is open and there is clearance of contrast as the blood without contrast enters the left ventricle from the left atrium. Anterior and posterior leaflets are separate in diastole. In this view, the lateral and the septal walls can be assessed. *AML,* Anterior mitral leaflet; *Ant PM,* anterolateral papillary muscle, *AV,* aortic valve; *PML,* posterior mitral leaflet; *Post PM,* posterolateral papillary muscle.

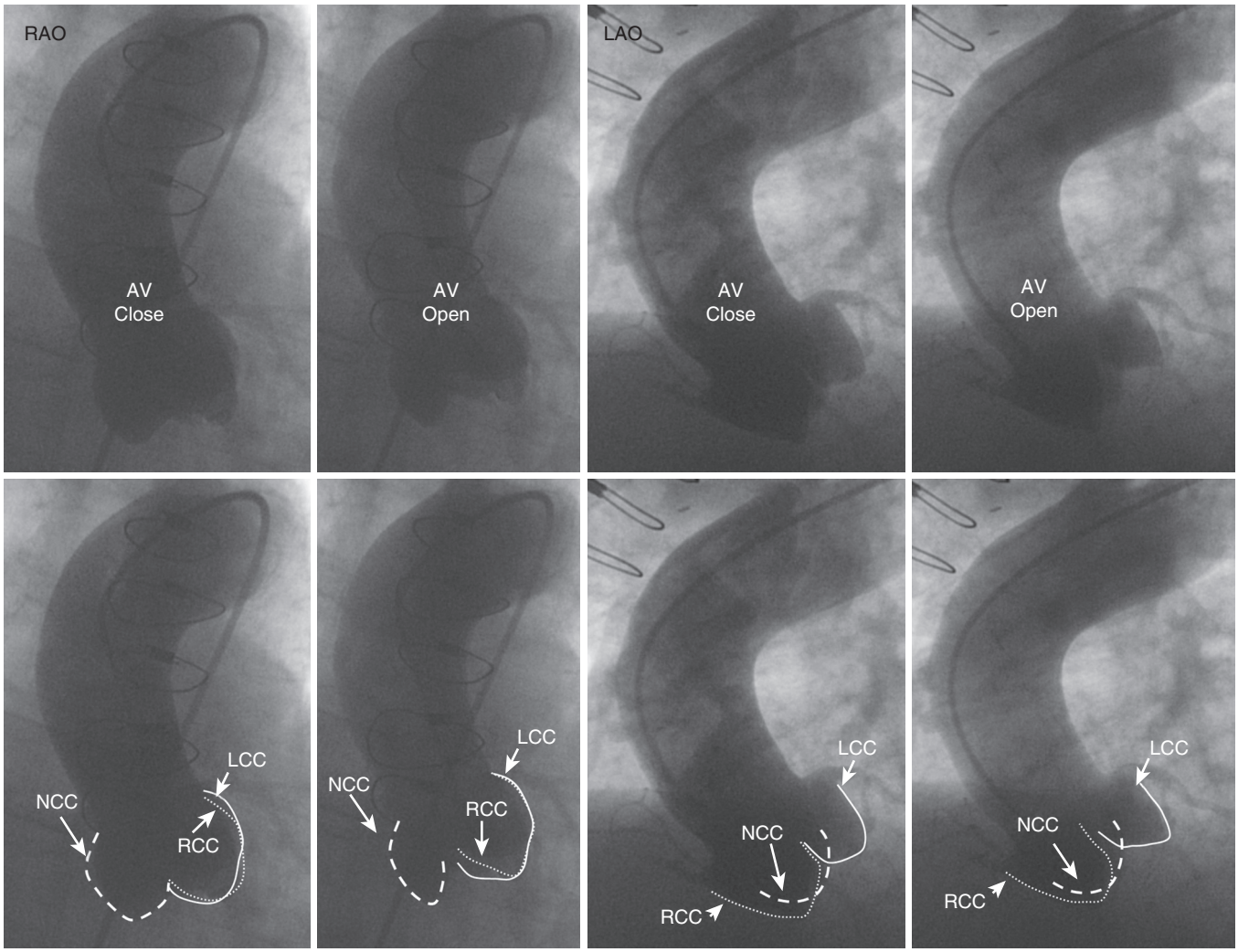


FIGURE 48-4 Shallow right anterior oblique (RAO) and left anterior oblique (LAO) aortograms in a subject with aortic stenosis and restricted leaflet motion *(top row).* For each view, the aortic valve (AV) is shown in closed and open position. The corresponding structures for each aortogram are delineated by dashed lines and arrows in the bottom panel. Notice the overlap of the left and right coronary cusps in the RAO projection and the right and noncoronary cusps in the LAO projection. *LCC,* Left coronary cusp; *NCC,* noncoronary cusp; *RCC,* right coronary cusp.

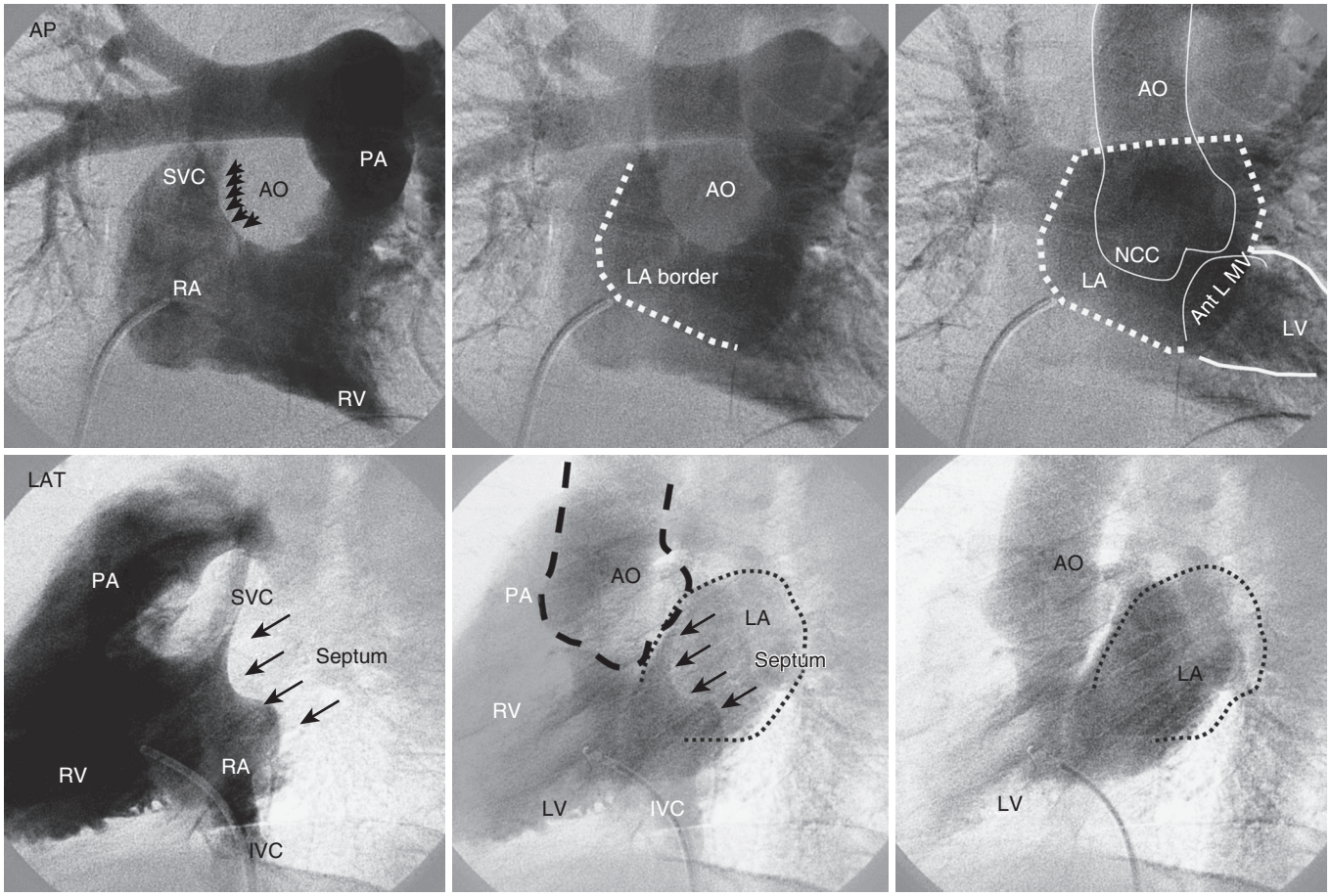


FIGURE 48-5 Anteroposterior (AP) and lateral (LAT) views of a right atrial angiogram are shown in the top and bottom row, respectively. Dextro phase *(left panel),* levo phase *(right panel),* and two phases superimposed on each other *(middle panel)* are presented. *antL MV,* Anterior leaflet of the mitral valve; *AO,* aorta; *IVC,* inferior vena cava; *LA,* left atrium; *LV,* left ventricle; *NCC,* noncoronary cusp; *PA,* pulmonary artery; *RA,* right atrium; *RV,* right ventricle; *SVC,* superior vena cava.

These relationships are well demonstrated in a posteroanterior (PA) view on a right atrial angiogram (Fig. 48-5).

Right-Sided Structures

Right Atrial Angiogram

A right atrial angiogram is typically performed to look at the IAS. A pigtail catheter, Berman Angiographic balloon catheter, or National Institutes of Health (NIH) catheter with rapid injection rate is used. Various anatomic structures are shown in Figure 48-5. This procedure can be used to guide transeptal puncture and closure of a patent foreman ovale (PFO) or atrial septal defect (ASD).

Right Ventriculogram

The right ventricle is a trabeculated ventricle with inflow and outflow tracts at right angles to each other. Most typically, a right ventriculogram is performed in anteroposterior (AP) and lateral projection with the catheter positioned in midcavity to prevent ventricular ectopy. A pigtail, Berman Angiographic, or NIH catheter can be used to perform a right ventriculogram. The rate of injection (>25 mL/sec) and the volume of contrast (60 mL) administered must be higher in order to delineate the components of the right ventricular cavity. A right ventriculogram can be used to assess the tricuspid valve, pulmonary valve, right ventricular outflow tract (RVOT), pulmonary arteries, left atrium (interatrial septum), and pulmonary veins (see Fig. 48-5).

Pulmonary Angiogram

Pulmonary angiography is the gold standard technique for diagnosing pulmonary embolism.[3] In addition, it is used to assess a variety of other conditions such as pulmonary valve stenosis, pulmonary artery stenosis, anomalous pulmonary venous return, and pulmonary arteriovenous malformation. Frequently, a pulmonary artery angiogram is performed in the AP and lateral views to visualize the left atrium and assess pulmonary vein drainage before ASD closure (Fig. 48-6). The most commonly used catheters are the multi-sidehole pigtail and NIH catheters; they deliver a high injection rate of 40 mL/sec to visualize pulmonary veins. The dextro and levo phases of the injections are shown in Figure 48-7.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Transesophageal echocardiography (TEE) has become an integral part of invasive cardiac procedures including ASD and PFO closure, mitral valvuloplasty, aortic valvuloplasty, percutaneous aortic valve replacement, and percutaneous edge-to-edge repair.[4] Most patients in catheterization laboratories tolerate TEE placement in the supine position without endotracheal intubation. Judicious use of short-acting sedatives such as midazolam and good suction of the posterior pharynx are critical for patient comfort.

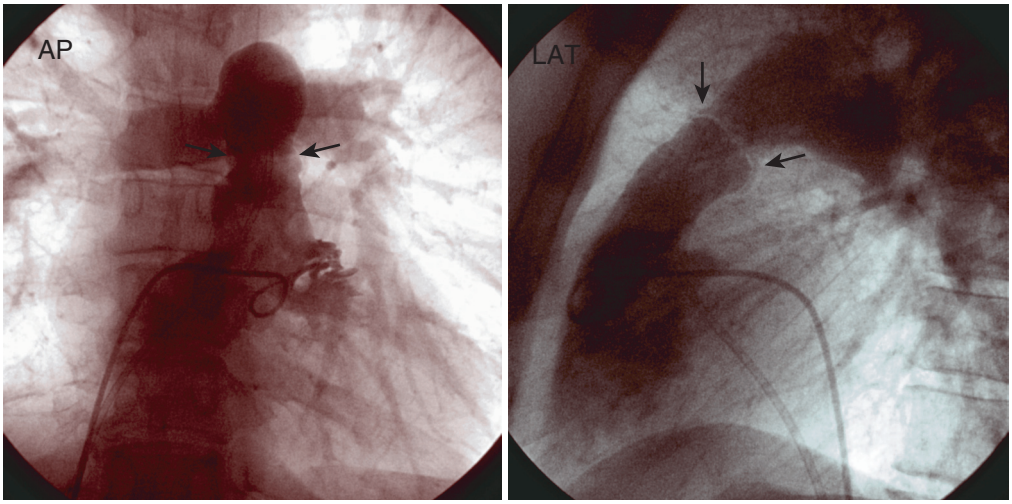


FIGURE 48-6 Anteroposterior (AP) and lateral (LAT) views of the right ventricle with a pigtail catheter in the right ventricular outflow tract. Notice the doming of the pulmonic valve *(black arrows)*.

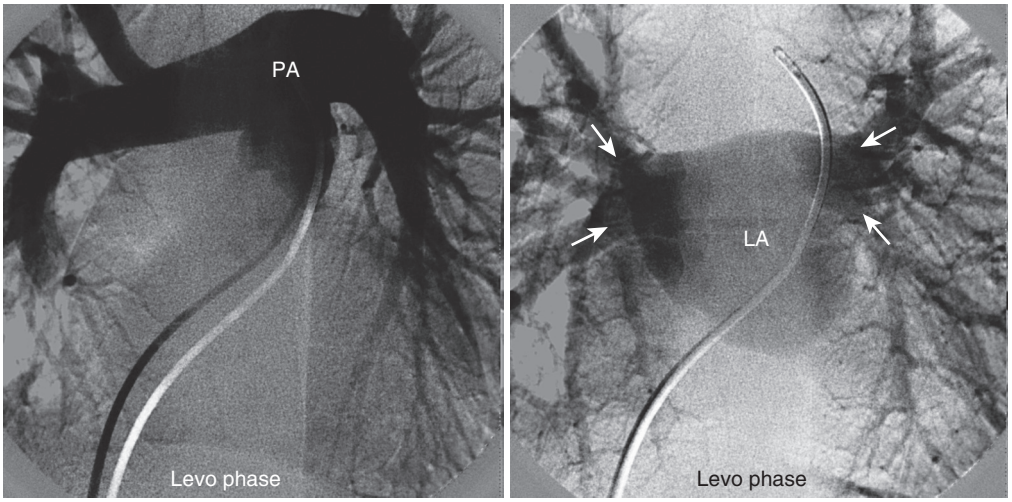


FIGURE 48-7 Normal pulmonary angiogram is shown in the anteroposterior view. A large volume of dye (40 mL/sec) is rapidly injected with the use of a National Institutes of Health (NIH) catheter. *Left panel* shows the pulmonary artery trunk and the left and right pulmonary arteries and their branches. *Right panel* shows opacification of the left atrium in levo phase. Digital subtraction is used to visualize the pulmonary veins *(solid white arrows)*. *LA,* Left atrium; *PA,* pulmonary artery.

The TEE probe contains a 3- to 7.5-MHz ultrasound transducer at its tip and can be advanced to the esophagus or stomach for proper visualization of cardiac structures.[5] The tip of the probe can be anteflexed, retroflexed, or moved side to side as needed. The currently available TEE transducers are multiplane and consist of a single array of crystals that can be rotated from 0 to 180 degrees. The most common views are the 0-degree, 40- to 60-degree, 90-degree, and 120-degree views. The common positions for the TEE transducer are the upper midesophagus, the midesophagus, and transgastric positions. The most import TEE views are the four-chamber, long-axis, and two-chamber views.

Three important planes can be visualized at 0 degrees, starting from the upper and moving to the lower esophagus (Fig. 48-8). From the upper midesophagus in a horizontal (0-degree) view or the basal short axis view, the aortic arch, pulmonary artery, LAA, pulmonary veins, and aortic valve can be visualized by scanning from left to right. In a 0- to 20-degree midesophageal view or the four-chamber view, the left atrium, left ventricle, right atrium, right ventricle, MV, tricuspid valve, and IAS can be seen. The 0-degree transgastric view shows a cross section of the left ventricle and the MV (see Fig. 48-8).

In a 40 to 60 degree, upper to midesophageal view, two important planes can be seen (Fig. 48-9). From this view, the aortic valve, RVOT, right atrium, IAS, and left atrium can be seen. From the 60-degree midesophageal level (the mitral commissural view), the MV, left ventricle, and left atrium can be seen (see Fig. 48-9). In this view, the posterior mitral leaflet is to the left of the image display, and the anterior leaflet is to the right. Typically, A2 is located in the middle of the left ventricular inflow tract with P1 and P3 on each side.

At 80 to 100 degrees from upper to lower esophagus, three important planes can be visualized (Fig. 48-10). From the 90-degree upper to midesophageal view (the bicaval view), the SVC, right atrium, inferior vena cava, IAS, and left atrium can be seen. From the 80- to 100-degree midesophagus view (two-chamber view), the anterior and inferior left ventricular walls, LAA, MV, and coronary sinus can be visualized (see Fig. 48-10). In this view, the LAA can be examined for presence of thrombus; P3 is to the left of the image display, and A1 is to the right (see Fig. 48-10).

In the 120- to 160-degree midesophagus view (long-axis view), the left ventricle, left atrium, aortic valve, LVOT, MV, and ascending aorta can be seen (Fig. 48-11).

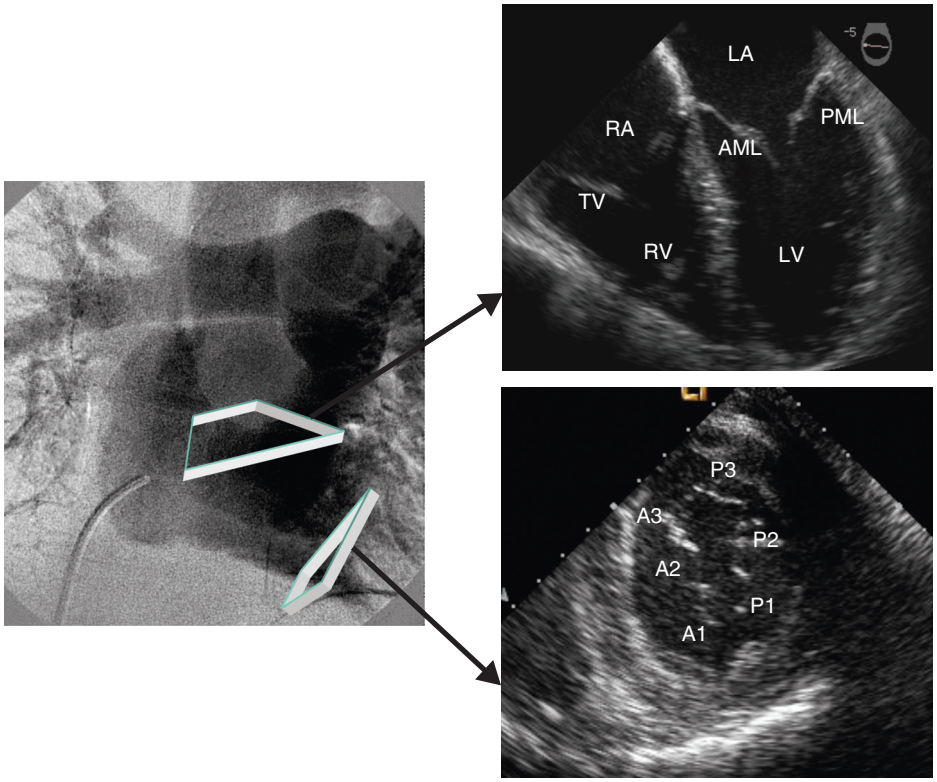


FIGURE 48-8 Transesophageal echocardiography "0-degree" (horizontal) midesophageal and transgastric views *(right panels)*. The *left panel* shows the heart in anteroposterior view (refer to Figure 48-5) and the orientation of the other images. The *upper right panel* is the four-chamber view, and *lower right panel* is a short-axis view of the mitral valve with the corresponding leaflet segments. The posterior leaflet is divided into P1 to P3, and the anterior leaflet into A1 to A3, from lateral to medial. *AML,* Anterior mitral leaflet; *LA,* left atrium; *LV,* left ventricle; *PML,* posterior mitral leaflet; *RA,* right atrium; *RV,* right ventricle; *TV,* tricuspid valve.

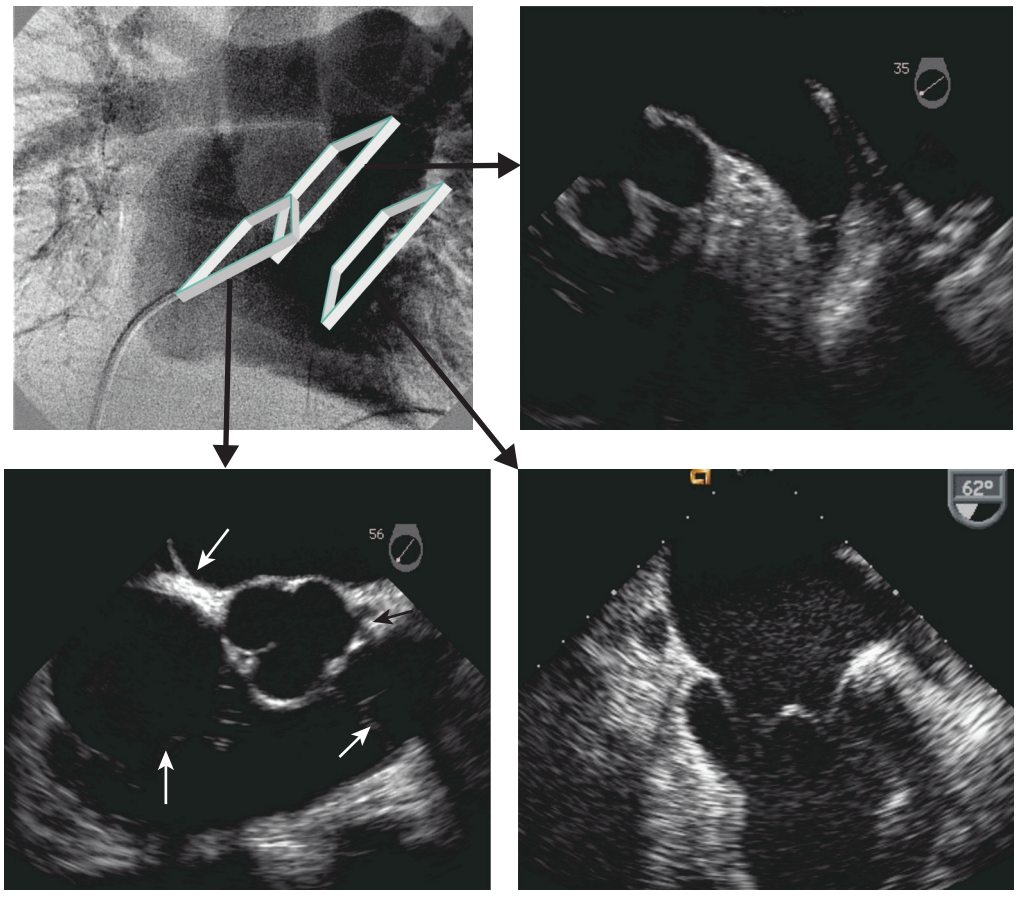


FIGURE 48-9 Transesophageal echocardiography "40- to 60-degree" views in the upper to middle esophagus with the probe turned to the left *(upper right)*, at the upper to middle esophageal junction with the probe directed anteriorly *(lower left)*, and in the midesophageal commisural view *(lower right)*. The *upper left panel* shows the heart in anteroposterior view (refer to Figure 48-5) and the orientation of the other images. *A1,* Lateral scallop of the anterior leaflet of the mitral valve; *IAS,* interatrial septum; *LA,* left atrium; *LAA,* left atrial appendage; *LCC,* left coronary cusp; *LV,* left ventricle; *NCC,* noncoronary cusp; *P1* and *P3,* lateral and medial scallops of the posterior leaflet of the mitral valve; *PA,* pulmonary artery; *PV,* pulmonic vein; *P valve,* pulmonary valve; *RA,* right atrium; *RCC,* right coronary cusp; *RV,* right ventricle; *TV,* tricuspid valve.

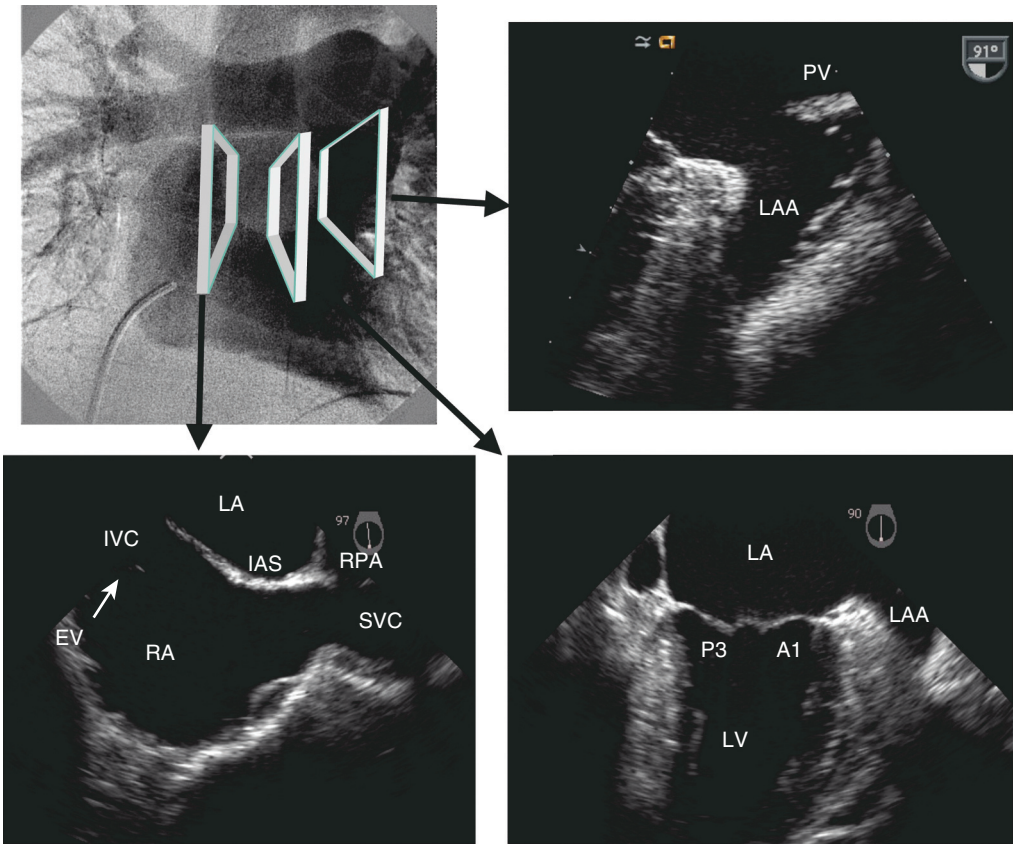


FIGURE 48-10 Transesophageal echocardiography "90-degree" midesophageal view of the left atrial appendage *(upper right),* the bicaval view *(lower left),* and the two-chamber view *(lower right)* as the probe is directed from left to right. The *upper left panel* shows the heart in anteroposterior view (refer to Figure 48-5) and the orientation of the other images. *A1,* Lateral scallop of the anterior leaflet of the mitral valve; *EV,* Eustachian valve; *IAS,* interatrial septum; *IVC,* inferior vena cava; *LA,* left atrium; *LAA,* left atrial appendage; *LV,* left ventricle; *P3,* medial scallop of the posterior leaflet of the mitral valve; *PV,* pulmonic vein; *RA,* right atrium; *RPA,* right pulmonary artery; *RV,* right ventricle; *SVC,* superior vena cava.

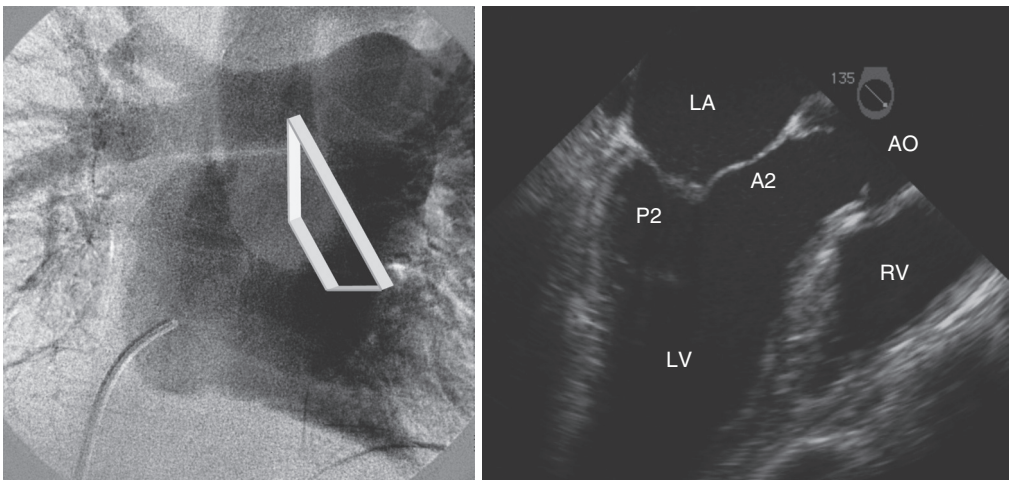


FIGURE 48-11 Transesophageal echocardiography "130-degree" midesophageal long-axis view of the ascending aorta *(right panel). Left panel* shows the heart in anteroposterior view (refer to Figure 48-5) and the orientation of the other image). P2 and A2 refer to the middle scallops of the posterior and anterior mitral leaflets. *AO,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle.

INTRACARDIAC ECHOCARDIOGRAPHY

Intracardiac echocardiography (ICE) provides excellent images of the intracardiac structures without the patient discomfort and airway issues associated with other modalities such as TEE.[6] In certain situations, ICE can produce a clearer, better-defined image compared with TEE. These situations include assessment of the posterior part of the IAS, where the TEE probe is too close to the area of interest; of the pulmonary valve because of its anterior position; of the aortic arch for dissection because of air shadowing from the bronchus; and in some cases, of a mechanical aortic valve because of shadowing. ICE is less optimal for evaluating mitral regurgitation, LAA, and left ventricular wall motion (e.g., contrast distribution for alcohol ablation).

The two main ICE transducer systems are the mechanical/rotational and the phased-array systems. The mechanical transducers typically operate at 9 MHz or higher and produce a circular scan path perpendicular to the catheter. Mechanical catheters are imaging catheters without color or Doppler capabilities; they are less useful than the phased-array systems, which allow a complete evaluation that is comparable to TEE. In our catheterization laboratory, we exclusively use phased-array systems to guide our structural heart disease interventions. The phased-array systems use 64 piezoelectric elements with frequencies of 5.5, 7.5, 8.5, and 10 MHz to produce a single sector scan that is perpendicular to the long axis of the catheter. The probe is available as an 8- or 11-Fr catheter with "monoplane" imaging. Each device has two handles that allows the operator to move the probe tip anterior, posterior, or from side to side. The maximum tissue penetration with ICE is approximately 10 to 12 cm.

ICE is currently being used for assessment of the IAS, pulmonary veins, crista terminalis, eustachian valve, tricuspid annulus, coronary sinus ostium, aortic valve, ascending aorta, aortic arch, and in some cases, the MV. In general, there are three standard views; however, modification of these views by clockwise or counter-clockwise rotation may be necessary. One can typically start from the SVC and pull the probe back caudally for visualization of different structures. The initial view is from the SVC when the transducer is in the neutral position (Fig. 48-12). Subsequent counterclockwise rotation will turn the transducer anteriorly, where the ascending aorta, the aortic valve, part of

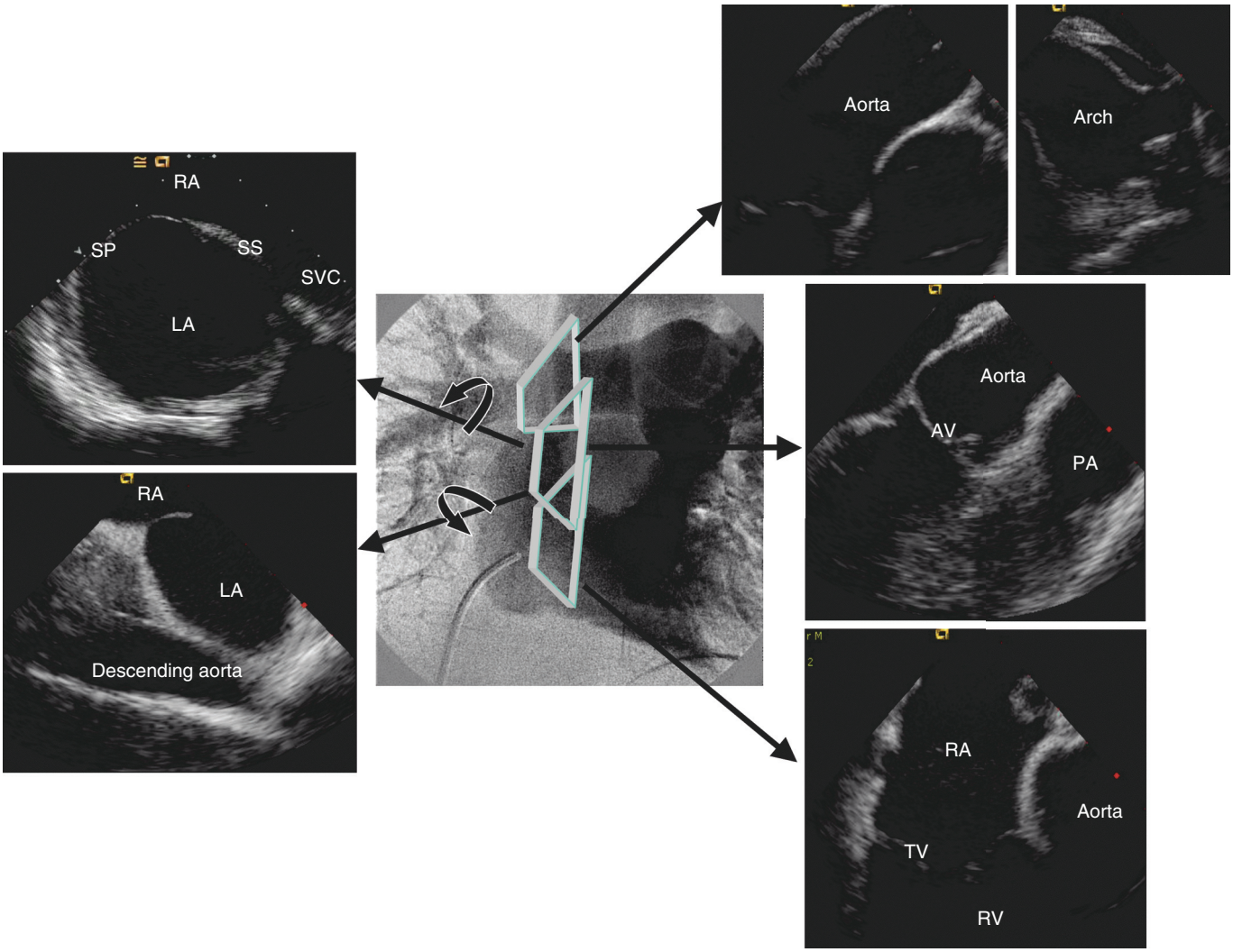


FIGURE 48-12 The basic views obtained by intracardic echocardiography (ICE) in the neutral position *(right panels)* and with progressive clockwise rotation *(left panels)*. The corresponding planes are shown on the fluoroscopic image *(center panel)*. Refer to Figure 48-5 for orientation of fluoroscopic image and the structures that are visible in the neutral position from the level of the superior vena cava *(top right)*, the middle right atrium *(middle right)*, and the tricuspid valve *(bottom right)*. The panels on the left were obtained by turning the probe clockwise from the middle right atrium to visualize the entire interatrial septum from anterior to posterior aspect. *AV*, Aortic valve; LA, left atrium; *PA*, pulmonary artery; *RA*, right atrium; RV, right ventricle; *SP*, septum primum; *SS*, septum secundum; *SVC*, superior vena cava; *TV*, tricuspid valve.

pulmonary trunk, and the tricuspid valve can be seen. Clockwise rotation from the neutral position rotates the transducer posteriorly, where the IAS, right pulmonary artery, and descending aorta can be seen. The next view is typically obtained from the right atrium at the level of tricuspid valve (see Fig. 48-12). This view shows the tricuspid valve and the ascending aorta. Further clockwise rotation delineates part of the IAS. In order to see the entire IAS, posterior flexion is applied to the probe. This allows enough depth so that the entire IAS can be visualized (Fig. 48-13).

The third standard view (anterior horizontal view) is obtained by flexing the probe in the middle right atrium with some clockwise rotation (Fig. 48-14). This generates a short-axis view of the aortic valve

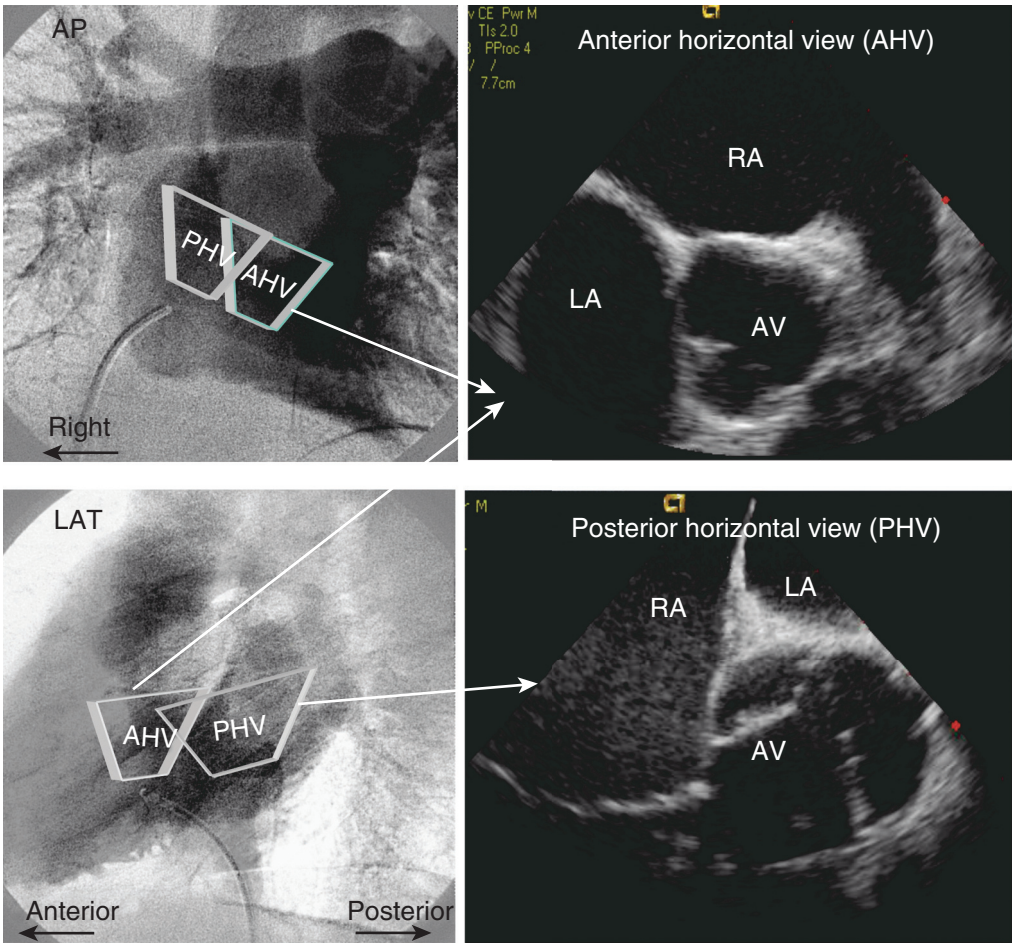
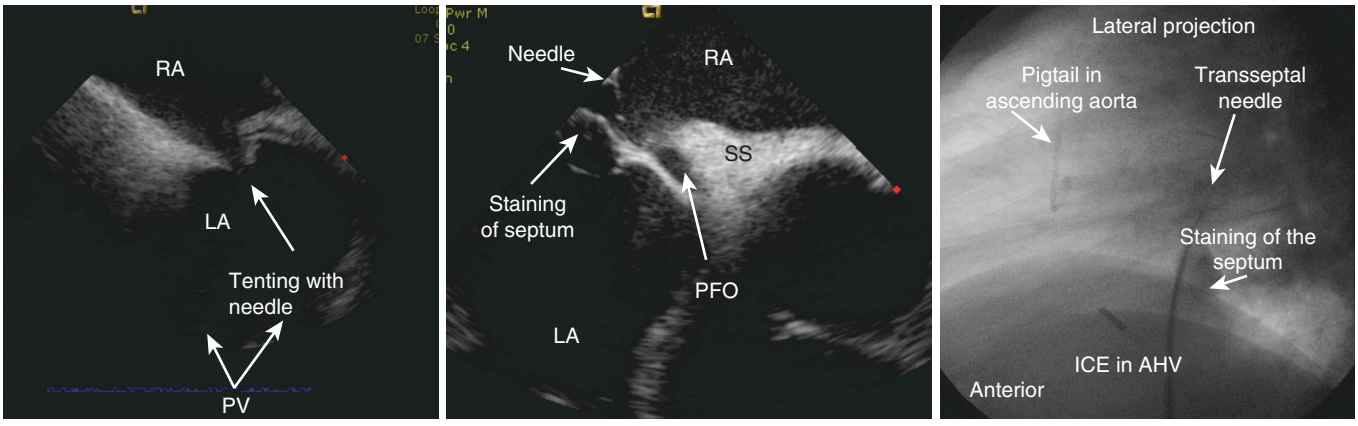


FIGURE 48-13 Intracardic echocardiography (ICE) in the anterior and posterior horizontal views *(right panels)*. The corresponding planes are shown in the AP *(upper left)* and lateral *(lower left)* fluoroscopic views (see text for details). *AP,* Anteroposterior; *AV,* aortic valve; *LA,* left atrium; *LAT,* lateral; *RA,* right atrium.



A B C

FIGURE 48-14 Intracardiac echocardiography (ICE) shows puncture in a good location as demonstrated by needle tenting opposite to the pulmonary veins (**A**). **B** and **C,** Transseptal puncture in a patent foreman ovale with a long tunnel. **B,** Needle with stained septum. Notice that the puncture site is close to the end of the septum secundum (SS). **C,** Position of ICE probe and septal staining in the lateral projection (same patient as in **B**). Notice that the ascending aorta is anterior and the Brockenbrough needle is pointing posteriorly (**C**). *AHV,* Anterior horizontal view; *LA,* left atrium; *PFO,* patent foramen ovale; *PV,* pulmonary vein; *RA,* right atrium.

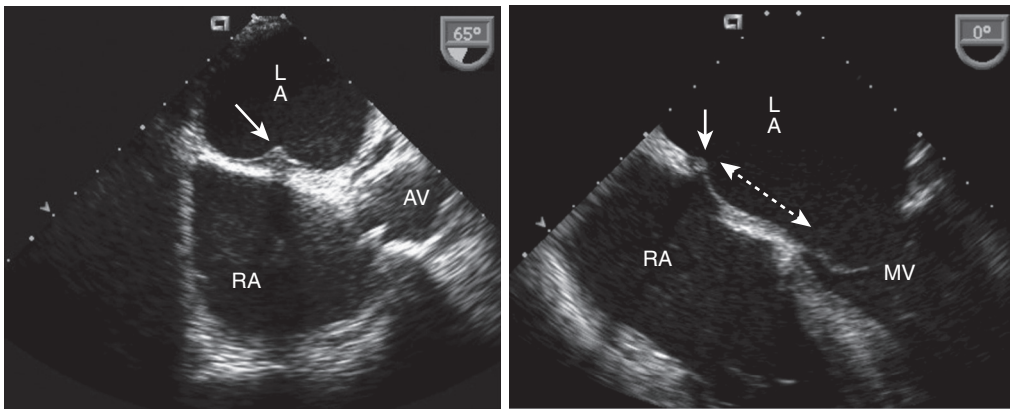


FIGURE 48-15 Transesophageal echocardiography "65-degree" (midesophagus) view *(left panel)* and "0-degree" (four-chamber) view *(right panel)* show the location of the puncture site. The distance between the puncture site and the aortic and mitral valves can be determined on these views (*left and right panels,* respectively). Presence of tenting *(white arrow)* confirms the location and position of the needle. The dotted line shows the distance from the transeptal site to the mitral valve annulus. *AV,* Aortic valve; *LA,* left atrium; *MV,* mitral valve; *RA,* right atrium.

and produces a better visualization of the anteroposterior section of the septum. Further clockwise rotation demonstrates the MV and its apparatus. It is possible to see the aortic valve in cross section by rotating the probe clockwise and posteriorly; however, this view is less reproducible than the anterior horizontal view (see Fig. 48-12). Occasionally, the MV can be visualized from the coronary sinus, the right ventricle, or the superior aspect of the right atrium.

SPECIFIC PROCEDURAL USES FOR INTRACARDIAC IMAGING

Transseptal Puncture

Transseptal puncture has become an integral part of many intracardiac procedures, including percutaneous mitral valvuloplasty, MV repair, LAA closure, some cases of PFO closure, and ablation of atrial fibrillation.[7] The goal is to cross the IAS through the fossa ovalis, an area 2 cm in diameter that is bounded superiorly by septum secundum called limbus. It is located posterior and inferior to the aortic root in the midportion of the IAS. The procedure is performed with the use of the Brockenbrough needle (USCI, Billerica, MA), which is introduced through an 8-Fr Mullins sheath and dilator combination. The procedure is performed primarily under fluoroscopic guidance, with ultrasound imaging (ICE or TEE guidance) as an important supplement. Fluoroscopically, the most important landmarks are the position of the aorta (determined by placing a catheter in the aortic root) and the margins of right and left atria. These can be determined by right atrial angiography in the AP and lateral projections (see Fig. 48-5). The needle is withdrawn caudally in the AP projection from the SVC; three medial drops are identified, corresponding to the SVC–right atrial junction, the noncoronary sinus of the aorta, and the limbus of the fossa ovalis. The needle position is then checked in lateral projection to ensure posterior direction in relation to the aorta. The needle is advanced to the left atrium with close monitoring of pressure through the needle to ensure that there is no drop in pressure as the needle traverses the IAS. Staining of the septum can be very helpful if there is any doubt regarding the location of the puncture site (see Fig. 48-14).

TEE can also help determine the appropriate location of the puncture site. The vertical distance from the MV and the aorta can be determined by the four-chamber and bicaval views, respectively (Fig. 48-15). TEE also helps to rule out thrombus in the left atrium or the LAA appendage and to monitor the pericardium for presence of effusion. The puncture site must be identified through recognition of tenting, which indicates the correct needle-tip position.

ICE is commonly used to guide this procedure and can identify the anteroposterior and superoinferior boundaries of the interatrial septum. The ICE catheter is introduced into the right atrium and then steered to the right with posterior flexion; this gives rise to the posterior horizontal view. In this view, the superior and inferior cavoatrial junction is delineated, the aortic rim is well seen, and the right upper pulmonary vein is seen. While the catheter is kept in this orientation, the whole system is rotated clockwise and placed below the aortic valve. This produces the anterior horizontal view that localizes the short axis of the IAS and delineates its posterior extent (see Fig. 48-14, *A*). The appropriate site can also be confirmed in the anterior horizontal view (Fig. 48-16).[8]

Patent Foramen Ovale

The details of this procedure are covered in Chapter 49. Briefly, under normal embryologic processes, the septum primum and septum secundum (two independent, crescent-shaped membranes) make up the IAS. During fetal life, the mobile septum primum allows right-to-left shunting to maintain life. However, after birth left atrial pressure increases and helps to fuse these two membranes. In about 15% to 20% of individuals, this fusion does not occur, allowing occasional right to left shunting; this is referred to as a PFO.

Fluoroscopy is used in conjunction with ICE for percutaneous PFO closure. The most common views are the shallow LAO (10-degree), cranial (10-degree), and lateral (or 60-degree LAO) views, which allow better appreciation of the PFO orientation. Typically, a Gudel-Lubin catheter is used to cross the PFO, and while the catheter is being pulled back, injection is made to visualize the PFO on fluoroscopy (see Fig. 48-16). This allows visualization of the length of the tunnel (overlap between septum primum and septum secundum) and the thickness of the septum secundum. Additionally, balloon inflation in the PFO helps to determine the size of the PFO and to delineate the shape and size of the tunnel, allowing one to "feel" the quality of the tissue around the PFO (see Fig. 48-16). Deployment of the device is usually done in the shallow LAO cranial (10-10) view, which allows perpendicular visualization of the IAS. Last, injection of contrast material under fluoroscopy from the guide catheter before release confirms good apposition.

ICE is commonly used to first assess the IAS in the longitudinal plane from top to bottom in the anterior and the posterior direction. This is done by turning the probe clockwise and counterclockwise at various heights in the right atrium (see Fig. 48-12). Next, the probe is flexed anteriorly, and the ultrasound beam is directed superiorly and posteriorly to visualize the anteroposterior length of the IAS (see

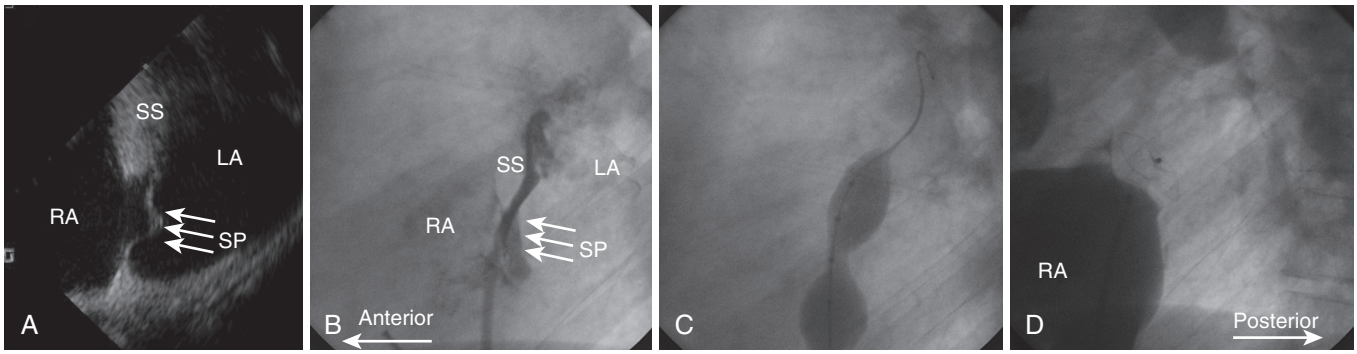


FIGURE 48-16 **A,** Patent foreman ovale (PFO) with septum primum (SP, *arrows*) and septum secundum (SS) is shown by intracardiac echocardiography. The image is rotated to match the fluoroscopic image (**B**). The SP is flimsy (atrial septal aneurysm). Lateral fluoroscopic views show a PFO (**B**), "feeling" of the PFO with a sizing balloon (**C**), and proper positioning of the device with a right atrial angiogram before detachment (**D**). *LA,* Left atrium; *RA,* right atrium.

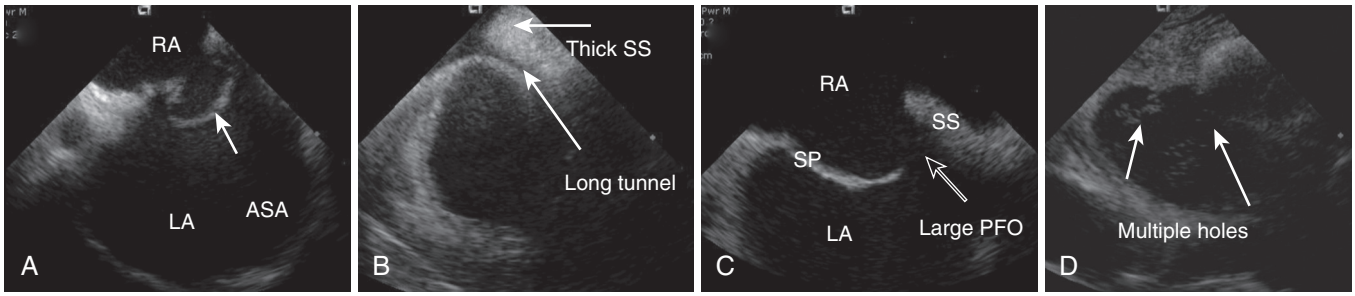


FIGURE 48-17 Intracardiac echocardiography shows the presence of an atrial septal aneurysm (**A**), the overlap of septum primum (SP) and septum secundum (SS) delineating the "tunnel" and the thickness of the SS (**B**), the size of the PFO (**C**), and the presence of additional openings (**D**). *ASA,* Atrial septal aneurysm; *LA,* left atrium; *PFO,* patent foramen ovale; *RA,* right atrium.

Fig. 48-13). ICE should be carefully performed with consideration of the following points: (1) presence or absence of an atrial septal aneurysm (Fig. 48-17, *A*); (2) relationship of septum primum to septum secundum to determine the length of the "tunnel" (see Fig. 48-17, *B*); (3) thickness of septum secundum (see Fig. 48-17, *D*); (4) size of the PFO (see Fig. 48-17, *C*); (5) presence of additional openings (see Fig. 48-17, *D*); (6) degree of shunt; and (7) presence of a prominent Chiari network. ICE can also show whether the wire has crossed the PFO when other holes are present. Similarly, ICE can be very useful when transseptal puncture for a tunneled PFO is necessary (see Fig. 48-16). Typically, the puncture must be made fairly anteriorly, near the PFO, to adequately cover the PFO with the device.

Device deployment is typically performed under ICE and fluoroscopy guidance. Proper but not excessive tension in device deployment can make the device sit well without the risk of deploying both disks into the left atrium. Once the device is deployed, proper interrogation of all margins provides reassurance that it will not embolize. "Push and pull" is performed, and simultaneous imaging with ICE confirms that the atrial tissue is between the disks. Once the operator is satisfied, the device is released and bubbles are injected to document any residual shunt.

In our institution, almost all PFOs are closed with the use of fluoroscopy and ICE guidance; however, TEE can also be used for this procedure. TEE is associated with greater patient discomfort and requires an additional operator. Two views are most helpful when using TEE: the (30 to 40 degree) midesophageal short-axis view of the aortic valve and IAS and the (90 to 100 degree) midesophageal bicaval view, which shows the IVC and SVC, the right atrium, and the IAS. However, every patient is different, and subtle changes in these views and angles may be necessary for better visualization.

Secundum Atrial Septal Defect

Secundum ASD results from underdevelopment of the septum secundum that leads to a true opening in the IAS. The key elements in the assessment of ASD with echocardiography for percutaneous closure are (1) the location of the defect in the septum secundum (superior, inferior, anterior, or posterior); (2) adequacy of rims (Fig. 48-18); (3) identification of multiple defects; and (4) size of the defect. Pulmonary angiography is the most helpful modality to identify anomalous venous drainage in the catheterization laboratory (see Fig. 48-7).

ICE is the preferred imaging method for this procedure.[9] In general, the two views described for PFO are adequate for visualizing ASD and its structural detail. Individualization of views should be considered, because ASD occurs in many different sizes and shapes. Obliteration of color flow with balloon inflation allows proper sizing without oversizing, as commonly happens when only the waist of the balloon is used with fluoroscopy. (Fig. 48-19). Device deployment is guided by ICE, and proper gripping can be tested with "push and pull" maneuvers. Impingement of surrounding structures (i.e., MV, SVC, roof of the left atrium, aorta, and coronary sinus) should be carefully assessed before the device is released. A right atrial angiogram with end-on view of the device allows clear visualization of the device margins and its relation to the left atrial walls and aorta (Fig. 48-20).

Left Atrial Appendage Occlusion

The LAA is derived from the embryonic left atrium and is a bland pouch located on the anterior surface of the heart, It can have several variations in morphology.[10] The ostium of the LAA is elliptical in shape and enlarges progressively with severity of atrial fibrillation.[1] The

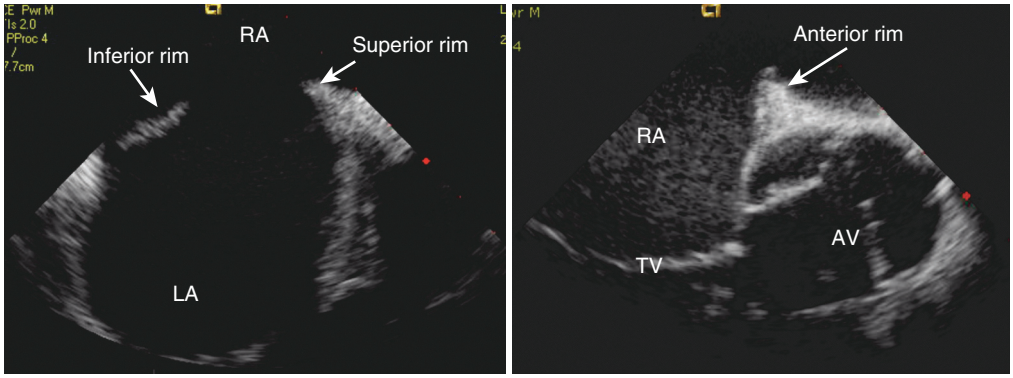


FIGURE 48-18 Intracardiac echocardiography shows the inferior and superior rims of a secundum atrial septal defect *(left panel)*. Notice the presence of a small anterior rim *(right panel)*. *AV,* Aortic valve; *LA,* left atrium; *RA,* right atrium; *TV,* tricuspid valve.

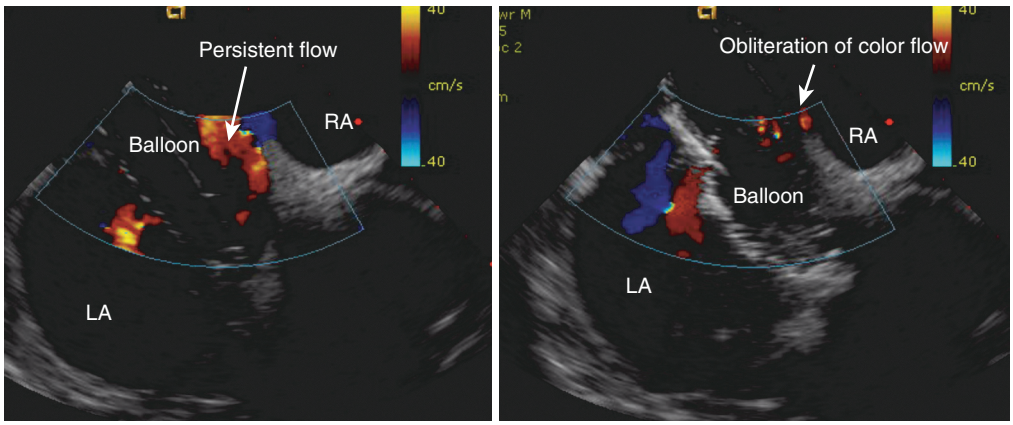


FIGURE 48-19 Intracardiac echocardiography shows the process of atrial septal defect (ASD) sizing. The balloon is inflated with color interrogation of the ASD. Initially, there is persistent flow around the ASD balloon *(left panel)*. The balloon is inflated further to barely obliterate flow across the ASD, and size is measured. This allows the operator to choose the proper size of ASD closure device without oversizing. *LA,* Left atrium; *RA,* right atrium.

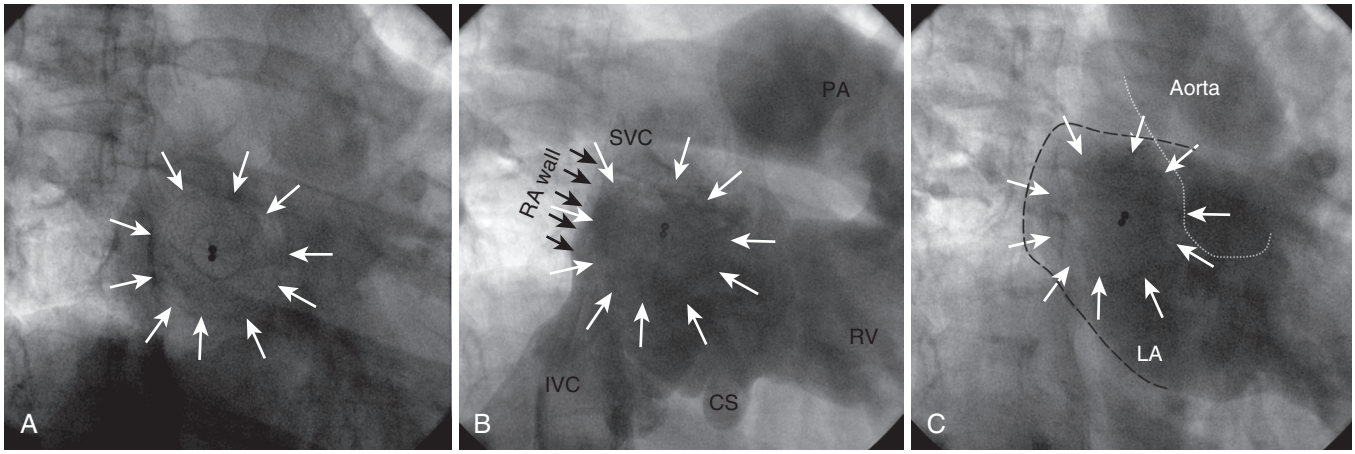


FIGURE 48-20 Right anterior oblique (RAO) caudal views of a right atrial angiogram show atrial septal defect (ASD) device end-on (**A**) with surrounding structures in the dextro (**B**) and levo (**C**) phase of contrast injection. Notice the relation of the device to the right atrial (RA) walls, left atrial (LA) walls, and aorta. *White arrows* show the margin of the left atrial device disk. *Black arrows* in **B** point to the right atrial wall. In **C,** the aortic silhouette is traced with *dashed white line,* and the left atrial border is shown by the *dashed black line*. *CS,* Coronary sinus; *IVC,* inferior vena cava; *PA,* pulmonary artery; *RV,* right ventricle; *SVC,* superior vena cava.

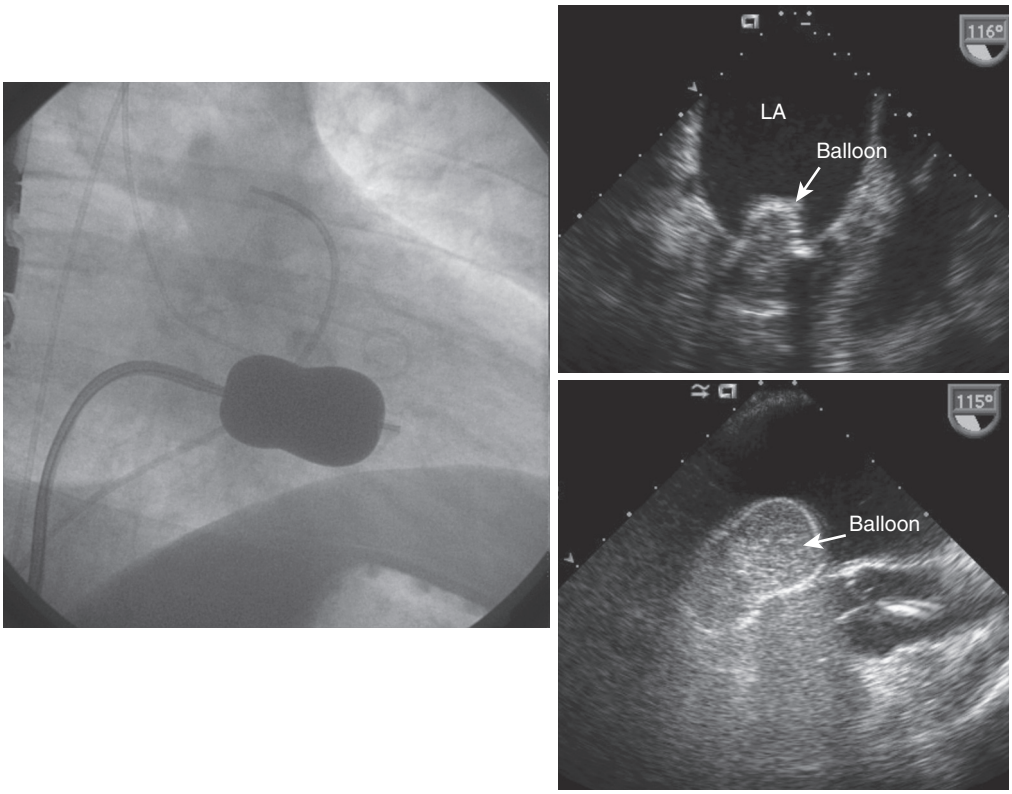


FIGURE 48-21 Mitral valvuloplasty using the Inoue-Balloon catheter in the right anterior oblique (RAO) projection under fluoroscopy *(left panel)*. *Upper right and lower right panels* show a stepwise balloon inflation in the 110- to 120-degree long-axis view under transesophageal echocardiography guidance. *LA,* Left atrium.

pectinate muscles within the LAA must be delineated, and they can be misread as thrombus. The use of real-time 3D TEE can help one distinguish between pectinate muscles and thrombi.[11] The combination of TEE and CT imaging is effective to assess the left atrial and LAA anatomy. The TEE can assess functional and anatomic features that increase risk for thrombogenicity. CT imaging can assess the morphology and provide anatomic information to guide LAA closure. Specifically, it can delineate the 3D orientation of the LAA relative to the pulmonary artery, the number and shape of lobes, and the orientation of the appendage.[12] The morphologic appearance of the LAA has four categories based on CT analysis: (1) wind sock (long, dominant lobe); (2) cauliflower (short length with complex internal structure); (3) chicken wing (one prominent bend in the LAA); and (4) cactus (dominant central lobe with secondary lobes).[13] CT imaging can be used to plan placement of an LAA closure device by determining the IA septal puncture site, the distance from the fossa ovalis to the LAA ostium, the geometry of the LAA ostium, and the relationship of the LAA ostium to the left superior pulmonary vein and the MV annulus.[14,15]

Once transseptal assess is obtained and the delivery sheath is placed in the LAA, a pigtail catheter is placed in the LAA and LAA images are obtained. The best working view is an RAO 30-degree oblique and 30-degree caudal, which correlates with the TEE image at 135 degrees. A simple RAO view correlates with the TEE image at 45 to 90 degrees, whereas the cranial RAO correlates with the TEE image at 0 degrees. Once the device is deployed, a TEE is used to interrogate adequate sealing of all the LAA lobes.

Mitral Valvuloplasty

Proper guidance with imaging can make percutaneous mitral valvuloplasty safer and more effective, especially in developed countries where patients are older in age and valves are less optimal for balloon valvuloplasty.[16] TEE is most helpful in guiding this procedure (Fig. 48-21). It helps with (1) providing guidance for transseptal puncture, (2) ruling out clots in the LAA before the procedure, (3) monitoring the degree and mechanism of mitral regurgitation with each balloon inflation, and (4) documenting the size of the hole at the site of interatrial puncture after removal of the balloon. We prefer to use TEE in the cardiac catheterization laboratory for this procedure.[17] This can be safely accomplished with the patient in supine position without endotracheal intubation if proper sedation and suction of the posterior pharynx are performed. Careful interrogation of the MV with TEE in the esophageal and transgastric views is helpful for determining the mechanism and severity of mitral regurgitation. Currently, ICE is not very helpful for MV interrogation and assessment.

Fluoroscopy is also an important component of this procedure. A left ventricular angiogram can be used to assess the severity of mitral regurgitation; however, an adequate volume of dye must be injected in patients with mitral stenosis who have a large left atrium. Fluoroscopy is also used to ensure that the balloon is in proper position and that it is not entangled with the mitral subvalvular apparatus. The RAO projection on fluoroscopy is helpful to ensure coaxial entry of the balloon through the MV without going through the chordae. Partial inflation of the Inoue Balloon and advancement of the balloon to the cardiac apex in this view before engagement and inflation can ensure that the balloon is not entangled with the chordae.

Aortic Valvuloplasty

Fluoroscopy plays a significant role in visualizing the aortic valve and its orifice. Use of fluoroscopy in the LAO and RAO projections can help determine which leaflet has the most motion (see Fig. 48-4). Typically, an AL-1 catheter should be pointed under the moving leaflet to cross the valve with a straight wire. If the right coronary cusp is

moving, this motion is best appreciated in the RAO projection. If the left coronary cusp or the noncoronary cusp has the most motion, then the LAO projection is helpful. The LAO view is the safest view to cross the aortic valve to prevent inadvertent entry into coronary ostia with a straight wire. This procedure is done with fluoroscopy only.[18,19] Hemodynamic measurements are important to guide the aggressiveness of balloon valvuloplasty. In the event of complication, TEE or ICE can help determine the exact cause (e.g., the severity and mechanism of aortic insufficiency).

Pulmonary Valvuloplasty

Pulmonary valve stenosis is a common congenital abnormality. Many of these patients undergo pulmonary valvuloplasty in adulthood. Cineangiography, transthoracic echocardiography (TTE), TEE, and ICE are helpful modalities used for this procedure.[20]

Pulmonary artery angiograms in AP and ateral views are helpful to visualize the pulmonary annulus size and preexisting pulmonary insufficiency (Fig. 48-22). Occasionally, right ventriculography in the same views may be performed to assess the RVOT (Fig. 48-23). Severe subpulmonary hypertrophy may be associated with significant dynamic RVOT obstruction after pulmonary valvuloplasty. Both TTE and TEE can be helpful in assessing pulmonary valve annular size. ICE provides useful assessment of pulmonary insufficiency and allows measurement of the annulus. An ICE probe can be placed in the RVOT for assessment of the pulmonary valve (Fig. 48-23).

Percutaneous Mitral Valve Repair

The MV apparatus consists of the annulus, two leaflets, chordae, and the papillary muscles. The mitral annulus is saddle-shaped, with a trigonal part and lateral commissures as the highest points. There is some suggestion that the shape of the annulus changes when the left atrium and left ventricle dilate. The anterior leaflet is longer but covers only one third of the circumference of the annulus. The posterior leaflet is shorter but covers two thirds of the annulus.[21] Unlike any other interventional procedures, the use of real-time echocardiographic imaging guidance is critical for percutaneous MV repair, and clear communication is needed between the interventionalist and the imaging specialist.

It is recommended that an imaging protocol consisting of predetermined views for each step be used. An ideal puncture site should be in the superior and posterior aspect of the IAS to achieve a height of 3.5 to 4.0 cm above the MV coaptation plane. The clip is then ideally positioned in the center of the regurgitant jet with the clip arm aligned perpendicular to the commissural line. The midesphageal long-axis view is used to guide the anteroposterior positioning, and the commissural view guides the medial-lateral position. The addition of 3D TEE to 2D TEE provides superior guidance for the MitraClip procedure. 3D Images of the MV from both the left atrial and the ventricular side provide better navigation, accurate alignment of the clip at the middle scallops of the MV, and visualization of the clip arms perpendicular to the commissural line (Fig. 48-24). In addition, TEE imaging is useful for assessment of mitral regurgitation with each attempt at treatment. The most common views are the midesophageal short-axis view (typically for transseptal puncture and to guide catheter manipulation), the

FIGURE 48-22 Pulmonary angiogram assessment of the pulmonic valve with the National Institutes of Health (NIH) catheter. Notice the presence of mild pulmonary insufficiency and poststenotic pulmonary artery dilatation. Digital subtraction was used for better visualization.

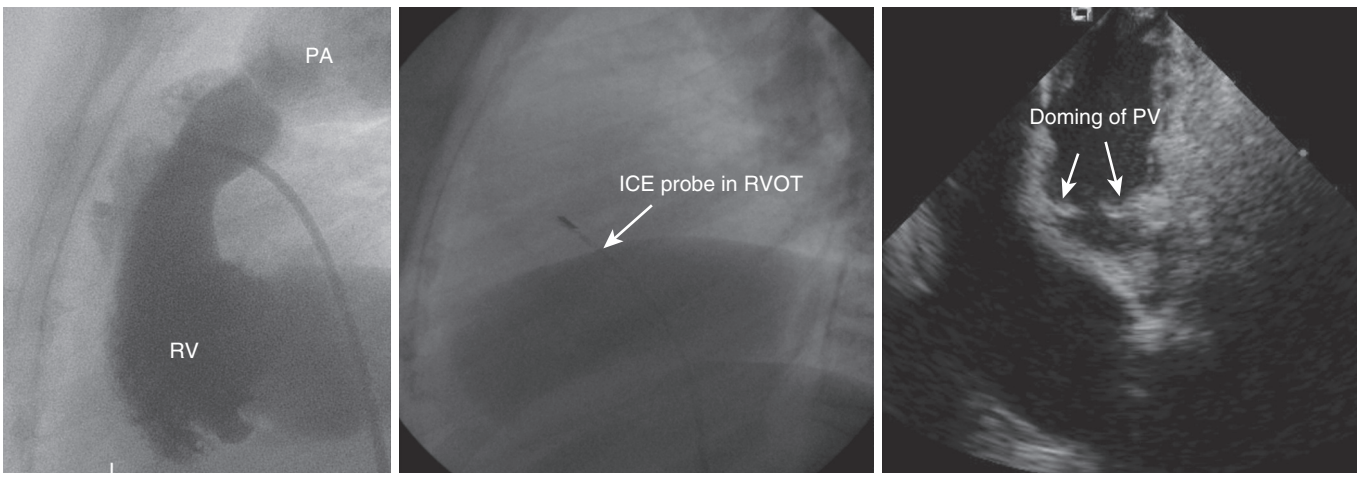


FIGURE 48-23 Pulmonary valvuloplasty. *Left panel,* Right ventriculogram shows pulmonary stenosis in the lateral view. *Middle panel* shows an intracardiac echocardiogram (ICE) probe in the right ventricular outflow tract, also in the lateral view. The *right panel* shows pulmonary valve (PV) doming in the corresponding ICE view. *PA,* Pulmonary artery; *RV,* right ventricle.

midesophageal commissural or two-chamber view, a midesophageal long-axis ("LVOT") view (multiplane angle of approximately 120° to 150°), and a transgastric short-axis view (multiplane angle 0° to 30°) at the MV level. For coronary sinus–related procedures, fluoroscopy and TEE are helpful for proper positioning of the device and evaluation of the effectiveness of the intervention. Angiography helps to determine left circumflex and coronary sinus relationships. CT can help patient selection by defining the relationships among the coronary sinus, mitral annulus, and left circumflex coronary artery.

Percutaneous Aortic Valve Replacement

Percutaneous aortic valve replacement is currently approved for patients with high-risk or inoperable aortic stenosis.[22] Many approaches are being investigated with balloon-expandable or self-expanding stented or unstented valves. Accurate positioning of the valve is critical for both balloon-expandable and self-expanding valves; therefore proper imaging in the catheterization laboratory is of paramount importance.

Several elements are important to make this procedure accurate and reproducible. The aortic valve plane must be accurately defined (see Fig. 48-4). Fluoroscopy with minimal contrast injection at times can determine appropriate angles so that the aortic valve plane is seen without any overlap of the sinuses (Fig. 48-25). Typically, the LAO cranial and RAO caudal views are used. It is also important to observe which leaflets and commissures are calcified and restricted. Accurate definition of leaflet morphology may help to identify patients in whom compromise of coronary ostia is likely at the time of valve deployment. Injection of dye at the time of balloon valvuloplasty may also help to predict this relationship. The ascending aortic slope (horizontal versus vertical in LAO projection) may determine the ease or difficulty in delivering the valve. Angiography is important in determining the size, calcification, and degree of tortuosity of the iliac and femoral vessels. TEE is also important for valve assessment (calcification, annulus size, and severity), for accurate positioning of the valve, and for assessment of the results of valve replacement (valvular or perivalvular leak and function). Again, complementary use of these imaging modalities is critical for the success of this procedure (Fig. 48-26). 4D Cardiac CT may allow better visualization of the aortic valve, its relation with coronary ostia, its morphology, and the extent of leaflet calcification (Fig. 48-27). Additionally, CT scanning is critically helpful in the assessment of iliac and femoral arteries for size, tortuosity, and extent of calcification.

Mechanical Prosthetic Valve Assessment

Occasionally, mechanical valves require a full assessment for the presence of dehiscence, vegetations, or obstruction secondary to thrombus or pannus formation. Although TTE and TEE can provide valuable information, some limitations persist. These include shadowing, pressure recovery phenomenon, and difficulty in visualizing the aortic valve because of its anterior location.

Fluoroscopy has been helpful in measuring opening and closing angles of the mechanical aortic valve. Fluoroscopy cameras should be positioned so that tangential views of the leaflets are obtained (Fig. 48-28). Because during the placement of the prosthetic aortic valve the rotational orientation can vary from patient to patient, there is no single view that can correctly visualize this valve. Therefore, we recommend a systematic approach starting with the 20- to 30-degree RAO caudal view and gradually increasing this angle toward an LAO cranial projection. Occasionally, ventriculography may be helpful to see the subvalvular pathology (e.g., pannus). In patients with a low-profile tilting disk (e.g., Björk-Shiley valve [Pfizer, New York], St. Jude valve [St. Jude Medical, St. Paul, MN], Medtronic Hall valve [Medtronic, Minneapolis, MN]), transseptal puncture and pressure measurements with or without ventriculography may be necessary for better assessment of the prosthetic valve. Although a prosthetic aortic valve can be crossed with a 0.014-inch pressure wire, the safety of such a procedure

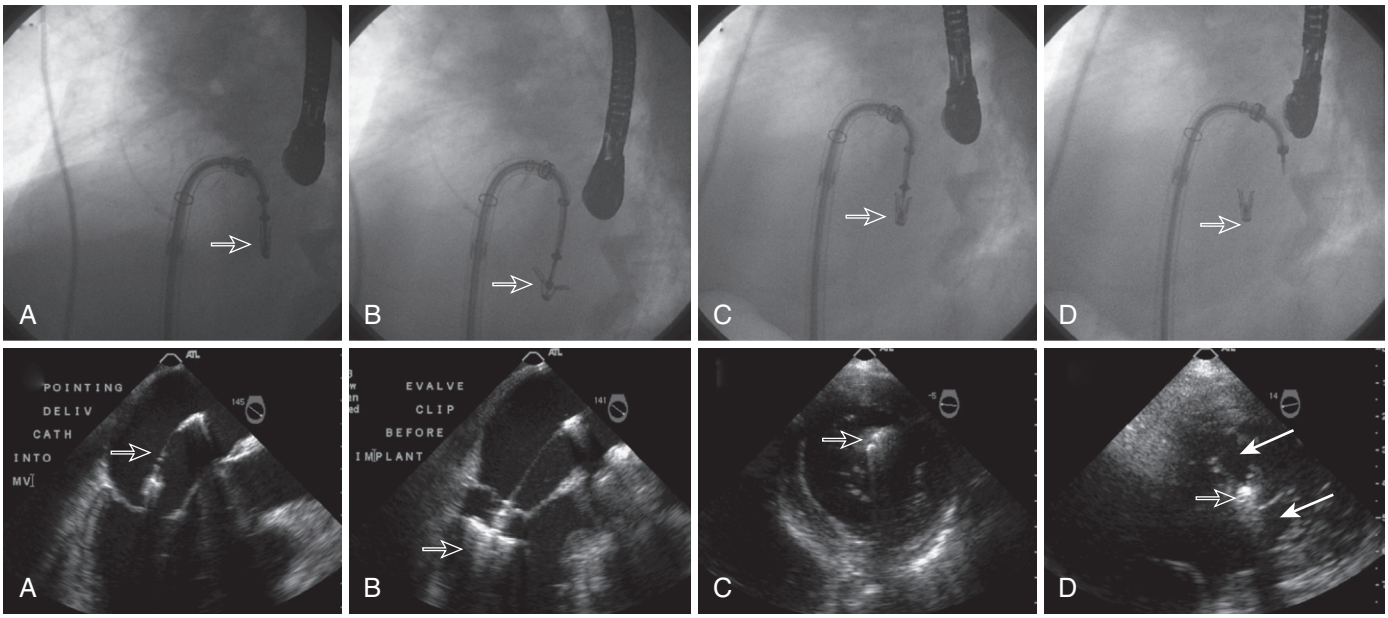


FIGURE 48-24 Percutaneous mitral valve repair. *Upper panel* shows the device in the left atrium pointing toward the mitral valve (**A**), the opening of the clip and advancement across the mitral valve (**B**), grabbing of the leaflet tips (**C**), and release of the clip (**D**). The *open arrows* indicate the MitraClip delivery system on angiography. *Lower panel,* Transesophageal echocardiography images show the device in the left atrium pointing toward the mitral valve (**A**), opening and advancement of the clip across the mitral valve (**B**), perpendicular orientation of the clip to the mitral valve coaptation line in the transgastric view (**C**), and the final result with a double orifice *(two white arrows)* (**D**). The *open arrows* indicate the MitraClip delivery system on transesophageal echocardiography.

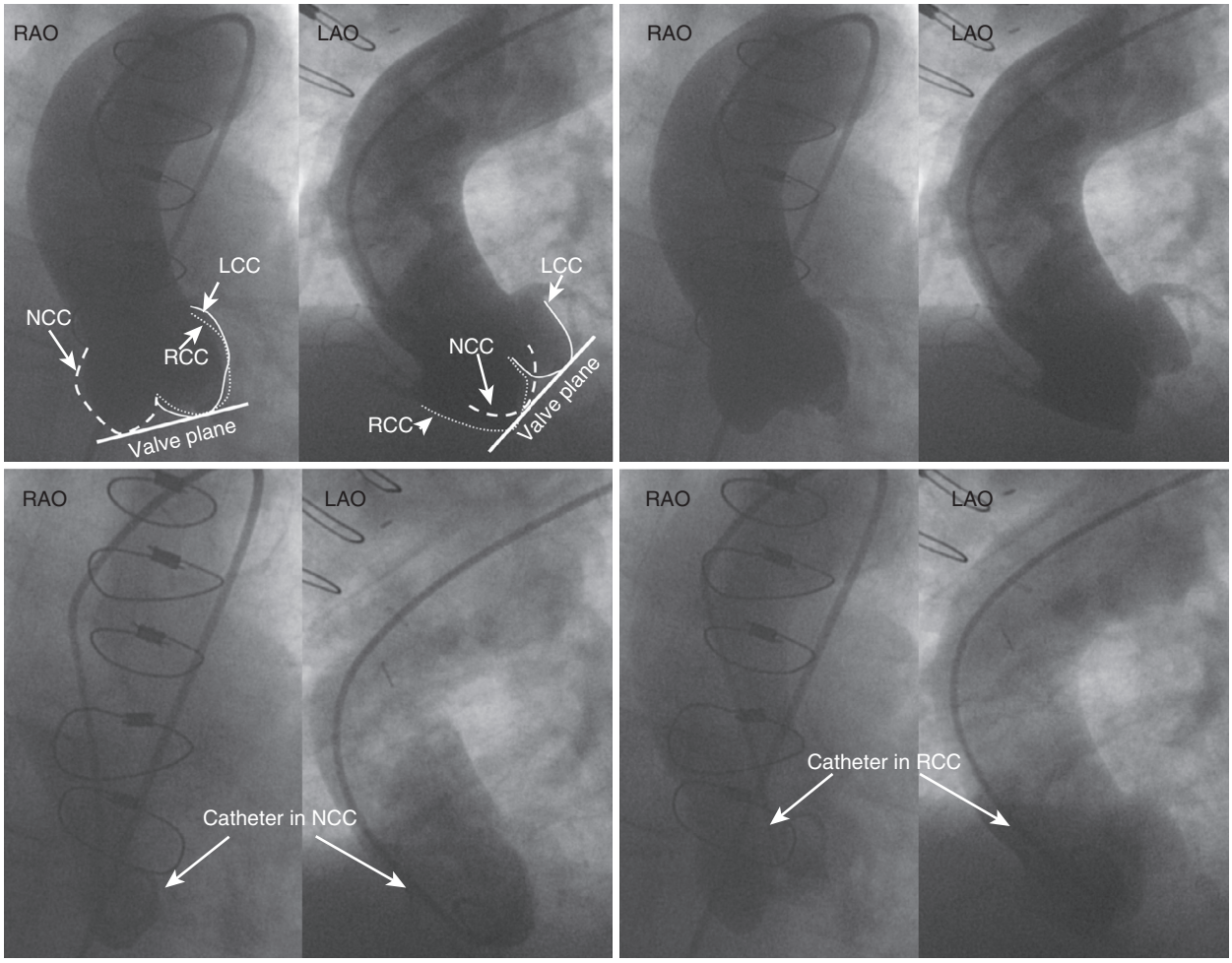


FIGURE 48-25 Left anterior oblique (LAO) cranial "40 to 20 degree" and right anterior oblique (RAO) caudal "20 to 20 degree" views of the aortic valve and its plane. The proper angulation of the camera must be customized in each patient so that the all cusps are superimposed. Notice that the catheter is in different sinuses in different phases of injection. *LCC,* Left coronary cusp; *NCC,* noncoronary cusp; *RCC,* right coronary cusp.

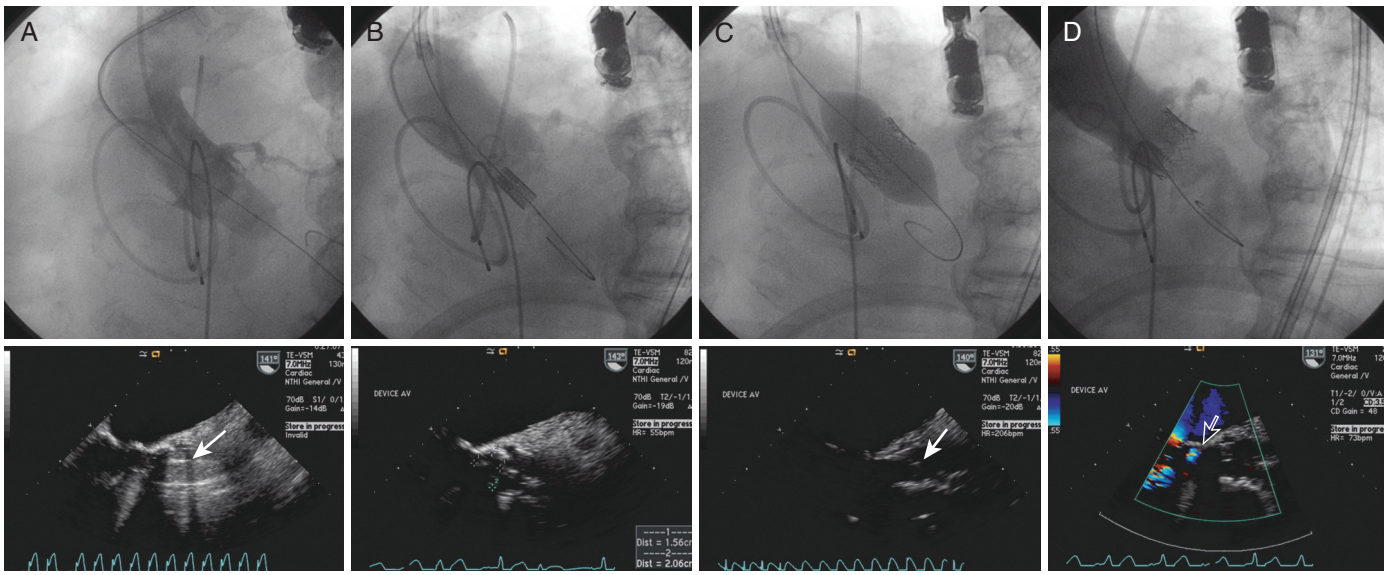


FIGURE 48-26 Percutaneous aortic valve replacement. *Upper panels* are left anterior oblique cranial projections, and *lower panels* show transesophageal echocardiography images in aortic long-axis view (130 degrees). **A,** Valvuloplasty balloon *(arrow)* in the aortic position with contrast injection depicting the distance from aortic cusp tips to coronary ostia. **B,** Proper positioning of the stent-valve. **C,** Once the valve is appropriately positioned *(arrow),* it is deployed with rapid pacing. **D,** Final aortogram shows good position of aortic valve with mild regurgitation *(open arrow).*

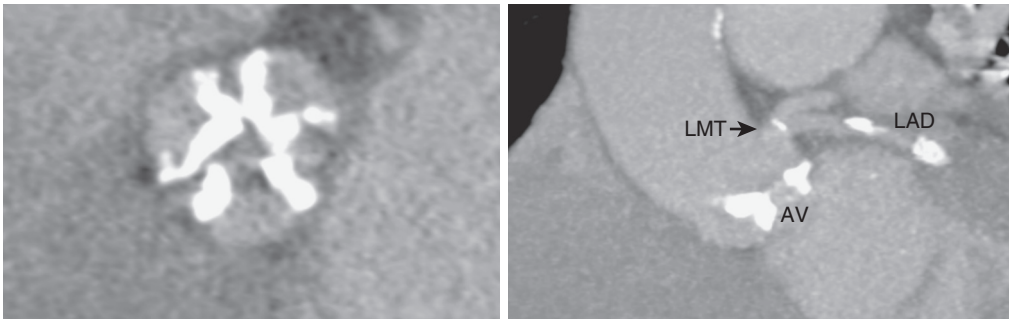


FIGURE 48-27 Four-dimensional computed tomography (CT) of the aortic valve in short-axis *(left panel)* and longitudinal *(right panel)* cuts. Notice the significant calcification on the aortic valve (AV) and left anterior descending artery (LAD). CT can also help to determine the distance between the AV and the left main trunk (LMT).

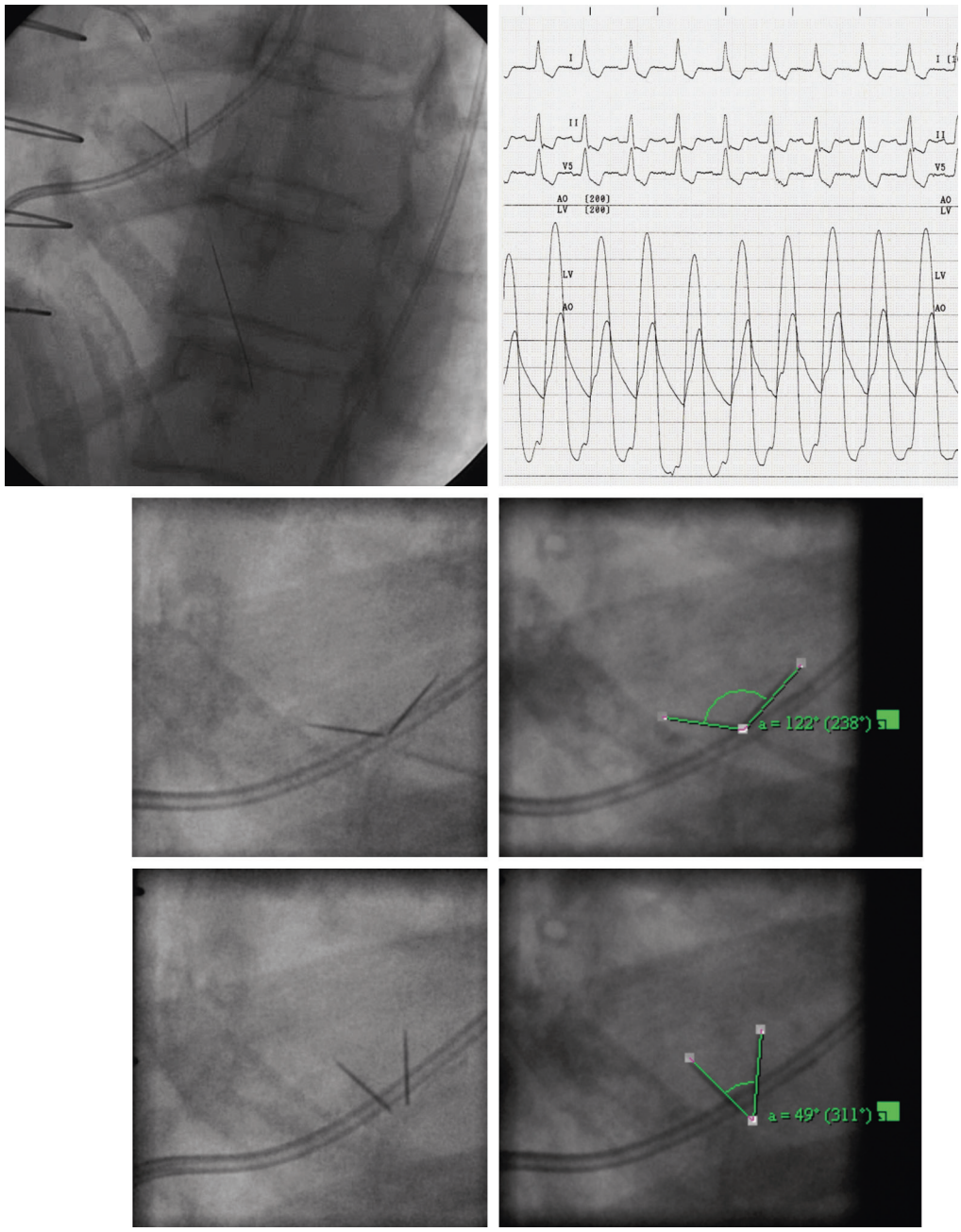


FIGURE 48-28 Prosthetic aortic valve assessment using fluoroscopy. *Upper left,* The valve was crossed with a 0.014-inch pressure wire. *Upper right,* Hemodynamic tracings show a significant gradient across the aortic valve. Opening *(middle panels)* and closing *(bottom panels)* angles are measured in the middle and lower row of images, respectively. Notice that the valve is imaged so that the leaflets are seen end-on.

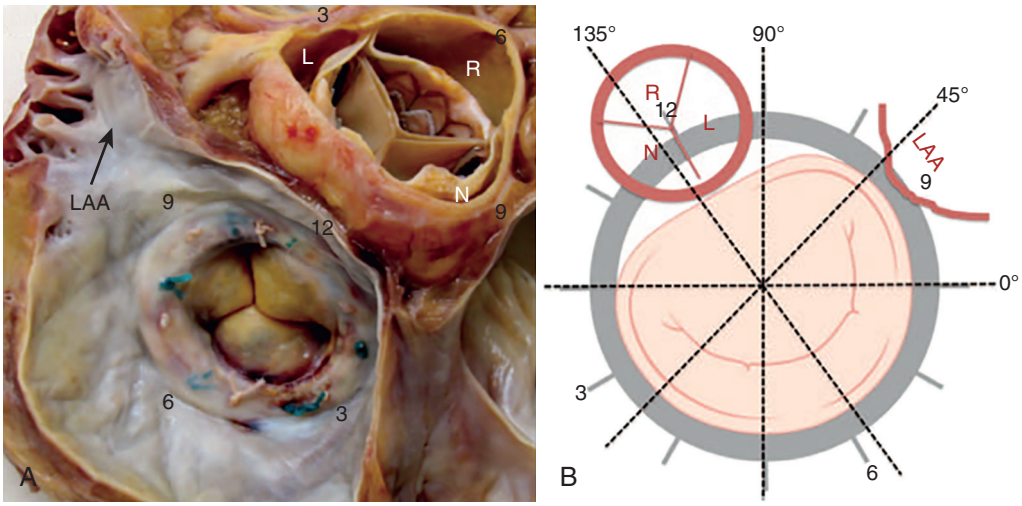


FIGURE 48-29 Mitral valve orientation. **A,** Clock-face designation of the mitral and aortic valves (left atrial view). **B,** TEE planes *(dashed lines)* along the mitral valve (viewed from the left ventricle); typical left anterior oblique (LAO) C-arm angulation. *L,* Left coronary cusp; *LAA,* left atrial appendage; *N,* noncoronary cusp; *R,* right coronary cusp; *TEE,* transesophageal echocardiography.

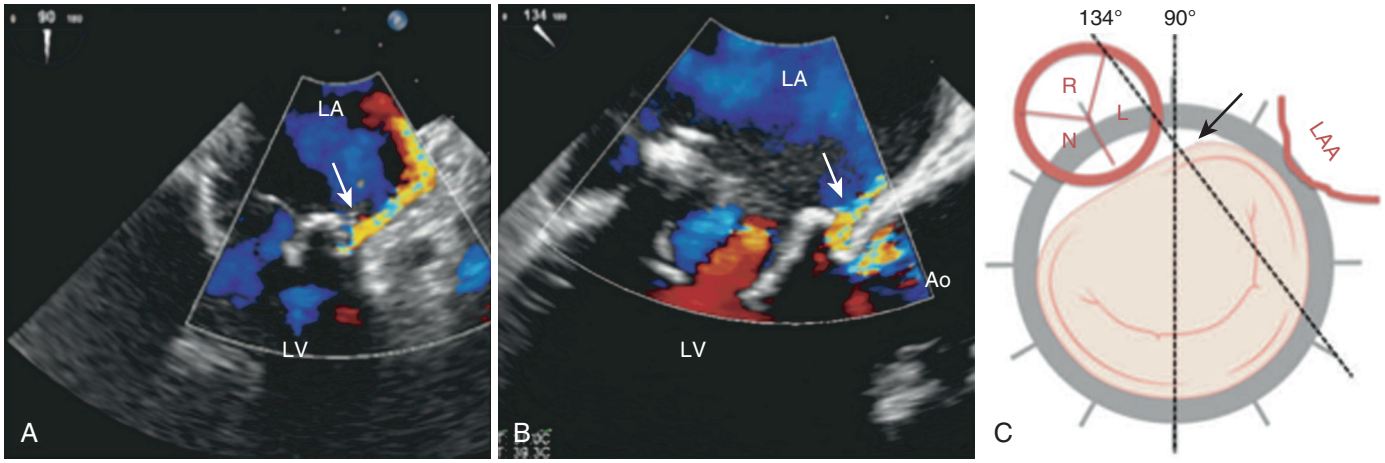


FIGURE 48-30 Mitral paravalvular leak localization. Both the TEE 90-degree view (**A**) and the TEE 134-degree view (**B**) demonstrate the leak *(arrows)*. **C,** The two TEE planes are interrogating the mitral valve: The leak is at the intersection *(arrow)*. *Ao,* Aorta; *L,* left coronary cusp; *LA,* left atrium; *LAA,* left atrial appendage; *LV,* left ventricle; *N,* noncoronary cusp; *R,* right coronary cusp; *TEE,* transesophageal echocardiography.

is unclear. In situations where both the mitral and the aortic valves have a mechanical prosthesis, apical puncture or crossing the aortic valve or MV with pressure wire can be considered.

Cardiac CT scanning also allows assessment of the opening and closing angles of the mechanical prosthetic valves. ICE can also be used to assess prosthetic aortic valve function. It is also possible to visualize the LVOT just below the mechanical aortic valve from right atrium using ICE.

Paravalvular Leak Closure

Multimodality imaging with TTE and TEE usually provides the initial diagnosis of paravalvular leak (PVL), and procedural guidance often requires 2D and 3D TEE, ICE, fluoroscopy/angiography, or more recently, the combination of CT, 3D TEE, and fluoroscopy. The MV is viewed from the left atrium, and the origin of the leak is defined by its position relative to surrounding structures close to the MV. The most anterior boundary is made by the aortic valve, the medial boundary is the LAA, and the lateral boundary is the LAA (Fig. 48-29). The most common locations for mitral PVL are anteromedial (between the LAA and the aortic valve) and posterolateral (the lowest portion of the MV away from the LAA and aortic valve).[23]

When TEE is used, the PVL can be localized relative to the defined boundaries described or, alternatively, a clock-face orientation can be used. Fig. 48-30 demonstrates the clock-face orientation of the MV as viewed from the left ventricle, which is also the position of the MV in the typical left anterior oblique C-arm angulation. The 90-degree TEE view demonstrates the leak origin (Fig. 48-30, *A*), which is confirmed by the 134-degree view (Fig. 48-30, *B*), and both views show the anteromedial PVL origin (11 o'clock). Similarly, the aortic valve can be referenced to a clock-face, as shown in Figure 48-29. Aortic PVLs are most commonly encountered at the 7 o'clock to 11 o'clock position (46%), followed by the 11 o'clock to 3 o'clock position (36%).[22,23] An alternative designation is to identify the origin of the PVL with respect to the

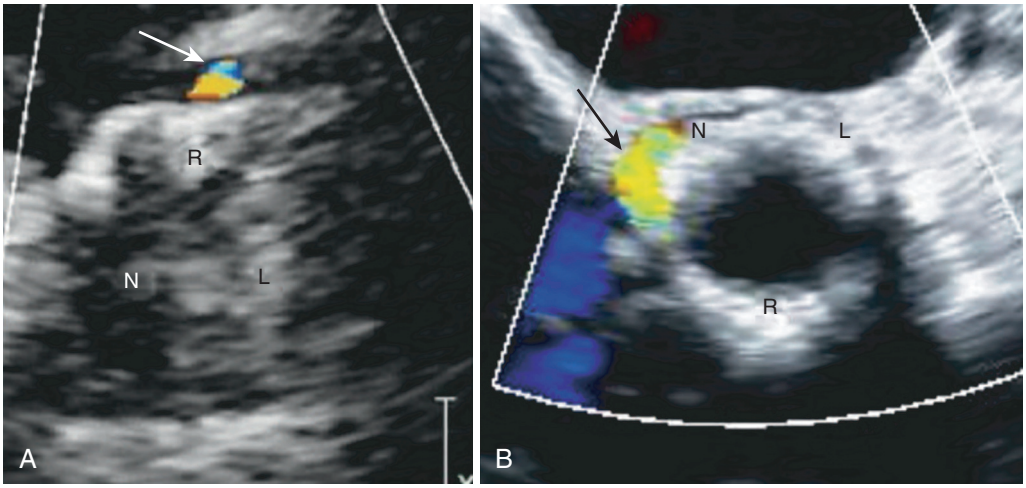


FIGURE 48-31 Aortic paravalvular leak localization. **A,** Transthoracic echocardiogram in the parasternal short-axis view shows a leak *(arrow)* at the native right (R) coronary cusp. **B,** Transesophageal echocardiogram in the short-axis view (45 degrees) shows a leak *(arrow)* at the noncoronary (N) cusp. *L,* Native left coronary cusp.

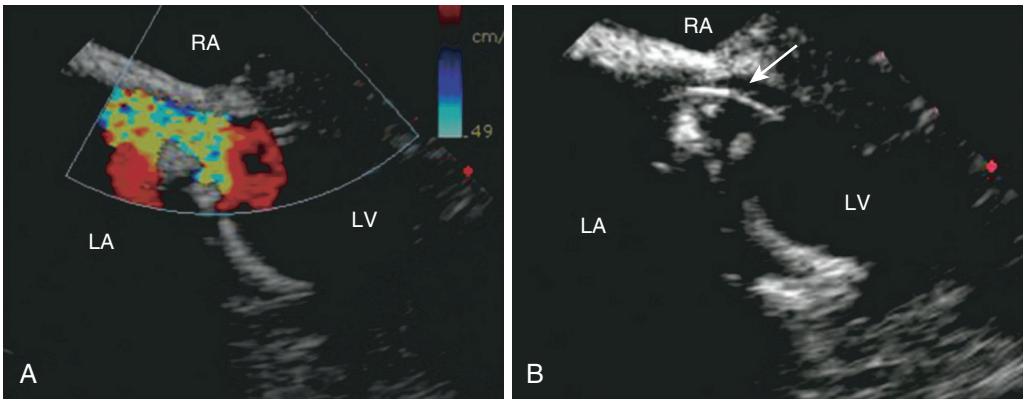


FIGURE 48-32 Use of intracardiac echocardiography (ICE) to guide mitral paravalvular leak (PVL) closure. **A,** Color flow Doppler image demonstrates the leak. **B,** Wire is placed across the leak *(arrow)*. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium.

native cusp location (i.e., right, left, and noncoronary cusps). The short-axis view of the aortic valve, by TTE or TEE, is usually the most helpful view in defining the leak with respect to the cusps (Fig. 48-31). In addition, we use ICE for puncture of the IAS and for initial wire or catheter guidance if the PVL is well seen (Fig. 48-32). In general, we place the TEE probe after crossing the leak with a wire (if possible) to minimize the duration of TEE intubation in patients who are usually under conscious sedation alone (without endotracheal intubation or general anesthesia). In cases of lateral mitral PVL, the ICE catheter situated in the right atrium is inadequate to provide appropriate procedural guidance.

The integration of CT angiography with fluoroscopy (CT angiography–fluoroscopy fusion imaging) now provides an alternative to conventional fluoroscopically guided intervention. The location of the PVL on TEE and markings are made on a preprocedural noncontrast CT (Fig. 48-33). A CT-like image is made using the catheterization laboratory's C-arm to establish the position of the patient on the table and landmarks needed to register the preprocedural CT using syngo DynaCT (Siemens Healthcare, Forchheim, Germany) or HeartNavigator system (Philips Healthcare, Best, The Netherlands). The overlay is then fused with the real-time fluoroscopic image to provide a dynamic, integrated record of the location of the PVL in relation to the mitral or aortic valve. Provision of these stenciled "targets" allows optimal guidance for wires and interventional devices.

Recently, integration of 3D TEE with fluoroscopy has provided another alternative to image guidance. A 3D TEE matrix phase-array transducer (X7-2t, Philips, Andover, MA) instantaneously acquires a 3D pyramidal dataset, which is fused with the dataset from live fluoroscopic imaging using the EchoNavigator (Philips). This combined display technology allows rotation and orientation of both datasets at the discretion of the interventionalist and allows for real-time wire or catheter guidance, evaluation of procedural success or need for additional devices, and assessment of complications.[25]

SUMMARY

The realm of imaging in intracardiac interventions is a large topic. Not all the procedures are covered in this chapter, but it provides a framework for understanding the different modalities available and their respective roles during these procedures. The ideal choice of modalities is based on the intervention planned, local expertise, operator confidence, training, and financial constraints. Multimodality imaging serves as the starting point for appropriate patient selection and for defining and guiding the intraprocedural and postprocedural strategy. Fluoroscopy and echocardiography are the primary imaging modalities for guiding intracardiac interventions, but rapid advances in CT, magnetic resonance imaging, and hybrid imaging with fluoroscopic registration are bringing multimodality imaging to the catheterization laboratory.

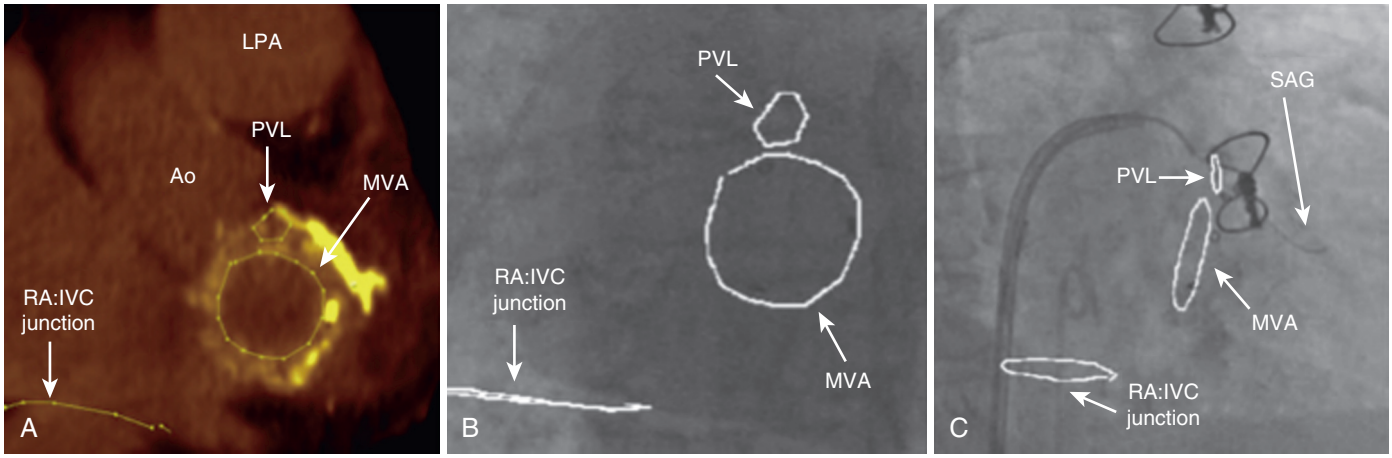


FIGURE 48-33 Integration of computed tomography (CT) and real-time fluoroscopy. **A,** Areas of interest are marked on the preprocedural CT (LAO projection). **B,** CT markings are overlaid onto the real-time fluoroscopic image in the catheter laboratory (LAO). **C,** Markings facilitate crossing of the leak (RAO projection). *Ao,* Aorta; *IVC,* inferior vena cava; *LAO,* left anterior oblique; *LPA,* left pulmonary artery; *MVA,* mitral valve annulus; *PVL,* paravalvular leak; *RA,* right atrium; *RAO,* right anterior oblique; *SAG,* stiff-angled Glidewire (Terumo Interventional Systems, Somerset, NJ).

REFERENCES

1. Di Biase L, Santangeli P, Anselmino M, et al: Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. *J Am Coll Cardiol* 60:531–538, 2012.
2. Hildner FJ, Furst A, Krieger R, et al: New principles for optimum left ventriculography. *Cathet Cardiovasc Diagn* 12:266–273, 1986.
3. Grollman JH, Jr: Pulmonary arteriography. *Cardiovasc Intervent Radiol* 15:166–170, 1992.
4. Shanewise JS, Cheung AT, Aronson S, et al: ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography. *J Am Soc Echocardiogr* 12:884–900, 1999.
5. Shanewise JS, Cheung AT, Aronson S, et al: ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography. *Anesth Analg* 89:870–884, 1999.
6. Kort S: Intracardiac echocardiography: evolution, recent advances, and current applications. *J Am Soc Echocardiogr* 19: 1192–1201, 2006.
7. Solomon SB: The future of interventional cardiology lies in the left atrium. *Int J Cardiovasc Intervent* 6:101–106, 2004.
8. Cafri C, de la Guardia B, Barasch E, et al: Transseptal puncture guided by intracardiac echocardiography during percutaneous transvenous mitral commissurotomy in patients with distorted anatomy of the fossa ovalis. *Catheter Cardiovasc Interv* 50:463–467, 2000.
9. Salome N, Braga P, Goncalves M, et al: Transcatheter device occlusion of atrial septal defects and patent foramen ovale under intracardiac echocardiographic guidance. *Rev Port Cardiol* 23: 709–717, 2004.
10. Al-Saady NM, Obel OA, Camm AJ: Left atrial appendage: structure, function, and role in thromboembolism. *Heart* 82:547–554, 1999.
11. Marek D, Vindis D, Kocianova E: Real time 3-dimensional transesophageal echocardiography is more specific than 2-dimensional TEE in the assessment of left atrial appendage thrombosis. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 157:22–26, 2013.
12. Nucifora G, Faletra FF, Regoli F, et al: Evaluation of the left atrial appendage with real-time 3-dimensional transesophageal echocardiography: Implications for catheter-based left atrial appendage closure. *Circ Cardiovasc Imaging* 4:514–523, 2011.
13. Abbara S, Mundo-Sagardia JA, Hoffmann U, Cury RC: Cardiac CT assessment of left atrial accessory appendages and diverticula. *AJR Am J Roentgenol* 193:807–812, 2009.
14. Wang Y, Di Biase L, Horton RP, et al: Left atrial appendage studied by computed tomography to help planning for appendage closure device placement. *J Cardiovasc Electrophysiol* 21:973–982, 2010.
15. Krishnaswamy A, Patel NS, Ozkan A, et al: Planning left atrial appendage occlusion using cardiac multidetector computed tomography. *Int J Cardiol* 158(2):313–317, 2012.
16. Guerios EE, Bueno R, Nercolini D, et al: Mitral stenosis and percutaneous mitral valvuloplasty (part 1). *J Invasive Cardiol* 17:382–386, 2005.
17. Roberts JW, Lima JA: Role of echocardiography in mitral commissurotomy with the Inoue balloon. *Cathet Cardiovasc Diagn* (Suppl 2):69–75, 1994.
18. Feldman T: Transseptal antegrade access for aortic valvuloplasty. *Catheter Cardiovasc Interv* 50:492–494, 2000.
19. Vahanian A: Balloon valvuloplasty. *Heart* 85:223–228, 2001.
20. Shively BK: Transesophageal echocardiographic (TEE) evaluation of the aortic valve, left ventricular outflow tract, and pulmonic valve. *Cardiol Clin* 18:711–729, 2000.
21. Feldman T, Wasserman HS, Herrmann HC, et al: Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the Everest Phase I clinical trial. *J Am Coll Cardiol* 46:2134–2140, 2005.
22. Cribier A, Eltchaninoff H, Tron C, et al: Percutaneous implantation of aortic valve prosthesis in patients with calcific aortic stenosis: technical advances, clinical results and future strategies. *J Interv Cardiol* 19:S87–S96, 2006.
23. Ruiz CE, Jelnin V, Kronzon I, et al: Clinical outcomes in patients undergoing percutaneous closure of periprosthetic paravalvular leaks. *J Am Coll Cardiol* 58:2210–2217, 2011.
24. Krishnaswamy A, Kapadia SR, Tuzcu EM: Percutaneous paravalvular leak closure- imaging, techniques and outcomes. *Circ J* 77:19–27, 2013.
25. Quaife RA, Salcedo EA, Carroll JD: Procedural guidance using advance imaging techniques for percutaneous edge-to-edge mitral valve repair. *Curr Cardiol Rep* 16:452, 2014.

Percutaneous Closure of Patent Foramen Ovale and Atrial Septal Defect

49

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KEY POINTS

- Although patent foramen ovale (PFO) and atrial septal defect (ASD) both involve an abnormal communication across the interatrial septum, their causes are different. PFO results from lack of fusion between the septum primum and the septum secundum, whereas a secundum ASD is caused by the absence of a segment of the atrial septum.
- PFO has been associated with paradoxical embolization, cryptogenic stroke, migraine headache, decompression sickness, and platypnea-orthodeoxia syndrome.
- The role of PFO closure for migraine headache and ischemic cerebrovascular events remains unclear in view of data from randomized controlled trials.
- Indications for ASD closure include right cardiac chamber enlargement, paradoxical embolism, and platypnea-orthodeoxia syndrome.
- Percutaneous closure of a PFO or a secundum ASD is a simple, safe, and effective treatment option for the appropriate candidates.
- Anatomic variations may require advanced closure techniques for successful closure.

The advent of cardiopulmonary bypass support revolutionized the management of many structural cardiac abnormalities. Since the first surgical repair of an atrial septal defect (ASD) in 1952, surgical techniques have been steadily refined, conferring excellent short-term and long-term outcomes. Previous management of ASD was primarily surgical. The past 2 decades witnessed the growth of percutaneous techniques for the management of coronary and other vascular pathologies.

Refinements in percutaneous interventional technology and advances in cardiac imaging techniques permitted percutaneous treatment of selected structural cardiac defects. ASD, one of the most common congenital cardiac anomalies, was one of the earliest to be approached percutaneously. King and Mills first reported ASD closure in five patients in 1976 using a double-umbrella device.[1] They have since reported a 27-year follow-up of the five patients.[2] The device required a very large delivery system, which limited its use. The early successes were followed by use of the Rashkind device and subsequently the Lock Clamshell Occluder in the late 1980s.[3,4] Technological improvements produced the next generation of devices, which made percutaneous closure of a secundum ASD preferable to the surgical approach. Patent foramen ovale (PFO), which had been rarely treated surgically despite its known association with paradoxical embolism, also became accessible to percutaneous closure.

The years since the U.S. Food and Drug Administration (FDA) approval of selected devices for closure of ASDs and PFOs in 2006 have seen a paradigm shift in their management. Treatment of ASD and PFO shifted away from the surgical arena and into the catheterization laboratory, and as a result, patient recovery time was shortened, complications were decreased, and treatment efficacy was maintained.

The association of PFO with other disease processes such as migraine was identified, which opened the door to new treatment options for many patients. Data from multicenter, randomized, controlled trials evaluating transcatheter PFO closure for recurrent stroke and migraines have added further complexity to the management of these diseases.

This chapter describes the percutaneous closure of ASDs and PFOs. Explanations of the embryology, pathophysiology, and clinical associations of these anatomic defects are followed by a description of the procedure for closure, its indications, and complications.

PATENT FORAMEN OVALE

Embryology

PFO is a remnant of the fetal circulation. By day 18 of gestation, the primordium of the heart becomes evident. At the end of the fourth week, the endocardial cushions fuse to form the right and left atrioventricular canals. The endocardial cushions serve as the primordium of the atrioventricular valves and the inferior wall of the atrium.

At this time, the common atrium undergoes a process of septation. The *septum primum* grows caudally toward the endocardial cushions, closing the interatrial communication *(ostium primum)*. As the septum primum reaches its destination, the cells in its superior portion undergo apoptosis and coalesce to form the *ostium secundum*. A muscular *septum secundum* forms to the right of the septum primum and extends to reach the caudal border of the ostium secundum, forming a flaplike valve between both atria (Fig. 49-1 and Video 49-1).[5]

Oxygenated placental blood enters the right atrium from the inferior vena cava (IVC) and is directed toward the interatrial septum (IAS) by the eustachian valve. The low left atrial pressure, the lack of blood flow through the pulmonary veins, and the preferential flow of the IVC to the IAS allow oxygenated blood to cross the foramen ovale and enter the systemic circulation. Blood entering the right atrium from the superior vena cava (SVC) is directed away from the IAS by the *crista interveniens*, preventing the mixture of nonoxygenated blood in this chamber. The right horn of the *sinus venosus* incorporates the SVC and IVC into the right atrium (Video 49-2).

At birth, the pulmonary vascular resistances and the right cardiac pressures fall, and the left atrial pressure increases, forcing the *septum primum* against the *septum secundum* and occluding the valvelike foramen ovale. Complete occlusion occurs in most of the population, but in approximately 25%, the fusion is incomplete, giving rise to a PFO[6] (Video 49-3).

Incidence

The echocardiographic estimate for the incidence of PFO in the adult population is approximately 25%.[6] Autopsy studies revealed probe-patent PFOs of 0.2 to 0.5 cm in 29%.[7] The frequency of PFO decreases with age and increases in size with each decade of life.[8] Spontaneous PFO closure may occur during adulthood, although data suggest that PFOs may recanalize over time.[9] The incidence rate of PFO is equal for both genders and among all ethnic groups; however, the PFOs in whites and Hispanics are larger and are associated with a greater degree of shunting.[10]

PFO was thought to be an inconsequential finding until 1877, when Cohnheim postulated that a venous thrombosis might paradoxically traverse a foramen ovale and produce a systemic embolism.[11] Since

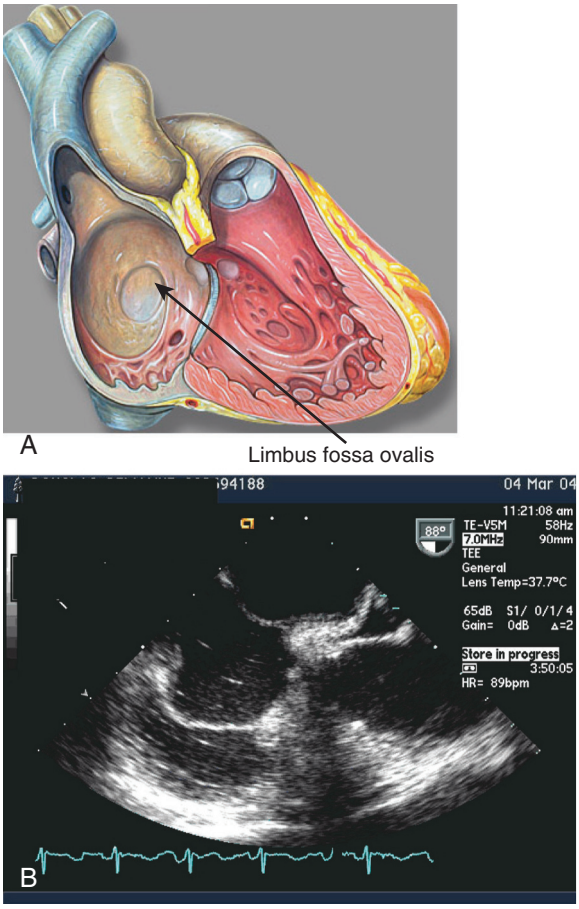

FIGURE 49-1 Diagram and sonogram of the interatrial septum depict the limbus of the fossa ovalis and the anatomic location of the patent foramen ovale.

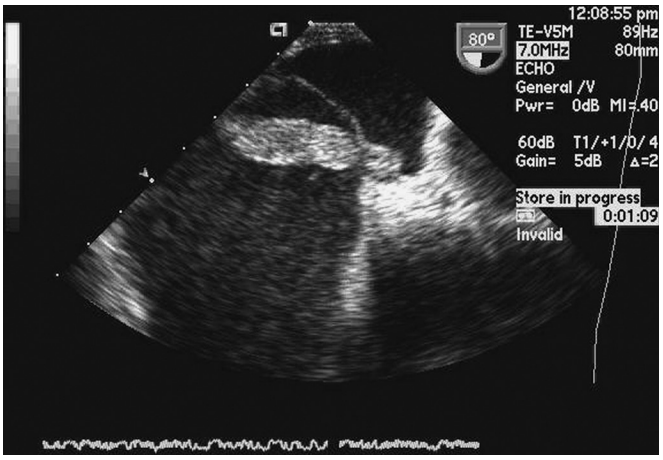

FIGURE 49-2 The thrombus in transit from the right atrium through a patent foramen ovale into the left atrium illustrates the concept of paradoxical embolization.

then, PFOs have been associated with various disease processes, including cryptogenic stroke, paradoxical embolization, platypnea orthodeoxia syndrome, hypoxemia with normal pulmonary pressures, decompression sickness (DCS) in scuba divers and high-altitude pilots, and migraine headaches.[12-17]

Cryptogenic Stroke

The cause of a cerebrovascular accident (CVA) varies among age groups. Atrial fibrillation and small vessel disease contribute to most strokes in patients older than 50 years. Among patients younger than 35 years, the most common causes include nonatherosclerotic arteriopathies, arterial dissection, and thromboembolism.[9] However, in 35% to 40% of patients with CVAs, the causes remain unknown even after a thorough evaluation, and the CVAs are classified as *cryptogenic*. Different causes that remain unidentified by current diagnostic modalities may be included under this classification.

The search for the probable causes of cryptogenic strokes has generated conflicting information. In a retrospective case-control study, PFOs were four times more prevalent among young adults who experienced a stroke without an identifiable cause compared with others with known causes.[13] In a meta-analysis, PFOs were found to occur up to six times more frequently among patients younger than 55 years who suffered a cryptogenic stroke compared with those who had identifiable causes of CVAs.[18] Others found a higher frequency of PFOs among patients with cryptogenic strokes irrespective of age (<55 years, 48% vs. 4%; >55 years, 38% vs. 8%; $P < .001$), although this observation is not generally accepted.[14] Among patients with cryptogenic strokes, patients with PFOs were less likely to have traditional cardiovascular risk factors such as hypertension, hypercholesterolemia, and tobacco use, which suggests a different mechanism for CVAs in this population subset.[19]

The mechanism by which a PFO may participate in the generation of a cryptogenic stroke is unclear. In situ thrombosis, paradoxical embolization, and predisposition to atrial arrhythmias have been proposed as mechanisms for PFO-associated cryptogenic strokes.[20] Paradoxical embolization (i.e., passage of a venous thrombus into the systemic circulation through a PFO) has been the predominant theory (Fig. 49-2 and Video 49-4). Evidence that supports the role of PFOs in cryptogenic strokes includes case reports of the transit of thrombi across PFOs; cerebral distribution of cryptogenic CVAs that suggests an embolic nature; and the increased frequency of deep venous thrombosis in patients who had cryptogenic CVAs.[21-23]

The Paradoxical Embolism From Large Veins in Ischemic Stroke (PELVIS) trial found an increased frequency of positive magnetic resonance venography testing for pelvic thrombus in patients with PFOs and cryptogenic CVAs compared with patients with known causes (20% vs. 4%, $P < .03$).[24] The corollary that patients with pulmonary emboli and PFOs have a significantly higher stroke rate (13% vs. 2%, $P = .02$) is also true.[25]

In a prospective trial of 503 patients, Handke and colleagues showed that PFOs were more frequent among patients experiencing cryptogenic strokes irrespective of age (<55 years: 43.9% vs. 14.3%, odds ratio [OR] = 4.70, $P < .001$; >55 years: 28.3% vs. 11.9%, OR = 2.92, $P < .001$).[26] These data underline the causative role of paradoxical embolization in patients who had cryptogenic strokes. However, this association is still being debated.

Most information available on the association of PFOs and cryptogenic strokes originates from small, case-control or retrospective studies. A large, population-based, case-control study that included 1072 participants (i.e., random controls, patients who had suffered noncryptogenic strokes, and patients who had suffered cryptogenic strokes) failed to show an association between cryptogenic strokes and PFOs.[27] The lack of association might have been related to the study design because case selection included patients who did not have recurrent CVAs.

Data from the Stroke Prevention: Assessment of Risk in a Community (SPARC) trial, a prospective trial that questioned the veracity of a causal relationship between PFOs and strokes of unknown origin, have been published.[28] The trial included 588 healthy volunteers in Olmstead County who underwent multimodality testing and follow-up for stroke risk assessment. Over 5 years, 41 of the subjects experienced

a stroke. After adjusting for age and other cardiovascular comorbidities, PFOs were not found to be an independent predictor of stroke (hazard ratio [HR] = 1.28; 95% confidence interval [CI], 0.65 to 2.50). The Kaplan-Meier estimate of CVA-free survival was 91% and 93% for patients with and without PFOs, respectively. The trial confirmed that a PFO does not pose an increased risk of stroke in asymptomatic patients. Unfortunately, this trial included an older population (66.9 ± 13 years) even though most other trials recognize the association between cryptogenic stroke and age in patients younger than 55 years; and the trial had a low prevalence of CVAs, which limited its ability to detect a statistically significant hazard. The hazard ratio may be as low as 0.65 or as high as 2.5 and still be consistent with the study's findings.

Stroke Recurrence and Risk Identification

Prospective data from an observational study presented in abstract form have documented the incidence of CVAs among patients with PFOs as 1.10 per 100 person-years and in patients without PFOs as 0.97 per 100 person-years.[29] The low incidence does not make primary prevention cost effective, and additional risk factors that may detect people at risk need to be identified.

The reported recurrence rate of cryptogenic stroke varies from 1.2% to more than 16% but usually is about 2%.[30,31] Retrospective studies have found the risk of recurrence to be related to PFO size, patency at rest, shunt severity, and the presence of atrial septal aneurysm (ASA).[32-34] A prominent eustachian valve has been associated with increased patency of the foramen ovale and the risk of stroke recurrence because it preferentially directs blood flow to the IAS (Fig. 49-3 and Video 49-5).[35] It has been postulated that a mobile IAS may increase the size of the foramen ovale, facilitating the passage of thrombi. Recurrences of cryptogenic CVAs have been associated with the degree of septal protrusion. Patients with a septum excursion greater than 6.5 mm had a risk of recurrence of 12.3% compared with 4.3% for controls at 3 years.[30]

The combination of ASA and PFO was associated with an increased risk of recurrence in a French PFO/ASA study (HR = 4.17; 95% CI, 1.47 to 11.84).[36] However, this finding was not supported by the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS).[37] The PICSS trial was designed to define the rate of recurrent stroke or death among patients with and without PFOs, who were randomly treated with aspirin or warfarin over a period of 2 years. The multicenter, double-blind study included 265 patients who had cryptogenic strokes and 365 who had noncryptogenic strokes. PFOs were more frequently found in the cryptogenic stroke group (48% vs. 38%, $P < .02$), and larger PFOs were more frequently associated with the same stroke subtype (20% vs. 9.7%, $P < .001$). There was no statistically significant difference in the time to recurrent stroke or death for the cryptogenic stroke group when categorized by PFO status (14.3% vs. 12%).

In all patients in the PICSS trial, there was no difference in stroke recurrence when categorized by the presence of PFOs and ASAs. However, the study has significant limitations that may alter the generalization of its results. The subjects were older and had a higher prevalence of CVA risk factors (i.e., diabetes and hypertension), and only 42% of the enrolled patients had had cryptogenic strokes. The subgroup analysis of patients who had cryptogenic stroke might have been underpowered for treatment assumptions. Because of the inherent limitations of the study design, the small patient population, and the differences in control groups, the association between PFOs and CVAs cannot be established at this time. Larger randomized trials are required to answer this question.

Diagnosis of a Paradoxical Embolic Stroke

The diagnosis of a cryptogenic stroke is a diagnosis of exclusion. A complete evaluation to rule out other causes must be performed before assigning this diagnosis, and it should include a hypercoagulable evaluation, echocardiogram, heart rhythm evaluation, and carotid Doppler as detailed in Table 49-1. If the working diagnosis of paradoxical embolization is still feasible, a right-to-left shunt should be evaluated with an echocardiogram with a bubble study or a transcranial Doppler.

Treatment of Cryptogenic Stroke

Medical Treatment

Controversy exists regarding the best method for the prevention of recurrent events in patients who have experienced cryptogenic strokes. Medical treatment with aspirin or oral anticoagulants has been reported. In the French PFO/ASA study, 267 patients who experienced cryptogenic strokes and had PFOs only or PFOs with ASAs were treated with aspirin or with aspirin and warfarin if they had a venous thrombosis.[36] After 4 years of follow-up, there were 12 episodes of recurrent strokes and 9 recurrent transient ischemic attacks (TIAs). All episodes occurred in patients treated with aspirin.

In the Lausanne study,[38] 140 patients with the same characteristics were followed for 36 months. Treatment was assigned on the basis of number of risk factors and included surgical PFO closure (8%), oral anticoagulation with a target international normalized ratio (INR) of 3 to 4 (26%), or aspirin (66%). There was 1.9% yearly event rate for CVAs and 3.8% for the combination of CVAs and TIAs. A meta-analysis,[39] which included 895 patients in the medical therapy arm, evaluated the benefit of medical therapy versus transcatheter closure of PFOs in patients with presumed paradoxical embolization. The analysis yielded a 1-year recurrence rate between 3.8% and 12%.

The PICSS trial was the only prospective, blinded, randomized trial that compared the efficacy of aspirin versus oral anticoagulation in patients with CVAs.[38] It found no statistically significant difference in stroke recurrence between patients with PFOs treated with aspirin and those treated with warfarin (17.9% vs. 9.5%; HR = 0.52; 95% CI, 0.16 to 1.67; $P = .28$). The high recurrence rate suggests other (non-PFO) mechanisms for CVAs in the older population. As expected, there was a slight increase in the rate of minor hemorrhage among patients on the warfarin arm. Currently, there is no consensus on the superiority of antiplatelet or oral anticoagulation therapy for patients with cryptogenic strokes and PFOs.[40]

Surgical Treatment

Surgical closure of PFOs in patients who had cryptogenic strokes has been reported. The largest series included 91 consecutive patients with a mean age of 44 years and one prior CVA. Surgery was evaluated with intraoperative transesophageal echocardiography (TEE), and suture or patch closure was employed. Closure was achieved in 98% of cases, and the actuarial freedom from recurrence was 93% at 1 year and 83% at 4 years. The surgical procedure was associated with significant morbidity in 21%.[41] Smaller series reflected similar closure rates and significant morbidity.

Percutaneous Treatment

Percutaneous closure of PFOs has been available for the past decade. The available data reflect single-operator or multiple-center experiences with moderate follow-up. Procedural success has been greater than 90% and may depend on the closure device used and associated anatomic variants. An ASA may decrease the rate of successful closure. Device modifications and growing experience and familiarity with the technique have greatly reduced the complication rate while maintaining appropriate closure rates.

Windeker and coworkers reported results for 80 patients, with a procedural success rate of 98% and a 2.5% recurrent TIA rate at 5 years.[42] Residual shunting has been identified as a risk factor for recurrent CVAs; overall, percutaneous closure has a recurrent rate similar to that of medical therapy.[43,44]

The only series that compared medical therapy to percutaneous closure in patients with PFOs and cryptogenic strokes was published by Windeker and colleagues.[45] Patients were nonrandomly assigned to percutaneous closure ($n = 150$) or medical treatment with aspirin ($n = 78$) or oral anticoagulation ($n = 78$) with an INR of 2 to 3. They were followed for 2.3 ± 1.7 years. Groups were comparable in terms of age, gender, and cardiovascular risk factors. Percutaneous closure led to a

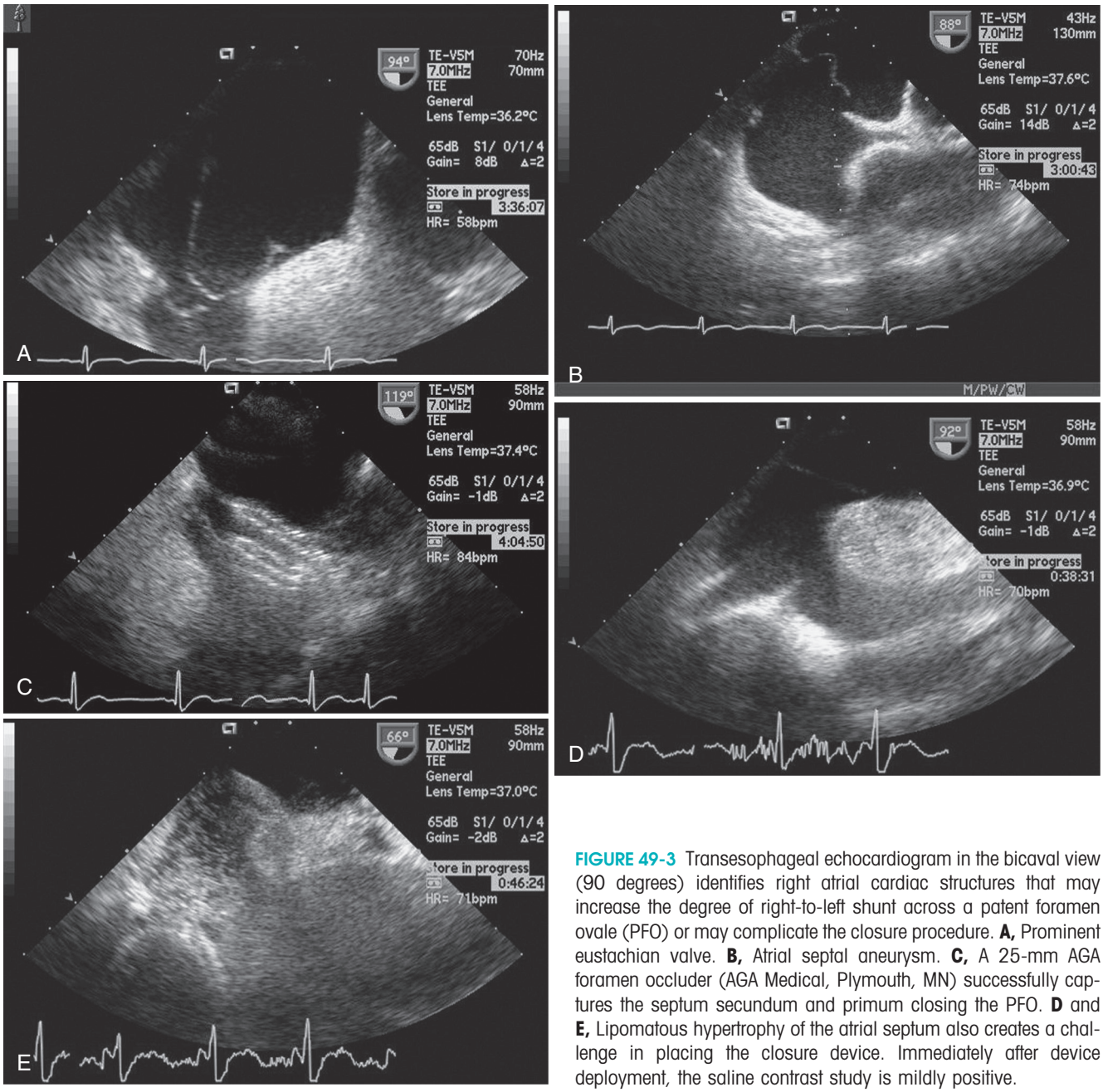

FIGURE 49-3 Transesophageal echocardiogram in the bicaval view (90 degrees) identifies right atrial cardiac structures that may increase the degree of right-to-left shunt across a patent foramen ovale (PFO) or may complicate the closure procedure. **A,** Prominent eustachian valve. **B,** Atrial septal aneurysm. **C,** A 25-mm AGA foramen occluder (AGA Medical, Plymouth, MN) successfully captures the septum secundum and primum closing the PFO. **D** and **E,** Lipomatous hypertrophy of the atrial septum also creates a challenge in placing the closure device. Immediately after device deployment, the saline contrast study is mildly positive.

TABLE 49-1 Evaluation of Cryptogenic Stroke

Condition	Diagnostic Test
Cerebrovascular disease	Carotid Doppler, magnetic resonance angiography
Cardiac source of embolism	
Left atrial appendage thrombus	Transesophageal echocardiogram
Left ventricular aneurysm	Transthoracic or transesophageal echocardiogram
Ascending aorta atheroma	Transesophageal echocardiogram
Paroxysmal atrial fibrillation	Holter monitor
Hypercoagulable state	Protein C and S activity Antithrombin III level Lupus anticoagulant Anticardiolipin antibody Factor V Leiden Prothrombin 20210A mutation

lower risk of the combined end point of death, recurrent stroke, or TIA (8.5% vs. 24%; RR = 0.48; 95% CI, 0.23 to 1.01; $P = .05$). Patients with more than one event at baseline and those with complete occlusion of the foramen ovale were at lower risk for recurrent stroke or TIA after percutaneous treatment compared with those receiving medical therapy (7.3% vs. 33.2%; $p = 0.01$; 95% CI 0.08 to 0.81, and 6.5% vs. 22.2%; $p = 0.04$; 95% CI 0.14 to 0.99, respectively). With its inherent limitations, this study demonstrated an advantage of percutaneous treatment of high-risk patients (i.e., recurrent CVAs), and the trials evaluating PFO closure have been developed as superiority trials rather than noninferior trials.

Percutaneous closure of PFOs in patients who experienced recurrent CVAs despite being on medical therapy carries a class IIb indication by the American Heart Association (AHA) guidelines on stroke prevention.[46] Data to support PFO closure after a first stroke are insufficient. The FDA has permitted the use of the Amplatzer and CardioSeal septal occluders under humanitarian device exemption only for

patients who have experienced recurrent CVAs while on conventional medical therapy (i.e., oral anticoagulation with a therapeutic INR).

Results are available for three multicenter, randomized, controlled trials comparing PFO closure for recurrent cryptogenic stroke with medical therapy: RESPECT, CLOSURE 1, and PC.[47-49] Two trials are ongoing: CLOSE and REDUCE.[50,51]

CLOSURE 1 (evaluation of the STARFlex septal closure system in patients with a stroke or transient ischemic attack due to presumed paroxysmal embolism through the patent foramen ovale) evaluated PFO closure with the CardioSeal and STARFlex septal occluders compared with aspirin or warfarin, or both, in 909 patients 18 to 60 years old with a cryptogenic CVA or TIA during the 6 months before enrollment. Over a 2-year follow-up, the composite end point of CVA or TIA, all-cause death at 30 days, and death from neurologic causes between 31 and 730 days was similar among groups: 5.5% versus 6.8% for closure compared with antiplatelet or anticoagulant therapy (HR = 0.78; 95% CI, 0.45 to 1.35; $P = 0.37$).

The RESPECT trial (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Standard of Care Treatment) compared PFO closure using the Amplatzer PFO occluder with antiplatelet or anticoagulation therapy (i.e., aspirin, warfarin, clopidogrel, aspirin plus dipyridamole, or aspirin plus clopidogrel) in 980 patients followed over a mean of 2.6 years. Although the primary end point was negative by intention-to-treat analysis (recurrent CVA for closure: 1.8% vs. 3.4% for antiplatelet/anticoagulant therapy; HR = 0.49; 95% CI, 0.22 to 1.11; $P = .08$), three patients randomized to device closure had a stroke before receiving the device. The as-treated cohort analysis showed a positive trend favoring the device closure cohort (1.1% vs. 3.3%; HR = 0.27; 95% CI, 0.10 to 0.75; $P = .007$), and the per-protocol cohort analysis favored transcatheter closure (1.3% vs. 3%; HR = 0.37; 95% CI, 0.14 to 0.96; $P = .03$). The subset analysis favored device closure for PFO with associated ASAs.

The PC trial (Patent Foramen Ovale and Cryptogenic Embolism) compared PFO closure using the Amplatzer PFO occluder with medical therapy (i.e., at least one antiplatelet or anticoagulant drug) in 414 patients age younger than 60 years with a history of cryptogenic stroke, TIA, or peripheral embolism and documented PFO. The composite end point of death, nonfatal stroke, TIA, or peripheral embolism was similar for the groups (3.4% vs. 5.2%; HR = 0.63; 95% CI, 0.24 to 1.62; $P = .34$).

The primary end points for the completed trials have been negative. However, a meta-analysis of the completed randomized controlled trials for secondary prevention of cryptogenic stroke shows a statistically significant trend favoring transcatheter PFO closure using a per-protocol analysis (HR = 0.64; 95% CI, 0.41 to 0.98, $P = .043$).[52]

The ongoing Gore REDUCE trial (Gore Helex Septal Occluder/Gore Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients) is evaluating PFO closure with the Gore Helex and Gore Septal Occluder devices compared with aspirin and estimates an enrollment of 664 patients with magnetic resonance imaging (MRI)–confirmed stroke followed over 24 months. The expected completion date is January 2015. This trial is evaluating freedom from recurrent CVA or imaging-confirmed TIA after 24 months of follow-up.

The ongoing CLOSE trial (patent foramen ovale closure or anticoagulants versus antiplatelet therapy to prevent stroke recurrence) is comparing stroke at 3 and 5 years after intervention using CE-marked devices approved by an interventional cardiology committee with aspirin, clopidogrel, or aspirin plus dipyridamole, with a separate group receiving warfarin, rivaroxaban, or dabigatran. The expected completion is December 2016.

Off-label transcatheter PFO closure during the randomized controlled trials' period exceeded trial enrollment. Patients who underwent off-label closure had a higher risk profile compared with the randomized cohorts.[53] The effects of these observations on trial results remains unclear. PFO remains a potential source for paradoxical embolism affecting other organs, especially in young patients without alternative explanations, including absence of atherosclerotic disease, arrhythmias, or hypercoagulable states.

Related Disorders

Migraine Headache

Migraine headaches affect 12% of the U.S. population and generate significant morbidity and economic burden. The cause of migraine headache with aura has remained elusive. People with migraine headaches have a twofold increase in the risk of stroke, and the risk increases to 3.5 for patients younger than 35 years of age.[54] Observational studies have revealed that patients who experience migraines have increased frequency of silent, deep, white matter lesions.[55] Migraine headaches are more frequently seen in patients younger than 45 years of age who had experienced an infarct in the posterior cerebral circulation.[56] These facts and the growing information obtained from the evaluation of PFOs and cryptogenic strokes prompted researchers to assess the frequency of right-to-left shunting in migraineurs.

Anzola and coworkers evaluated right-to-left shunting by transcranial Doppler (TCD) in 113 patients with migraine with aura and compared these patients with 53 patients with migraine without aura and 25 healthy age-matched controls.[57] The incidence of PFO was significantly higher among the migraineurs with aura compared with the migraineurs without aura or the controls (48% vs. 23% vs. 20%).[57] Retrospective analysis of patients who underwent PFO closure for cryptogenic strokes revealed a decrease in the frequency of attacks of migraine with aura in 80% or even complete resolution in 56%.[58,59] Unfortunately, these studies might have been influenced by recall bias; the therapeutic effect of aspirin or clopidogrel, which might have been used for migraine prophylaxis; a high placebo effect; and the fact that migraine frequency decreases with age. Retrospective studies also do not demonstrate a causal association. The high frequencies of PFOs and migraine headaches in the general population may favor a spurious association.

Anzola and colleagues prospectively compared patients with PFOs and cryptogenic strokes who underwent PFO closure ($n = 23$) with patients who had migraines, peripheral embolic events, or TIAs who underwent PFO closure ($n = 27$) and patients with migraines and PFOs who were treated medically ($n = 27$).[60] After a 12-month follow-up, the frequency and intensity of the migraine attacks were significantly decreased in patients who underwent PFO closure.[60]

Nonrandomized registries of patients suffering from migraines with aura have shown a 70% to 90% improvement or symptom resolution after successful PFO closure.[61-63] The association between migraine headache with aura and PFOs has generated new hypotheses on the cause of migraines. It is postulated that migraines may be related to microembolic events or high concentrations of circulating vasoactive substances that are not filtered by the lung because they cross to the systemic circulation through PFOs.

The Migraine Intervention with STARFlex Technology (MIST) trial[64] tested the association between PFOs and migraine headaches with aura. It was a multicenter, blinded study that randomized 432 patients with migraine to PFO closure with a STARFlex Septal Repair (NMT Medical, Boston, MA) implant or a sham procedure. The primary end point of cessation of migraines was not met. However, reduction in headache days in at least 50% occurred more frequently in the PFO closure group (42% vs. 23%, $P = .038$).[64] The discrepancy between the results from the MIST trial and other registries may be related to the exclusion of patients with previous CVAs or TIAs and the lack of complete PFO closure in the MIST trial. The exclusion of patients with previous TIAs or CVAs potentially filtered out those most likely to experience paradoxical embolization and clinical benefit.

There is an ongoing attempt to study such patients in a randomized fashion. The U.S.-based MIST II trial (evaluated PFO closure to treat migraine with aura; sponsored by NMT Medical, Boston, MA) and the ESCAPE trial (Effect of Septal Closure of Atrial PFO on Events of Migraine With the Premere PFO Occlusion Device; sponsored by St. Jude Medical Corp., Fullerton, CA) have been discontinued because of slow enrollment. The PREMIUM trial (evaluating use of the Amplatzer PFO occluder; sponsored by AGA

Medical, Golden Valley, MN), which began enrolling in 2006, is ongoing but no longer recruiting patients.[65] Until these results are available, PFO closure should not be considered for the treatment of migraine headache with aura.

Platypnea-Orthodeoxia Syndrome and Hypoxia

PFO has been associated with the rare platypnea-orthodeoxia syndrome. *Platypnea* refers to the feeling of dyspnea when in an upright posture, and *orthodeoxia* is arterial desaturation that occurs on standing. It is postulated that right-to-left shunting occurs across a patent foramen, particularly in the setting of an ASA.

Platypnea-orthodeoxia syndrome is seen primarily in very old patients and is associated with an event that alters the geometry of intrathoracic organs, such as a pneumonectomy or an enlarged ascending aorta. Extrinsic compression of the right atrium or decreased compliance of the right ventricle may also predispose to shunting at the atrial level in these patients.[66] It is postulated that in patients with an elongated aorta, the heart is shifted laterally so that the IVC drains directly toward the atrial septum, although this is not fully understood. This anatomic shift maintains the PFO open throughout the cardiac cycle and generates the physical findings.[67]

The diagnosis of platypnea-orthodeoxia syndrome is made by using saline contrast echocardiography with the patient in the supine and seated positions.[11] Surgical or percutaneous closure has been done successfully, leading to marked improvement in the patient's symptoms.[68,69]

Hypoxia related to PFOs may be observed in patients with severe pulmonary hypertension or obstructive sleep apnea.[70] The mechanism involves transient or persistent elevation of the right atrial pressure in relation to the left atrial pressure or redirection of the IVC blood flow toward the IAS. Hypoxia related to right-to-left shunting at the atrial level has been associated with pulmonary arteriovenous malformations, liver disease, amiodarone toxicity, pulmonary emboli with transient pulmonary hypertension, positive-pressure ventilation, hypovolemia, aortic aneurysm, right ventricular infarction, Ebstein anomaly, and carcinoid valve disease.

Making the diagnosis may be challenging because it requires documentation of right-to-left shunting while the patient is hypoxic, and frank improvement occurs after closure. In patients with severe pulmonary hypertension with decreased right ventricular function, the PFO serves as an escape valve, which aids emptying of the right atrium into a lower pressure circuit (i.e., left atrium). In these patients, PFO closure may be fatal.

Decompression Sickness

DCS is caused by nitrogen bubbles that come out of solution in blood as the ambient pressure decreases when a person ascends from a dive. The amount of nitrogen bubbles generated depends on the total time spent in the dive, the speed of ascent, compliance with decompression stops, and individual factors such as cardiac output. The nitrogen bubbles usually stay in the venous circulation and make it to the lungs, where they are rapidly diffused. In a person with a PFO, the nitrogen bubbles may enter the systemic circulation and travel superiorly toward the brain, occluding a small arterial branch.

DCS in patients with PFOs is associated with early onset of cerebral or vestibular symptoms, which occur within 30 minutes after a dive, even after the person has performed all the appropriate rest stops.[71] The association of PFOs and DCS is relatively new. In a case-control study, Germonpre found an odds ratio of 2.25 for the development of DCS in divers with PFOs.[72] In a small case-control study, divers with PFOs had a 4.5-fold greater risk of developing DCS than divers without DCS, and they were more likely to have silent ischemic lesions as shown on brain MRI.[73] Torti found that divers with PFOs had a higher risk of developing DCS, required treatment for DCS, and had DCS that lasted more than 24 hours.[74] Currently, PFO closure to prevent DCS is not indicated because of the low overall incidence and ease of avoidance of DCS.

Diagnosis of Patent Foramen Ovale

Echocardiography plays an important role in the diagnosis of abnormalities of the atrial septum. Traditionally, TEE has been considered the gold standard to diagnose a PFO. The advantage of TEE is that it can identify all portions of the IAS, enabling the diagnosis of all subtypes of ASDs, fenestrated atrial septum, and PFOs. TEE also allows detailed identification of lipomatous hypertrophy of the septum, atrial septal aneurysms, a prominent eustachian valve, or a long PFO tunnel that may alter a planned closing procedure (Video 49-6; see Fig. 49-3).

TEE can identify other potential sources of embolization (e.g., left atrial appendage thrombus, cardiac tumors, aortic atheroma). An ASA is defined as a redundancy of the atrial septum with excursion greater than 10 mm into either of the atria and a 15-mm base. The degree and direction of the interatrial shunt depend on the net pressure difference between the atria. The interatrial shunt direction changes with the phase of respiration and the cardiac cycle. It can be documented by color Doppler interrogation of the IAS (Fig. 49-4). Color interrogation along the fossa ovalis may cause erroneous identification of a PFO because of color cross-contamination when lowering the Nyquist limit.

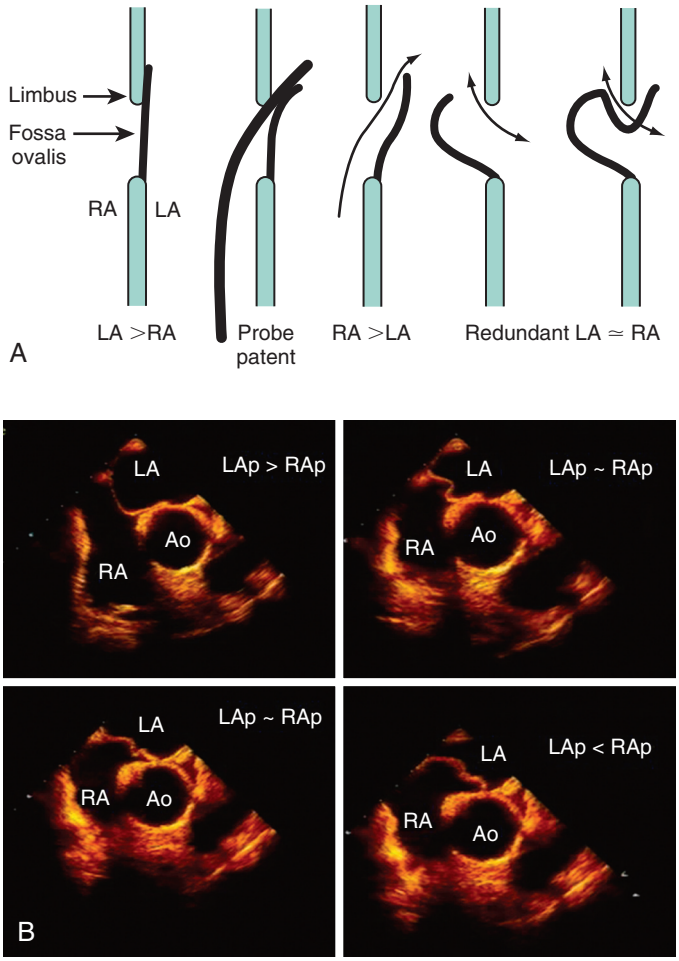

FIGURE 49-4 **A,** Association of interatrial septal anatomy and direction of interatrial shunt. **B,** Transesophageal echocardiograms depict interatrial septal mobility related to left and right atrial pressures. *Ao,* Aorta; *LA,* left atrium; *LAp,* left atrial pressure; *RA,* right atrium; *RAp,* right atrial pressure. (Modified from Amplatz K, Moller H: *Radiology of congenital heart disease.* St. Louis, 1993, Mosby.)

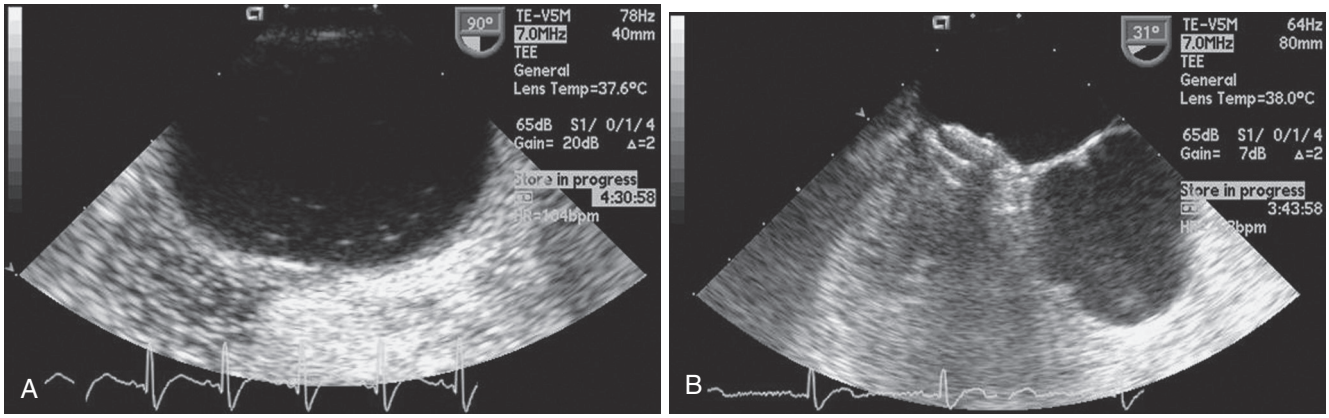

FIGURE 49-5 Transesophageal echocardiogram before (**A**) and after (**B**) placement of a 25-mm AGA foramen occluder (AGA Medical). Saline contrast is present in the left atrium before device placement. After device placement, the saline contrast study is negative.

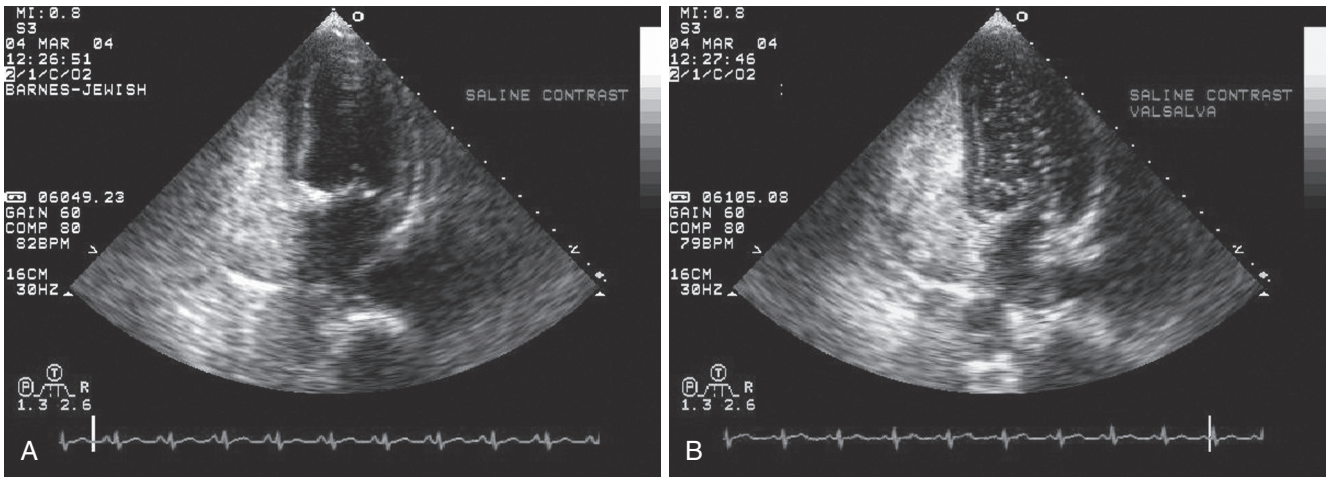

FIGURE 49-6 Transthoracic echocardiogram with a saline contrast study at rest (**A**) and during a Valsalva maneuver (**B**). Transient increase in the right atrial pressure during the release phase of the Valsalva maneuver demonstrates a large right-to-left shunt at the atrial level due to a patent foramen ovale.

TEE's diagnostic sensitivity is significantly lower than that of a saline contrast study; the addition of saline contrast improves TEE's diagnostic sensitivity.[75] The injection of saline contrast through the femoral vein is superior for the diagnosis of PFOs by TEE and for the appropriate sizing of ASDs.[76] Appropriate provocative measures that transiently increase the right atrial pressure (i.e., Valsalva maneuver) may be difficult to perform during a TEE because of the patient's sedation, relative hypovolemia from a fasting state, and the inability to close the glottis against the echo probe (Fig. 49-5 and Videos 49-7 through 49-9).

Fundamental imaging transthoracic echocardiography (TTE) has been considered inferior for the diagnosis of PFOs. However, the advent of second harmonic imaging has improved the sensitivity of TTE to 90%.[77] An easier and more effective performance of a provocative maneuver (e.g., no sedation, euvolemia, complete glottic closure) during TTE may improve the image quality and is associated with a higher sensitivity than that of TEE for the diagnosis of PFOs.[78] The lack of invasiveness makes TTE a more attractive screening tool for PFOs (Fig. 49-6).

TCD also has a role in the detection and quantification of right-to-left shunt. TCD insonates the middle cerebral artery and detects high-intensity transient signals when injected through a vein. Its sensitivity is similar to that of TEE, but its major limitation is its inability to detect the origin of the shunt. The number of transient signals correlates with PFO size and postprocedure PFO patency.[75,79]

Closure Devices

Two PFO septal occluder devices—the Amplatzer PFO occluder and the STARFlex septal closure system—were approved by the FDA under a registry and trial basis only for the treatment of recurrent paradoxical embolization in the setting of a therapeutic INR. NMT Medical has ceased operations, and the STARFlex septal closure device is no longer available. The Premere PFO closure device by St. Jude Medical is no longer under investigation for migraine treatment. The Gore Helex septal occluder (W.L. Gore, Flagstaff, AZ), Amplatzer multifenestrated cribriform septal occluder (ACSO) (AGA Medical, Golden Valley, MN), and the Amplatzer septal occluder (ASO) (AGA Medical, Plymouth, MN) (Figs. 49-7 through 49-9; see Fig. 49-20) have been used for off-label PFO closure and are described later in this chapter.

Amplatzer Patent Foramen Ovale Occluder

The APO is a self-expanding, double-disk device made from 0.005-inch nitinol wire (i.e., nickel-titanium alloy), with a polyester fabric sewn into both disks (Fig. 49-10). In the APO, the left atrial disk is smaller

FIGURE 49-7 Photograph of the Helex septal occluder. (Courtesy W.L. Gore & Associates, Newark, DE.)

FIGURE 49-8 Photograph of the AGA cribriform septal occluder. (Courtesy AGA Medical, Golden Valley, MN.)

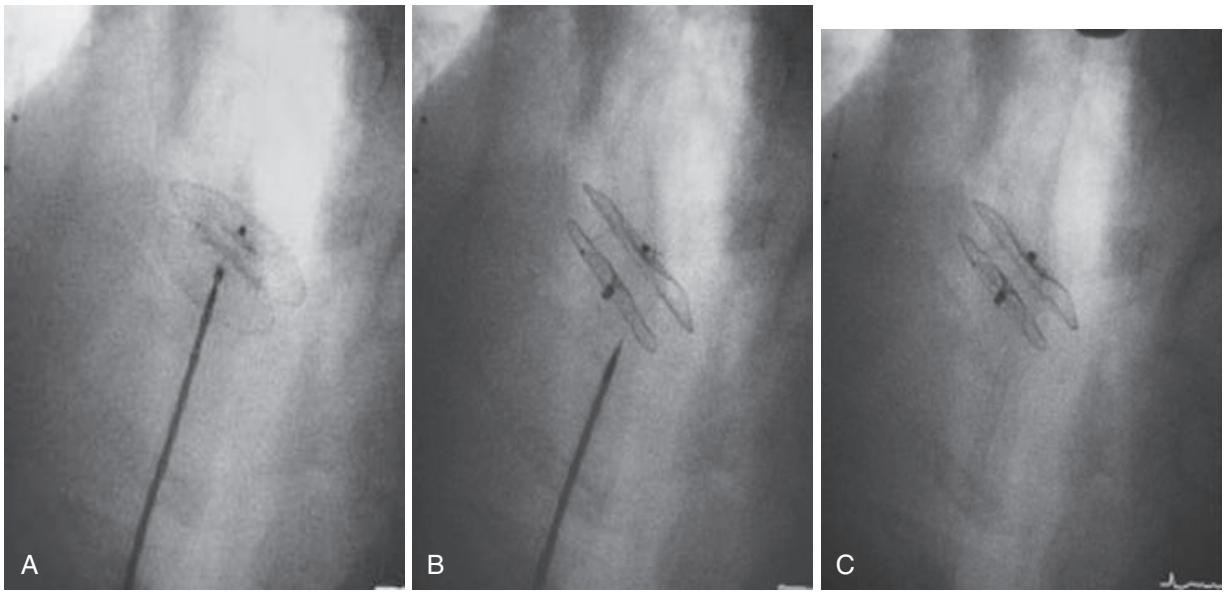

FIGURE 49-9 **A,** Deployment of an AGA septal occluder (AGA Medical). **A,** Once in place, the device is wiggled to ensure stability. **B,** After stability is confirmed, the device is released by rotating the delivery cable. **C,** After it is released, the cable is withdrawn into the delivery sheath to avoid trauma.

than the right atrial disk except for the 18- and 30-mm devices, which have matched disk sizes. This relationship is inverted for the ASO. The ACSO has matched disk sizes. Both the APO and ACSO come in 18-, 25-, 30-, and 35-mm sizes and have a 3- to 4-mm central component.

Device size represents the right atrial disk diameter. The right atrial disk stabilizes the device, preventing embolization from right to left. The thin stem allows various degrees of disk mobility that permits the PFO occluder to seat appropriately in a long tunnel or around a hypertrophied septum. The left atrial disk dimensions are designed to decrease interference with pulmonary venous drainage or with the mitral valve and to minimize the thrombogenic material in the systemic circulation.

Device sizing depends on the measurement from the foramen ovale to the SVC and from the foramen ovale to the aorta. The right disk radius should not exceed the shortest distance obtained (Table 49-2). The 25-mm device is used in most cases. The APO has the advantage of being self-expanding, has a simple deployment, and is placed through a small venous sheath (8 Fr for 18-, 25-, and 30-mm sizes, and 9 Fr for the 35-mm size). It is fully retractable until it is released. Its major disadvantage is that it is bulky within the atrial septum.

Premere Patent Foramen Ovale Closure System

The Premere PFO closure system was available to patients participating in the PFO for migraine trial sponsored by St. Jude Medical (Fig. 49-11), which has been discontinued.

The Premere system has a very small profile and may be difficult to detect with echocardiography. Placement requires balloon sizing. Its unique design allows the operator to increase tension between the left

FIGURE 49-10 Frontal view of the AGA Amplatzer PFO occluder. (Courtesy AGA Medical, Golden Valley, MN.)

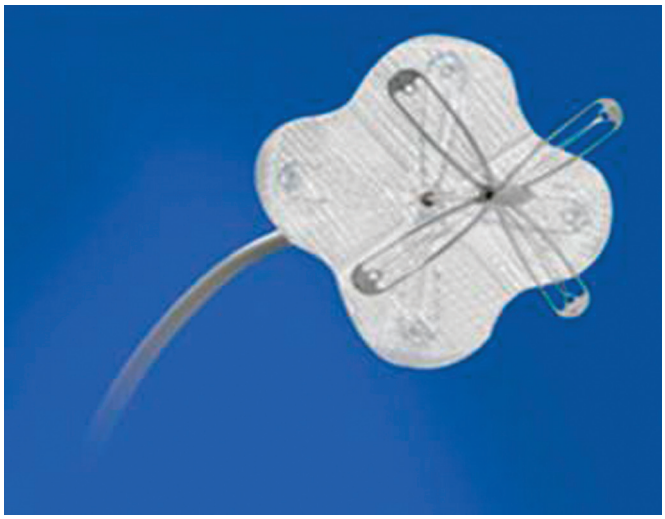

FIGURE 49-11 Photograph of the St Jude's Premere patent foramen ovale (PFO) occluding system. (Courtesy St. Jude's Medical, St. Paul, MN.)

TABLE 49-2 Selection Criteria for AGA Medical Patent Foramen Ovale Occluders and Delivery Systems

Distance From Defect to Superior Vena Cava or Aorta	Suggested Device Size	Delivery Sheath Size
>17.5 mm	35 mm	9 Fr
12.5-17.4 mm	25 mm	8 Fr
9-12.4 mm	18 mm	8 Fr
<9 mm	None	

and right atrial components by pulling the suture linking the two components together until locked, allowing it to conform to various tunnel lengths. Its major disadvantages are the need for larger venous sheaths (11 Fr) and the many steps required for closure. The operator must be extremely careful not to overtighten the knot that holds the two disks together because excessively tightened knots cannot be loosened later and may lead to device fracture or malapposition.

Future Devices

The Gore septal occluder is undergoing trials in the United States. It offers ease of deployment and retrieval and improved conformability to anatomy. Although the manufacturer closed operations, bioabsorbable devices such as BioSTAR (Fig. 49-12) and BioTREK (NMT Medical) point to the next generation of devices that minimize the material that persists within the atria after closure.

The Coherex device (Coherex Medical, Salt Lake City, UT) (Fig. 49-13), which uses technology to selectively close the PFO tunnel without leaving significant material in the atrial chambers, has been approved for commercial use in Europe. SeptRx Intrapocket PFO Occluder (SeptRx, Inc., Fremont, CA) consists of a self-expanding nitinol frame that expands the PFO pocket and apposes the septum. Alternative methods of closure are being developed and include a suturing device (HeartStitch, Sutura, Inc., Fountain Valley, CA), tissue cauterization with radiofrequency (Cierra PFX Closure System, Cierra, Inc., Redwood City, CA) (Fig. 49-14), and the Coaptus RFA PFO Sealing System (CoAptus Medical Corporation, Redmond, WA).

Closure of Patent Foramen Ovale

Indications

The AHA and the American Academy of Neurology (AAN) guidelines identify PFO closure after one CVA as a class IIb indication.[46] There is no FDA-approved indication for PFO closure for the primary prevention of cryptogenic strokes, but PFO closure for cryptogenic stroke is FDA approved in patients who experience recurrent strokes presumed to be paradoxical in nature and who have failed conventional drug therapy or have had complications from drug therapy. Conventional drug therapy requires a therapeutic INR on oral anticoagulants.[80]

On October 31, 2006, the humanitarian device exemption label given to the CardioSeal septal occluder and the Amplatzer PFO occluder for PFO closure expired. PFO closure is performed only in patients enrolled in ongoing research protocols or registries, with the exception of off-label use of ASD closure devices used for PFO treatment. There is no indication for PFO closure in patients who have migraines with aura and PFOs.

Percutaneous treatment for refractory hypoxemia related to right-to-left shunting across a PFO is still available under humanitarian device exemption or by off-label application of the cribriform (AGA Medical) or Helex (Gore) occluders.

Preprocedure Considerations

The diagnosis should be confirmed before arrival at the catheterization laboratory. Percutaneous closure of secundum ASDs or PFO is performed under ultrasound (TEE or intracardiac echocardiography [ICE]) and fluoroscopic guidance. The procedure begins with an explanation of the risks and benefits of the procedure and with patient consent to treatment.

Adequate hydration decreases the risk of an air embolism. To decrease the risk of prosthetic infection, procedures are postponed until indolent infections (e.g., urinary tract infections, upper respiratory infections) are cleared. Patients are given intravenous antibiotics (i.e., cefazolin, vancomycin, or clindamycin) in transit to the catheterization laboratory. Indwelling urinary catheters are not recommended to avoid transient bacteremia or a nidus for infection.

Venous Access

Femoral venous access provides a favorable angle of entry and is obtained with a 7- to 8-Fr short sheath. Generous soft tissue predilation is advised in preparation for a larger sheath exchange. A second venous sheath (8 or 10 Fr) is placed for ICE. If the contralateral vein is punctured, a 25-cm sheath is preferred for ease of catheter manipulation.

An accessory venous variant should be suspected if resistance is met, which should lead to cessation of sheath advancement and to wire and catheter repositioning toward the larger venous channel

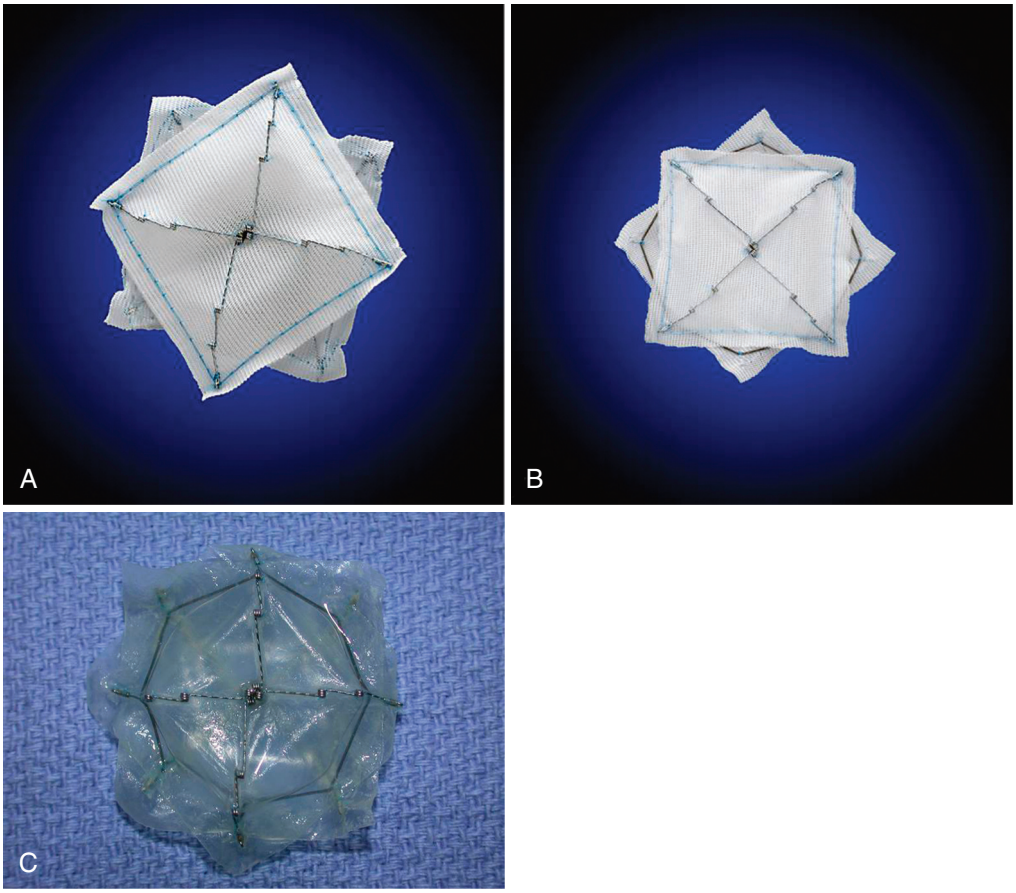

FIGURE 49-12 Photographs of the CardioSeal (**A**), STARFlex (**B**), and BioSTAR (**C**) septal occluders. These devices are no longer available. (Courtesy NMT Medical, Boston, MA.)

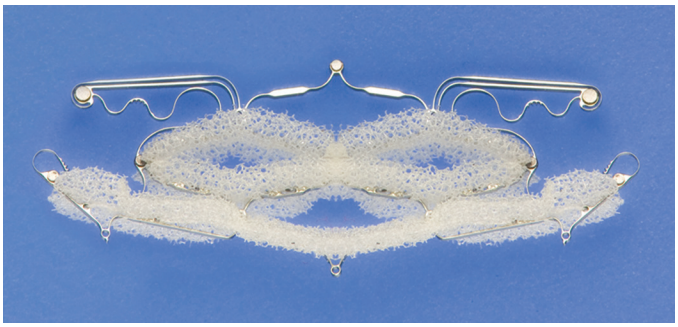

FIGURE 49-13 Photograph of the Coherex FlatStent EF. (Courtesy Coherex Medical, Salt Lake City, UT.)

(Fig. 49-15). Hepatic vein access (Fig. 49-16) may be used for infrahepatic venous interruption as an alternative to a jugular approach.

Crossing the Interatrial Septum

An end-hole multipurpose catheter (MPA) is advanced over a stiff 0.035-inch or 0.038-inch, 1.5-mm-long, J-tipped guidewire (Amplatzer wire). On arrival to the junction of the right atrium and IVC, the wire is advanced toward the IAS at the level of the aortic valve. The catheter may be advanced or rotated medially to direct the wire across the PFO.

If the guidewire does not cross easily, a Judkins right coronary catheter may be used instead. If the wire still cannot be threaded through the PFO, a hydrophilic-coated wire (Glidewire, Terumo Medical Corporation, Tokyo, Japan) may be used to negotiate through

FIGURE 49-14 Photograph of the PFx closure catheter with radiofrequency ablation. (Courtesy Cierra, Inc., Redwood City, CA.)

FIGURE 49-15 Venogram demonstrates accessory venous drainage into the left common iliac vein. Finding an aberrant wire course or resistance during sheath advancement should prompt a search for variations.

the tunnel. If the crossing cannot be achieved after a significant amount of time or effort, it is important to confirm or refute the diagnosis of a PFO by repeating a bubble study from the femoral vein. For an extant PFO, intracardiac shunting occurs within the first five beats; the presence of late bubble passage into the left atrium implies an intrapulmonary shunt. If significant passage of contrast is seen, septal puncture and closing the opening of the PFO with a device instead of inserting the device through the tunnel itself may be considered.

After entry into the left atrium, the guidewire is advanced to the left upper pulmonary vein, extending beyond the left main stem bronchus. Passage of the guidewire should occur without resistance. The wire tip should be kept in the pulmonary vein to avoid perforation of the left atrium or stimulation of a cough reflex. Placing the guidewire in the left atrial appendage is not recommended because it may lead to perforation. Incorrect localization of the wire is visualized as the wire coiling within the cardiac silhouette or detected as premature atrial depolarizations.

Anticoagulation

After passage across the foramen ovale, systemic anticoagulation is done with heparin to yield an activated clotting time of 200 seconds or greater. Heparin is administered. Aspirin (325 mg) should be administered before the procedure and clopidogrel after the procedure.

Measurement for Device Selection

Echocardiographic measurements are made to aid in device selection (see Table 49-2). Some operators prefer to measure the PFO diameter with a sizing balloon to select the appropriate device (as with the St. Jude and CardioSeal devices) or identify a long PFO tunnel. Balloon

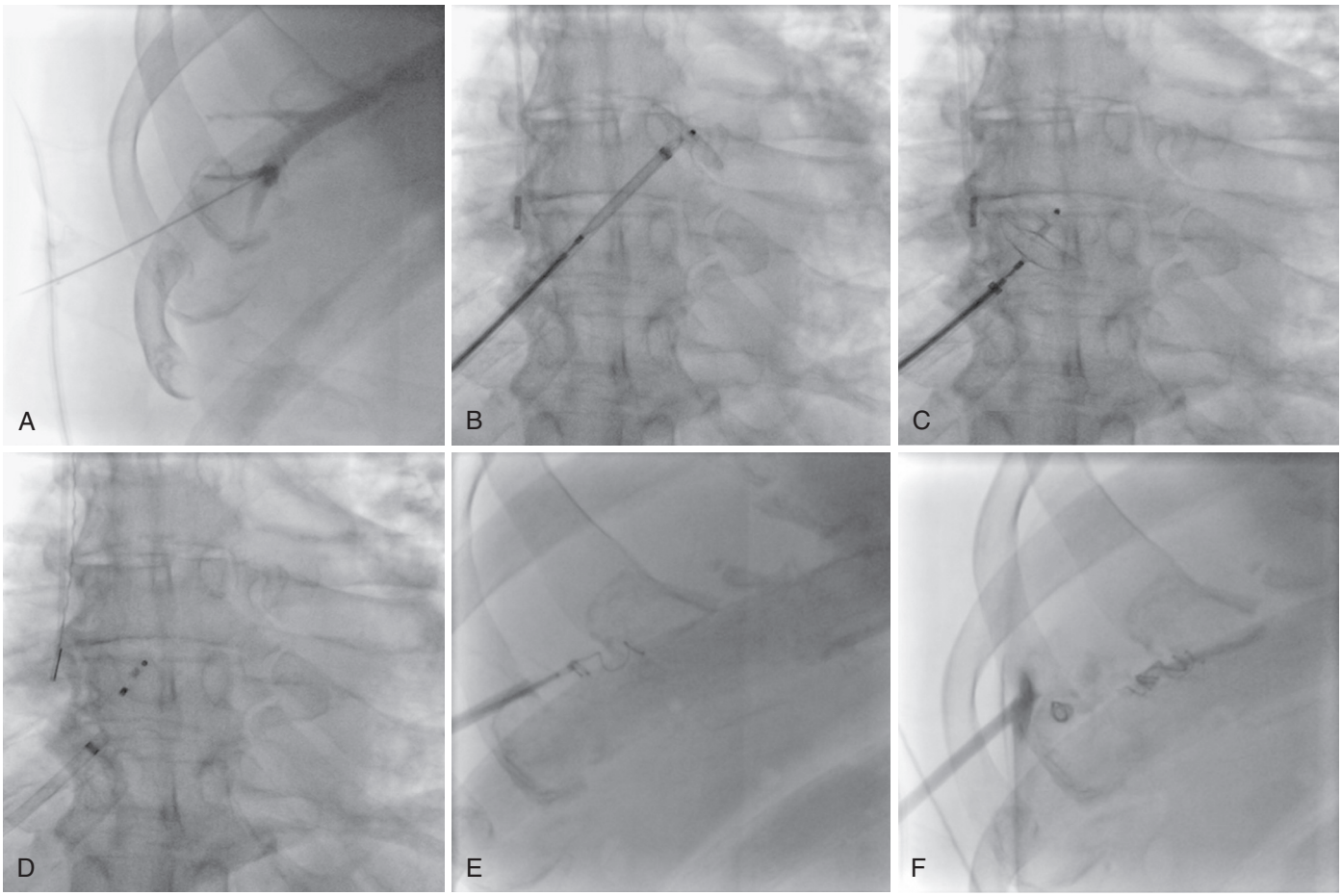

FIGURE 49-16 Cine images. **A,** Hepatic vein access is obtained. **B, C,** and **D,** Amplatzer multifenestrated cribriform septal occluder components are serially deployed. Coils are then deployed at the hepatic venous entry site (**E**) and near the liver capsule (**F**) to ensure hemostasis.

inflation must be done carefully to avoid tearing of the septum primum. With the use of the Amplatzer occluder, more than 95% of cases are done with a 25-mm or 30-mm device. The use of a sizing balloon is controversial with this device.

Delivery Sheath Insertion and Device Preparation

After the device is selected, the short sheath is removed and replaced with a long delivery sheath. The sheath is advanced until the dilator has crossed the IAS. The dilator is then separated, and the sheath is advanced slowly into the middle left atrium. The dilator and the guidewire are removed, and the sheath is connected to the manifold while ensuring that air bubbles are cleared meticulously. The occluder devices are loaded according to the manufacturers' instructions. The device usually is attached to its delivery cable and retracted into the delivery catheter. Special care must be exercised to meticulously flush the delivery catheter and device to remove all air bubbles from the system. The delivery catheter is then introduced into the delivery sheath.

Device Positioning and Release

The device is pushed through the delivery sheath under fluoroscopy. If air bubbles are seen, the device is removed and prepared again while the sheath is allowed to bleed back. After the device reaches the tip of the delivery sheath, the sheath is withdrawn slowly until the entire left atrial disk is exposed. Echocardiographic confirmation of left disk deployment is required to ensure that the left atrial disk is not in the PFO tunnel. Traction is then applied on the device and the delivery sheath to ensure that the left atrial disk abuts the atrial septum.

After the left disk is in place, the delivery sheath is withdrawn until the right atrial disk is expanded. As this is confirmed by fluoroscopy and echocardiography, the device is wiggled back and forth to ensure appropriate seating. Echocardiographic evaluation of pulmonary veins and the mitral valve is performed to avoid device obstruction by these structures. It is normal to see color flow across the center but not around the newly placed and anticoagulated Amplatzer PFO occluder device, particularly those positioned in patients with ASAs.

If no obstruction exists and the device appears stable, in appropriate position, and fully expanded, release can be done according to the manufacturer's recommendations. It is important to retract the delivery cable back into the delivery sheath to avoid cardiac perforation. After the device is released, its conformation changes slightly as a result of released tension. Rotation of up to 45 degrees is not unusual. A saline contrast study is performed to assess shunt severity. Shunting may be absent or significantly decreased after the device is released. Results of the bubble study become progressively negative as the device reaches its normal conformation and becomes endothelialized (Videos 49-10 through 49-12).

Postprocedure Care

Our preference is to hospitalize patients overnight in a telemetry unit and administer two more doses of antibiotics. A chest radiograph is obtained to confirm or correct device position the day after the procedure. A TTE and bubble study are done to quantify residual shunting 24 hours and 6 months after the procedure. Patients are prescribed 75 mg of clopidogrel daily for 1 to 3 months and daily aspirin for 6 months. For patients with histories of CVAs or TIAs, aspirin therapy may be continued indefinitely. Standard precautionary measures against subacute bacterial endocarditis should be followed for 6 months.

Special Considerations

Transseptal Puncture

Transseptal puncture is rarely required to close a PFO. It is favored in two instances: when the PFO tunnel is long and passage with a guidewire or delivery sheath is unsuccessful; and when the inferior border of an appropriately measured device interferes with the mitral valve. A SafeSept transseptal guidewire (Pressure Products Medical Supplies, Inc., Santa Barbara, CA), Bovie cauterizer attached to the transeptal needle, or laser or radiofrequency energy may be used for cases with a redundant septum to enhance puncture safety.

Prominent Chiari Network and Redundant Eustachian Valve

Herniation of the Chiari network or a redundant eustachian valve should be sought before device release. These structures can be deflected using a steerable radiofrequency ablation catheter.

Multiple Shunts

For an ASD associated with a PFO, a single cribriform septal occluder may be used to minimize the shunt. If there is persistent shunting, a second device may be placed as long as there is no interaction with the mitral valve or pulmonary veins (Fig. 49-17).

Atrial Septal Aneurysms

Closure of an ASA with a PFO usually does not require a larger device. Closure of these PFOs is successful with a standard technique at 6 months (see Fig. 49-3).[81] It is imperative to capture the septum secundum with the device to ensure a stable position, closure, and prevent device embolization or slippage.

Lipomatous Hypertrophy of the Atrial Septum

When closing a PFO in patients with lipomatous hypertrophy of the atrial septum, the device needs to straddle the septum secundum. Under fluoroscopy, a properly seated device produces the Pacman sign, in which cranial halves of the left and right atrial disks look like open jaws biting into the septum secundum. This position ensures device stability and PFO closure. The off-label use of an ASD or VSD occluder may be required for hypertrophy greater than 2 cm.

Complications

Percutaneous closure of PFOs is a safe procedure. Procedural complications occur in 4% to 7% of patients but are usually mild.[45,82,83] A short procedural learning curve and significant device modifications have transformed PFO closure into an effective and safe procedure. Periprocedural complications include air embolism, device migration, cardiac rupture and device erosion, vascular complications, and atrial arrhythmias. Complications occurring after discharge include endocarditis, device fracture, and device thrombosis.

Procedure-Related Complications

Air embolus is a potentially devastating complication, but it can be easily recognized and avoided. Air embolus is caused by air entering the delivery sheath as the dilator is removed or during its preparation. It may also be associated with incomplete flushing of the device when introducing it to the delivery catheter or delivery sheath.

Adequate hydration before starting the procedure minimizes negative pressure swings and decreases the chances of air entry into the equipment. Maintaining catheters below atrial level at all times is key. Gentle flushing during slow dilator and wire withdrawal can offset the negative pressure void created by their retrieval. Preemptive use of positive-pressure ventilation in patients with airway or pulmonary disease helps minimize dangerous wide intrathoracic pressure swings during sedation.

Air bubbles in the delivery catheter can be easily recognized as the device is being pushed through the delivery sheath if done under fluoroscopy. Air embolism can manifest as sudden onset of hypotension, heart block, ventricular tachycardia, inferior ST-segment elevation (because the right coronary artery is anterior), and transient neurologic decline. If air is seen within the delivery sheath, it is important to remove the device slowly to reduce the ensuing vacuum and let the delivery sheath bleed back. If the air bubble has entered the circulation, hypotension or ensuing arrhythmias should be treated with the standard advanced cardiac life support (ACLS) protocol. Supplemental oxygen may aid in bubble resolution. The placement of patients in the Trendelenburg position may decrease the risk of cerebral embolization. Direct aspiration of the right coronary artery may be warranted if an

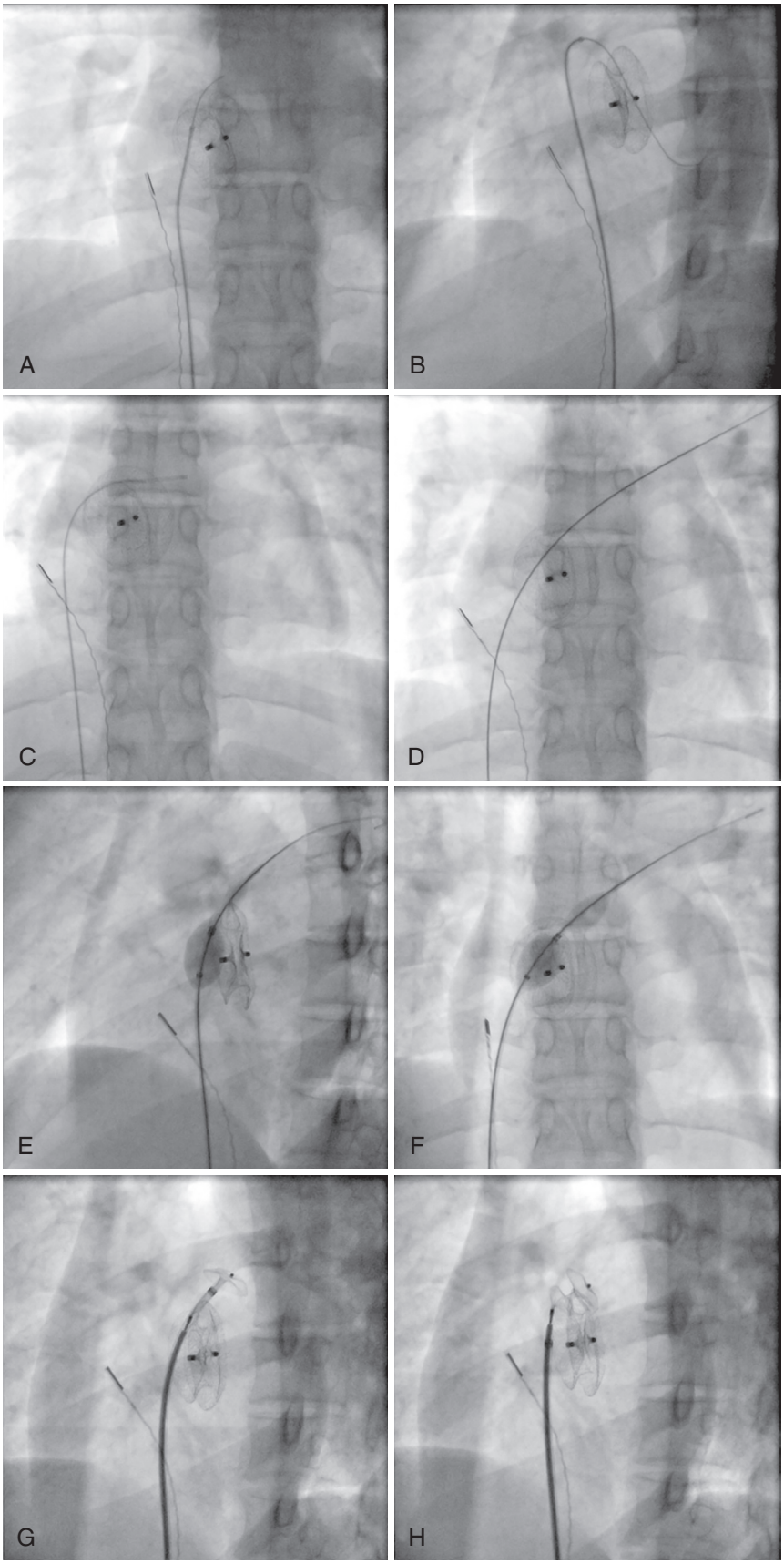

FIGURE 49-17 Cine images of a symptomatic patient with a residual shunt after closure of an atrial septal defect. **A** and **B,** A multipurpose catheter and guidewire are used to cross the defect. **C,** The catheter is then advanced into the left atrium. **D,** The wire is exchanged for an Amplatz Extra Stiff guidewire positioned in the left upper pulmonary vein. **E** and **F,** The "stop flow" diameter and residual defect contour are obtained with the use of a sizing balloon. **G** and **H,** A second device is deployed.

airlock exits. If warranted, transfer to a hyperbaric chamber may be considered.

Device-Related Complications

Device migration is characterized by the loss of the correct position of the device (Fig. 49-18). It may be related to incomplete device exit from the tunnel or placement of a smaller device in a large PFO or in an unrecognized ASD. If migration occurs, devices may be removed percutaneously with a snare. If this cannot be done, surgical removal is recommended.

Device arm fracture was mostly seen with the use of the earlier-generation PFO-Star closure device. However, it is now rarely encountered.

Device erosion is not seen in PFOs. However, data show that erosion does occur in patients with closures of large ASDs that lack an appropriate aortic rim of tissue.

Device thrombosis has been seen in patients with concomitant hypercoagulable states who undergo PFO closure. It was also seen in up to 2% of the patients who received STARFlex devices, but newer generations of the device have addressed this limitation.[45] A device thrombus requires surgical removal. A hypercoagulability workup should be performed for every patient who undergoes PFO closure for paradoxical embolization. If the workup is positive for hypercoagulability, therapeutic anticoagulation is warranted. Thrombus formation associated with AGA PFO closure devices has not been reported.

Transient arrhythmias may occur. Atrial arrhythmias may occur spontaneously in the first 6 weeks after the procedure and do not usually require treatment.

Case reports have documented an increase in headaches after device placement in patients with *nickel allergy*. Although the extent has been difficult to prove, nickel desensitization should nevertheless be performed before elective PFO closure.

Endocarditis may complicate PFO closure. Bacterial device infection or colonization may prove catastrophic. Strict sterile technique should be followed throughout the procedure, and antibiotic prophylaxis for subacute bacterial endocarditis should be continued for 6 months. Surgical excision is warranted if endocarditis occurs.

Conclusions

Percutaneous closure of PFOs is an effective procedure that can be performed safely. Although the data support the association between PFO and various clinical syndromes, randomized controlled trial data have failed to confer superiority for transcatheter PFO closure compared with medical therapy for migraine headaches or for prevention of recurrent events in patients with a prior cryptogenic stroke or TIA, rendering treatment decisions more complex. Patients will likely benefit most from a personalized approach by a multidisciplinary team.

ATRIAL SEPTAL DEFECT

Among the various congenital cardiac anomalies encountered in the adult population, ASD is one of the most common. It is easily treated and has an excellent long-term prognosis. Less than a decade ago, surgical repair was considered the standard of care and provided durable long-term results. Since the FDA approved a device for percutaneous ASD closure in December 2001, there has been a dramatic shift toward catheter-based closure of ASDs, which provides durable results paralleling surgical techniques, with remarkably less morbidity and extremely short recovery time and hospitalization. Patients and physicians alike prefer the less invasive percutaneous approach, although no studies have directly compared the surgical and percutaneous techniques for efficacy and safety.

The preceding section provided an in-depth discussion on the PFO with regard to its embryology, physiology, clinical pathophysiology, diagnosis, and catheter-based management. Because there is a considerable overlap between the PFO and ASD, the following discussion highlights salient characteristics that are specific to ASD.

Embryology

Unlike a PFO, an ASD occurs when a portion of the interatrial septum is absent. Incomplete caudal growth of the septum secundum or excessive resorption of the septum primum gives rise to a *secundum ASD*. If the septum primum fails to reach the endocardial cushions, a primum ASD occurs with its associated abnormalities (e.g., cleft mitral valve, inlet ventricular septal defect). A sinus venosus ASD occurs when there is abnormal resorption of atrial septal tissue adjacent to the caval-atrial junction. An unroofed coronary sinus or the absence of atrial tissue adjacent to the site of coronary sinus drainage into the right atrium results in a coronary sinus ASD (Table 49-3 and Fig. 49-19).[84]

Anatomic and Morphologic Considerations

The secundum defect is located at the center of the atrial septum involving the fossa ovalis. This is a true tissue defect compared with a PFO. This is the only type of ASD that is amenable to transcatheter closure techniques. To permit percutaneous closure, there should be adequate tissue margins of the defect for securing the closure device to the tissue. Lack of an adequate tissue margin predisposes to device prolapse or potential embolization. Large defects also predispose the device to encroaching on the adjacent aortic root and the mitral valve, which can result in major complications.

A thorough assessment of the atrial septum using echocardiography is a prerequisite for optimal closure. The choice of imaging depends on the operator's experience and preferences. Sinus venosus–type defects are located in the perimeter of the atrial septum near the entry of the SVC. This defect prevents the normal separation of pulmonary veins from the right lung, the SVC, and the right atrium, and the result is anomalous drainage of one or more pulmonary veins.[85] Typically, defects located close to the IVC are rare and are called *caval defects*. They can be associated with anomalous pulmonary venous drainage. Ostium primum ASDs, also known as *endocardial cushion defects or atrioventricular canal defects*, may be accompanied by ventricular septal defects and a cleft mitral valve. With the exception of secundum defects, management of other types of ASDs requires surgical repair and are not detailed here.

Clinical Presentation

Patients with ASDs usually remain asymptomatic during childhood. Typically, the pulmonary outflow murmur or a fixed split of the second heart sound detected during routine physical examination prompts further evaluation, which results in the diagnosis. Some patients may experience recurrent heart failure, have a predilection for recurrent respiratory infection during childhood, and have easy fatigability and exertional dyspnea.[86] In adults, a long-standing ASD with significant shunting may manifest with atrial arrhythmias, pulmonary arterial hypertension, and heart failure.

Hemodynamics

The direction and magnitude of the shunt across an ASD depend on the size of the defect, right and left atrial pressures, right and left ventricular compliance and end-diastolic pressures, vascular resistance in the pulmonary and systemic circuits, the phase of respiration, intrathoracic pressure, and intravascular volume status.[87] In most patients with moderate- to large-sized ASDs, both atria are in open communication, and the mean atrial pressure is equal. The shunt is directed left to right because compliance of the right atrium and right ventricle is higher than that of the left atrium and left ventricle. In those with very small ASDs without equalization of atrial pressures, the gradient across the atria also plays a role in the direction of the shunt.

A close review of the Doppler performed across the defect shows that the flow occurs during the entire cardiac cycle. Left-to-right shunting occurs mostly during late systole and early diastole, but atrial contraction also provides additional flow augmentation. The shunt

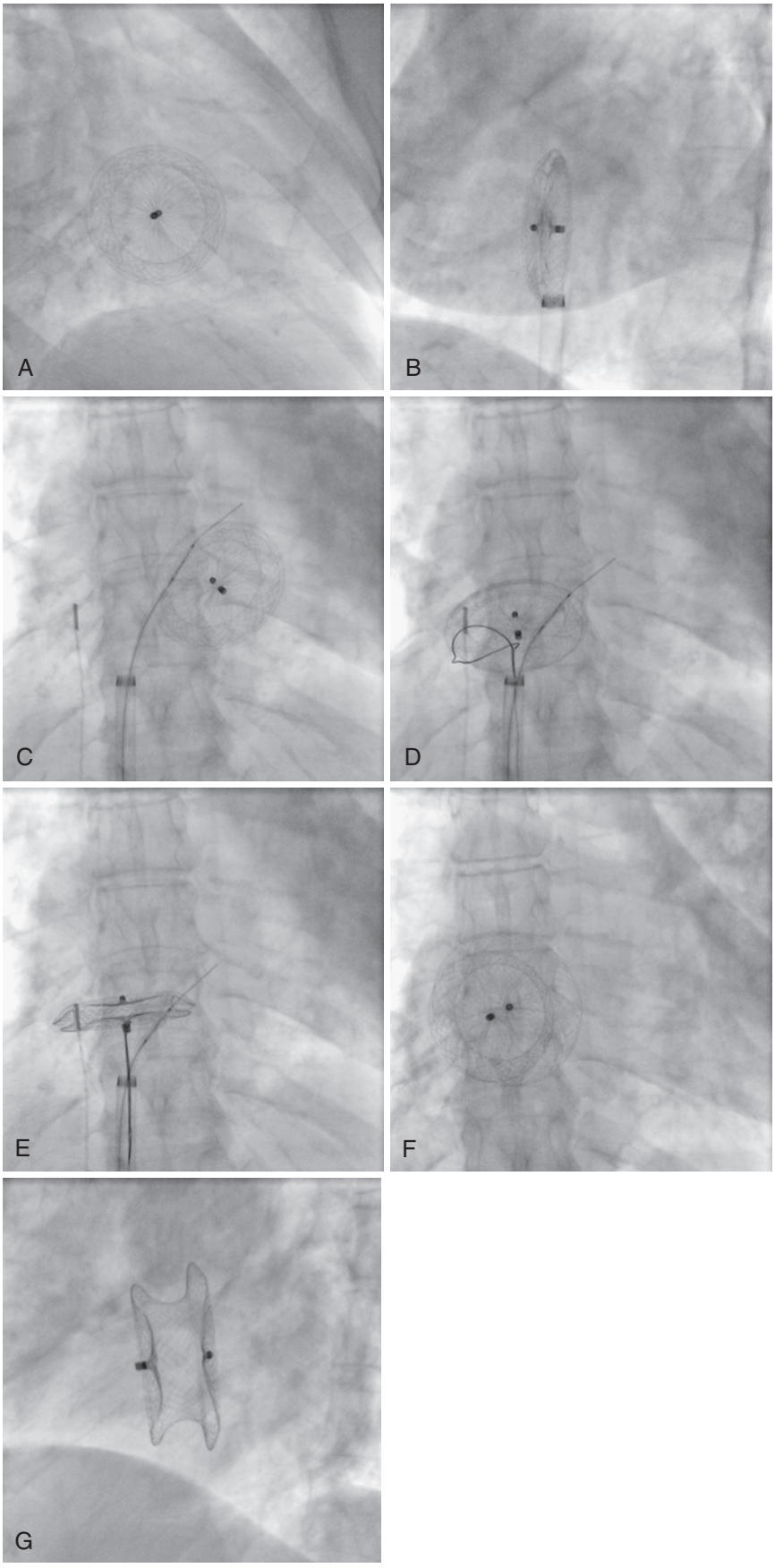

FIGURE 49-18 Cine images of device migration noticed after development of ventricular ectopy after closure of a large atrial septal defect (ASD). **A** and **B,** A 32-mm Amplatzer septal occluder (AGA Medical) migrated into the right ventricular cavity. **C,** An internal mammary artery (IMA) guide catheter directs a Cook retrieval forceps (Cook Medical, Bloomington, IN) to hold the device position. **D,** After device migration to the right atrium, the Cook retrieval forceps holds the device position, and a 25-mm Gooseneck Snare is used to lasso the detachment pin. **E,** The device is externalized with a large sheath. **F** and **G,** A new 34-mm Amplatzer septal occluder device is then successfully deployed across the ASD.

TABLE 49-3 Atrial Septal Defect and Patent Foramen Ovale Characteristics

Feature	Patent Foramen Ovale	Atrial Septal Defect
Embryology	Failure of the septum primum and the septum secundum to fuse completely Pathway or channel between tissue flaps	Failure of the septum primum or the septum secundum, or both, to develop normally Tissue defect
Direction of shunt	RA pressure greater than LA pressure; shunts right to left LA pressure greater than RA pressure; may stay closed or shunt left to right Shunt is dynamic and bidirectional Shunt direction depends on RA-to-LA pressure difference, RVEDP-to-LVEDP difference, phase of respiration, and volume status	Usually RA pressure equal to LA pressure but shunts left to right because the RV is more compliant Shunt reverses with Eisenmenger physiology Shunt is dynamic and bidirectional Shunt direction depends on RA-to-LA pressure difference, RVEDP-to-LVEDP difference, phase of respiration, and volume status

ASD, Atrial septal defect; LA, left atrium; *LVEDP,* left ventricular end-diastolic pressure; *PFO,* patent foramen ovale; *RA,* right atrium; *RV,* right ventricle; *RVEDP,* right ventricular end-diastolic pressure.

results in diastolic overloading of the right ventricle and increased pulmonary blood flow. Depending on the size of the defect, pulmonary blood flow may be as high as five times the systemic flow. In those with long-standing and untreated ASDs, pulmonary hypertension may ensue, which can result in reversal of the shunt's direction, depending on the status of the right ventricle. Even in an uncomplicated ASD, a transient and small right-to-left shunt occurs during the early phase of ventricular systole and is further accentuated by respiration that decreases intrathoracic pressure. This is the rationale behind performing a saline contrast study during echocardiography for the detection of ASDs (Video 49-13).

Diagnosis

Physical examination findings usually initiate the evaluation for suspected ASDs. This includes a hyperdynamic precordium, a fixed split of the second heart sound without respiratory variation, a loud pulmonic component of the second heart sound, and pulmonary outflow tract murmur. Primum-type defects may have associated tricuspid and mitral regurgitation murmurs. The electrocardiogram further supports the clinical findings. Right-axis deviation, right ventricular hypertrophy, rSR′, and rsR′ pattern in the right precordial leads with normal QRS duration are common electrocardiographic findings in ostium secundum defects. An inverted P wave in lead III is seen in sinus venosus defects, whereas left-axis deviation may denote an ostium primum defect. Lengthening of the PR interval due to atrial enlargement and conduction delay can be seen in all three types of ASD.[88] Chest radiographic findings include right atrial and ventricular enlargement, prominent pulmonary artery, and increased pulmonary vascular markings.

Echocardiography

Echocardiography has replaced cardiac catheterization techniques for the diagnosis of ASDs.[89,90] Even shunt fraction can be reliably calculated using an echocardiogram. A TTE with a saline contrast study should be done first. The defect may be visualized directly by TTE imaging, particularly from a subcostal view of the interatrial septum, but a TEE can provide much better anatomic characterization of the septum and the adjoining structures.[91,92]

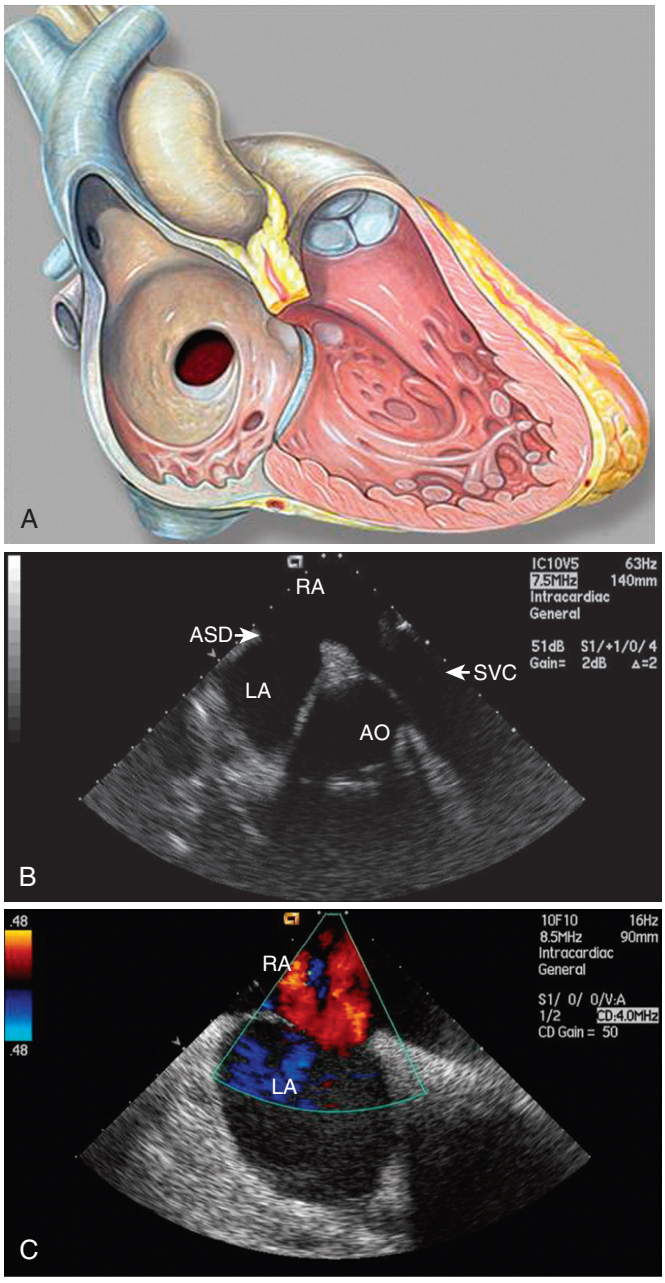

FIGURE 49-19 A, Diagram of a secundum atrial septal defect (ASD). **B,** ASD as seen on an intracardiac echocardiogram. **C,** Color Doppler interrogation identifies a left-to-right shunt. *AO,* Aorta; *LA,* left atrium; *RA,* right atrium; *SVC,* superior vena cava. (Modified from Patrick J. Lynch, Director, ITS Web Services Department, Yale University, New Haven, CT.)

Typical echocardiographic findings include right atrial and right ventricular enlargement, increased pulmonary artery pressure, and Doppler demonstrating continuous flow across the atrial septum.[93] Three-dimensional echocardiography with image reconstruction has been used to plan closure procedural details. ICE can also be used, but its use is mostly restricted to providing imaging guidance for percutaneous closure (Video 49-14).

Cardiac Catheterization

In current clinical practice, cardiac catheterization primarily for diagnostic purposes is uncommon, but it is used when there is a

discrepancy between the clinical and echocardiographic findings. Invasive hemodynamic assessment (i.e., cardiac catheterization) is performed during a planned percutaneous closure. A defect in the atrial septum is usually obvious when the guidewire or the catheter crosses the midline (i.e., atrial septum) into the left atrium. The site at which the catheter crosses provides diagnostic clues about the defects. In secundum defects, the site of crossing is midseptal, whereas in sinus venosus and primum defects, the catheter crosses the IAS at a high level and a low level, respectively. Angiograms can further demonstrate shunting and other associated anomalies.[94] In the past, an injection in the right upper pulmonary vein was recommended, but this is rarely performed in current clinical practice.

We recommend a pulmonary arteriogram in a straight pulmonary artery projection to rule out associated partial anomalous pulmonary venous return (PAPVR). A right heart catheterization with measurement of oxygen saturations in the innominate vein, the SVC, the right atrium, the right ventricle, and pulmonary arteries is also important to assess the magnitude of the shunt and rule out associated problems such as pulmonary hypertension and PAPVR. It is also important to measure left atrial pressure or left ventricular pressure, or both, especially in older adults (discussed later).

Closure of Atrial Septal Defect

Indications

Unrepaired ASDs that result in right heart volume overload can lead to progressive exertional dyspnea and exercise intolerance, atrial arrhythmias, and pulmonary hypertension. Calculation of the pulmonary to systemic flow ratio (Qp/Qs) estimates shunt direction and magnitude, which is related to defect size and interventricular pressure and compliance differences. Over time, long-standing right-sided volume overload may alter Qp/Qs. A small Qp/Qs in the setting of right atrial or right ventricular overload should not preclude closure.

Right chamber enlargement as documented by echocardiography is accepted as an indication for percutaneous ASD closure. Other indications, including platypnea-orthodeoxia syndrome, paradoxical embolus, decompression sickness, and migraine headaches, are controversial (these were discussed earlier).

Devices for Percutaneous Closure

Percutaneous closure of ASD has proved to be reliable, safe, and effective as indicated by the available data, but choosing defects with appropriate anatomic characteristics is critical for successful closure. Only two devices are approved by the FDA for percutaneous closure of secundum ASD. The ASO received FDA approval in December 2001, and the Gore Helex occluder received approval in August 2006.

Amplatzer Septal Occluder

The ASO is a self-expandable, double-disk device made from nitinol wire mesh (Fig. 49-20). The two disks are linked together by a connecting waist, which corresponds to the balloon size of the ASD. To increase its closing ability, the disks and the waist are filled with polyester fabric. The polyester fabric is securely sewn to each disk by a polyester thread. The device is available in various sizes ranging from 4 to 38 mm (4 to 20 mm at 1-mm increments, 22 to 38 mm at 2-mm increments), and the size refers to the diameter of the waist. Device selection is based on the stretched diameter of the defect (i.e., a 10-mm stretched defect requires a 10-mm device). Devices are chosen to be the same size as or 1 mm larger than the balloon-stretched diameter to ensure an appropriate fit and to avoid oversizing.

The pivotal study reported technical success rates of 95.7%.[95] Technical success was defined as successful deployment of a device. The 12-month closure success rate was 98.5%, with closure success defined as a shunt of less than 2 mm in patients in whom a device was successfully placed. Patient selection and optimal imaging are key to success.

Multiple ASDs in a patient may be closed with more than one device (Fig. 49-21). A cribriform device that is approved for closure of multifenestrated ASDs is available in four diameters: 18, 25, 30, and 35 mm. Modifications to the basic technique may be needed to close very large ASDs; they are discussed separately.

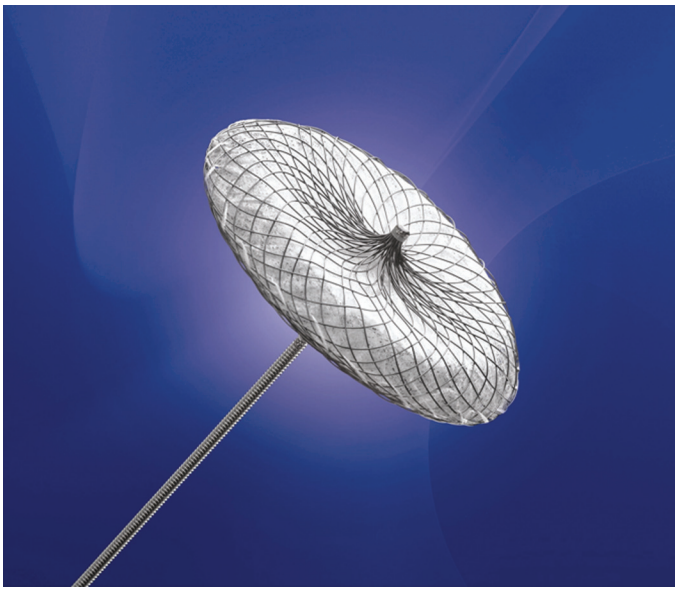

FIGURE 49-20 Amplatzer septal occluder. (Courtesy AGA Medical.)

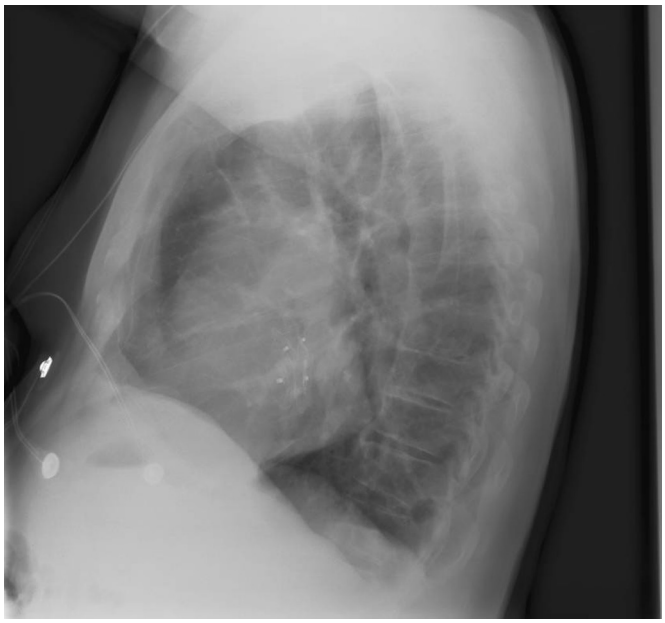

FIGURE 49-21 Chest radiograph obtained after deployment of two AGA septal occluders.

The reported advantages of the Amplatzer device include ease of use, delivery with smaller-diameter catheters, and the facility to retrieve and reposition it before complete deployment. The device design also permits it to self-center across the defect.

Gore Helex Occluder

The Gore Helex septal occluder consists of a device and special delivery system (Fig. 49-22). The device is a non–self-centering, double-disk device that consists of a nitinol wire frame covered by an expanded polytetrafluoroethylene (ePTFE) membrane. The ePTFE membrane is treated with a hydrophilic coating to facilitate echocardiographic imaging during device implantation.

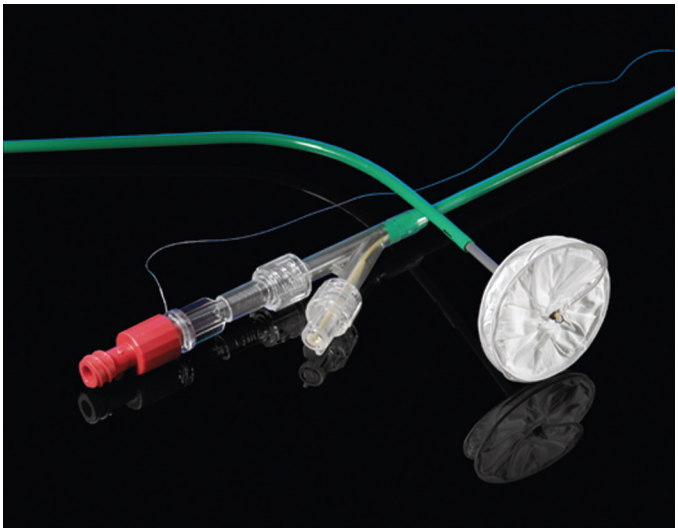

FIGURE 49-22 Gore Helex septal occluder and delivery system. (Courtesy W.L. Gore & Associates, Newark, DE.)

The device is approved for closure of ASDs less than 18 mm in diameter. The device is available in 5-mm increments, from a 15-mm to 35-mm open disk diameter. Because the device is not self-centering, a ratio of the device to balloon-stretched defect of at least 2:1 is required to prevent residual shunting or device embolization.

In the pivotal study and the continued-access trial, technical success rates of 88.1% and 85.6% were achieved, respectively, with technical success defined as successful delivery of a device in patients in whom it was attempted.[96] The clinical closure success rate for patients who had technical success was 98.1% in the pivotal study and 98% in the continued-access trial at 12 months from implantation. Clinical closure success was defined as a completely occluded defect or one with a clinically insignificant leak.

Theoretical advantages for the Helex occluder compared with the ASO are that it is a lower-profile device, has less nitinol and therefore less nickel exposure, and may have a lower risk of erosions. Disadvantages include the larger and more complicated delivery system, the lower overall success rate, and the inability to close defects larger than 18 mm in diameter.

Procedural Details

Aspirin therapy is started days before the procedure. Antibiotics are given within 30 minutes of achieving access. Patients should be adequately anticoagulated with unfractionated heparin during the entire procedure and the activated clotting time maintained above 250 seconds before device placement.

Typically, femoral venous access is used, and the size of the sheath is based on the size and type of the device and delivery sheath system chosen. TEE or ICE is used for imaging guidance during the procedure. If ICE is used, a second venous sheath is required during the procedure.

We recommend performing a right heart catheterization with every ASD closure. This includes measurements of oxygen saturations and pressures in the innominate vein, SVC, right atrium, and pulmonary arteries, as well as performance of pulmonary arteriography. This information is important to assess PAPVR and pulmonary hypertension. If PAPVR is documented in the setting of a secundum ASD, it is important to decide how much of the total lung parenchyma is draining anomalously. If a single segmental vein is anomalous in the setting of a moderate-sized or larger ASD, device closure of the ASD is still indicated, and the anomalous vein can be left in situ. It is also important to measure left atrial pressure or left ventricular end-diastolic pressure, or both, especially in older adults because left ventricular diastolic dysfunction can complicate transcatheter ASD closure and precipitate left heart failure due to an inability of the left ventricle to adjust to the increased preload.

After the right heart catheterization has been completed, a 0.035-inch J-tipped guidewire guided through a 6-Fr multipurpose catheter is the best tool to cross the defect. The wire is positioned in the left upper pulmonary vein. After crossing the defect, the ASD diameter is measured with a balloon specifically designed for sizing atrial communications, such as the Amplatzer (AGA Medical, Plymouth, MN) or the NuMed (NuMed, Inc., Hopkinton, NY) sizing balloon.

Under fluoroscopic and echocardiographic guidance, the balloon catheter is placed across the defect and gently inflated with diluted contrast until the left-to-right shunt ceases, as observed with echocardiography. The maximum achieved occlusive diameter is measured at the balloon waist. This is the stop-flow diameter. It is critical not to overinflate the balloon because this can lead to selection of an inappropriately large device and increase the risk of erosion. The diameter of the balloon is measured fluoroscopically and with echocardiography, and the measurements should be in close agreement (<1 mm difference).

If an ASO is chosen, the sizing balloon is removed, and the appropriately sized sheath for delivery is advanced into the right atrium. The dilator is removed, and the sheath is de-aired and then advanced over the wire into the left atrium. Alternatively, the sheath and the dilator can be advanced over the guidewire into the left upper pulmonary vein, and the wire and the dilator can then be removed. It is important to de-air the sheath completely if the latter approach is taken because an air embolus can otherwise result.

The device is loaded and advanced into the delivery sheath under fluoroscopic and echocardiographic guidance (see Fig. 49-9 and Videos 49-10 through 49-12). Meticulous attention must be paid to avoid suction of air into the system, which occurs particularly when using large-caliber delivery sheaths.

If the Helex occluder is chosen, its size needs to be at least two times the stop-flow diameter of the defect. The device can be delivered in two ways: by removing the sizing balloon and guidewire and advancing the chosen device and delivery system through a 10-Fr sheath across the defect under echocardiographic guidance or by removing the sizing balloon and leaving the guidewire in place and then sliding the guidewire through the tip of the catheter. The catheter is then advanced across the defect and into the left atrium, at which point the guidewire is removed.

Complications

Complications are common with closure of ASDs. Most are minor. The Amplatzer pivotal trial described a major adverse cardiac event (MACE) rate of 1.6% (7 of 442 patients). This included two arrhythmias requiring treatment, three device embolizations with surgical removal, one embolization with percutaneous removal, and one delivery system failure. This compares with an MACE rate of 5.2% (8 of 154) in the surgical control group in this study. Minor adverse cardiac events occurred in 6.1% of patients (27 of 442) compared with a rate of 18.8% (29 of 154) in the surgical group.

Erosions associated with the use of the ASO are the most common life-threatening complication. They are reported to occur with a frequency of approximately 1 to 3 per 1000 implants (0.1% to 0.3%); however, the true incidence is unknown because the number of device implants is unknown.

Amin and colleagues described erosions associated with the use of the ASO and, based on a panel of physicians, developed recommendations to avoid this complication.[97] They recommended using the stop-flow method of balloon sizing. They also recommended only a gentle to-and-fro motion on the device after it is implanted. Patients at high risk for erosions were thought to be those needing an ASO greater than 1.5 times the unstretched diameter of the defect and those with deficient superior or aortic rims. It was also thought that devices that were deformed at the level of the aortic root (splayed around the aorta) were at higher risk of erosion.

These recommendations were derived from a panel of expert implanters and have not been verified in a prospective manner. Nevertheless, the recommendations have led to a general change in clinical practice, although they are not without controversy. El-Said and Moore reported a survey of members of the Congenital Cardiovascular Interventional Study Consortium (CCISC), in which 71.7% thought that a device in which the disks approximated each other and touched the aorta without splaying were at the highest risk of an erosion.[98]

The FDA convened an advisory panel on May 24, 2012, to address the erosion issue. The executive summary report that was prepared for this meeting[99] listed 95 documented erosions and 8 suspected erosions. The time from ASO implant to erosion was 0 to 3139 days (8.6 years); 50% of erosions occurred within the first week, 61% within the first month, and 87% within the first year. Thirteen percent of erosions occurred more than 1 year after implantation, with one erosion occurring at 5.3 years and one at 8.6 years. The mortality rate for on-label adjudicated erosion events was 8.4% (8 of 95 patients).

The exact mechanisms by which erosions occur are unknown, but the current instructions for use for the ASO state, "Absence of the anterior superior (aortic) rim and device oversizing may be related to causation of erosion due to increased likelihood of device-tissue contact in the dynamic anatomic area of highest risk for erosion."[100] The instructions for use and the FDA recommend clinical follow-up with a cardiologist and an echocardiogram at implantation, 1 day after the procedure, before discharge, and at 1 week, 6 months, and 12 months after implantation. Annual cardiology follow-up is recommended thereafter (without the specific recommendation for an echocardiogram).

Embolization can occur with the ASO, and the implanters need to be familiar with retrieval techniques (see Fig. 49-18). Levi and Moore reported a survey of AGA Medical proctors, which demonstrated an embolization rate of 0.55% (21 of 3824 device implants).[101] DiBardino and coworkers reported an estimated embolization rate of 0.62% using data from the FDA's Manufacturer and User Facility Device Experience (MAUDE) database.[102] In the latter study, two deaths were associated with embolization. Device embolization can occur to the right heart, the left heart, or the aorta. Most device embolizations occur at the time of or shortly after implantation, although late embolization has been reported.

Percutaneous device retrieval is possible in a significant number of cases. The device should initially be stabilized with a bioptome or a snare so that it does not cause hemodynamic compromise. This may require a second venous line from an inferior or superior approach; one site of access is used to hold the device, and the second is used to snare and subsequently retrieve the device. A long, relatively stiff sheath can be advanced adjacent to the device. The tip of the sheath can be beveled by cutting it at a 30- to 45-degree angle. This facilitates pulling the device into the sheath. The right atrial microscrew can then be snared using a gooseneck snare delivered through a 6-Fr cut pigtail catheter or other angled guiding catheter delivered through the retrieval sheath. The pigtail can be cut such that the distal end assumes a 90-degree angle in relation to the shaft of the catheter. This allows turning of the snare so that it may be steered to the microscrew.

After the microscrew is snared, the device is pulled back into the sheath. This may require rotation of the delivery sheath, the snare, or traction placed on the device from the bioptome to allow the microscrew to enter the beveled portion of the sheath. After the microscrew enters the sheath, the entire device may be withdrawn. A fully deployed device should not be pulled across the mitral or tricuspid valves because of the risk of valve damage. Instead, the long delivery sheath should be placed next to the device for retrieval if the device lies within the ventricle. Devices that embolize to the atria may be snared and pulled into the IVC. Traction using a bioptome from above may then be applied to the superior portion of the device to facilitate entry into the retrieval sheath. Devices may also be retrieved from the pulmonary artery or aorta using modifications of this technique.

If the device cannot be percutaneously removed, surgical removal is necessary. The Helex pivotal trial and the continued-access trial reported MACE rates of 5.9% (7 of 119) and 3.9% (3 of 77), respectively.[96] This included a total of four cases of device embolization requiring percutaneous removal, one device removal due to wire fractures, one skin allergy, two patients with migraines, one with paresthesia, one hemorrhage requiring treatment, one allergic reaction (thought to be device related), and two possibly inappropriately sized devices. This compares with a MACE rate of 10.9% (14 of 128) for the surgical patients in the pivotal trial.

Minor adverse cardiac events occurred in 28.6% (34 of 119) of patients in the pivotal study and 27.3% (21 of 77) of patients in the continued-access study. Wire fractures were reported in 5% (6 of 119) of patients in the pivotal group and 6.5% (5 of 77) in the continued-access group. Minor adverse cardiac events were reported in 28.1% (36 of 128) of patients in the surgical arm of the pivotal study. No erosions related to the Helex device have been reported.

Wire frame fractures are a relatively common problem associated with the Helex device. Fagan and colleagues reported data on wire frame fractures for every Helex device implanted in the United States from April 2000 to April 2005.[103] During this 5-year period, there were 298 implants, of which 19 (6.4%) developed wire frame fractures. Two devices fractured by 1 month, 10 by 6 months, and 7 between 12 and 18 months. Eight of the devices had multiple fractures. Multivariate analysis found large device size to be an independent predictor for wire frame fracture. The 30-mm and 35-mm devices accounted for 84% of all fractures. There were no clinical problems such as embolization or increased shunting related to the wire frame fractures in this study; however, Qureshi and coworkers subsequently reported a case of wire frame fracture that resulted in increased shunting and perforation of the mitral valve, resulting in severe mitral regurgitation requiring surgical repair.[104] Close follow-up of a patient experiencing a wire frame fracture is required. Embolization of the Helex occluder appears to be more common than that associated with the ASO. Fortunately, the Helex device is relatively easy to retrieve.

Latson and colleagues reported a postprocedural embolization rate of 2.3% (6 of 260 implants) in patients with 12-month follow-up data.[105] Five of the embolizations occurred within 24 hours of the implantation procedure. In all six patients, the devices were removed by using transcatheter retrieval techniques, but these procedures were not explained further. We have used a vascular retrieval forceps and a gooseneck snare on separate occasions to grasp the device and pull it into a delivery sheath. As reported by Tan and colleagues, Latson suggested snaring the locking loop and pulling the device into the delivery sheath.[106] One case report details failure of percutaneous retrieval attempts of a Helex device that had embolized to the pulmonary artery in a small child.[107]

Special Considerations

Closure of Large Atrial Septal Defects

Closure of large ASDs (30 to 36 mm) or those with deficient rims (<5 mm) can be difficult. Because the Helex device cannot be used to close large ASDs, the focus of this discussion is on techniques that have been described for use with the ASO.

In patients with a deficient SVC (superior or anterosuperior rims [retroaortic]), it is very easy for the left atrial disk to prolapse through the defect on initial deployment. This can also occur with deficient posteroinferior rims. If multiple rims are deficient, the likelihood of successful closure decreases further. The operator's familiarity with advanced techniques of deployment greatly improves the chances of procedural success, and it is imperative that the implanter become comfortable with several of these techniques.

In right upper pulmonary vein deployment, the delivery sheath is positioned with the tip in the right upper pulmonary vein.[108] The left atrial disk is partially deployed in the os of the right upper pulmonary vein or near the roof of the left atrium, and the remainder of the device is then rapidly deployed by pulling down on the delivery sheath while fixing the delivery cable. After the device is fully exposed, the cable can

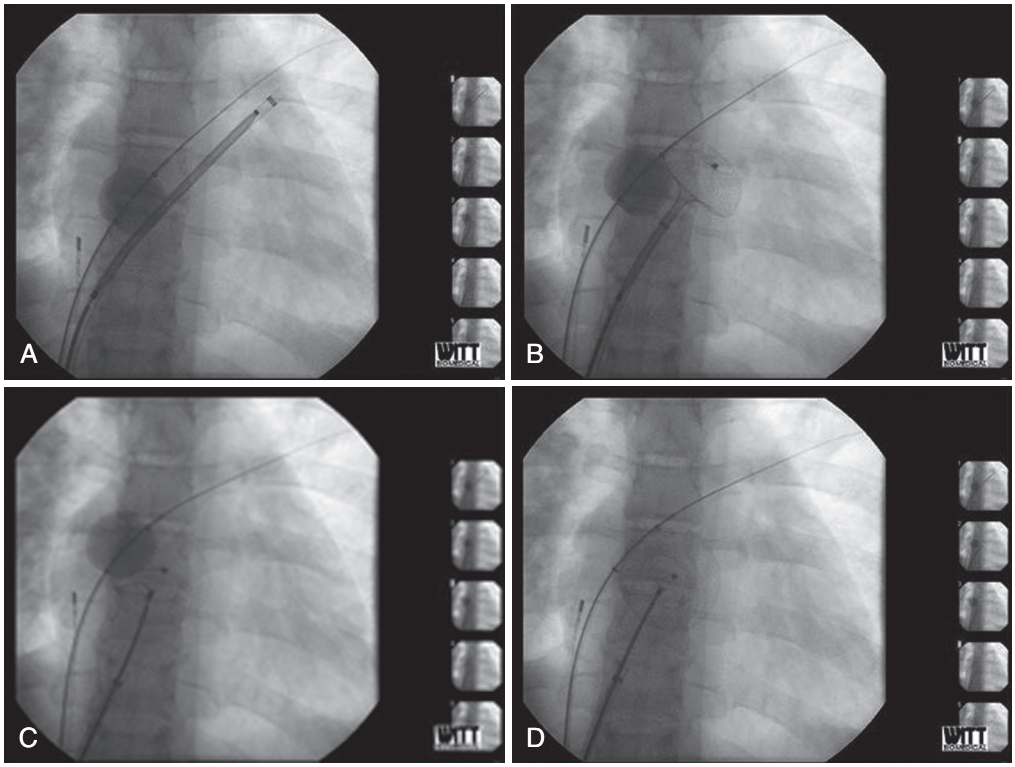

FIGURE 49-23 Steps in balloon-assisted technique. **A,** Inflation of an occlusion balloon against the right atrial side of the atrial septum with the Amplatzer delivery sheath in place. **B,** Deployment of the left atrial disk using an occlusion balloon as a buttress to prevent prolapse of the disk. **C,** Deployment of the right atrial disk with the occlusion balloon still in place. **D,** Deflation of the occlusion balloon and reconfiguration of the Amplatzer device without prolapse of disk (see Videos 49-14 and 49-16 through 49-18).

be pushed forward to reorient the device if necessary. Unsheathing of the device in this technique must be performed rapidly to be successful (Video 49-15).

In the left upper pulmonary vein (LUPV) deployment, the delivery sheath is placed in the LUPV, and the left atrial disk is deployed.[109] The left atrial disk is held in place in the LUPV and assumes an oblong shape. The remainder of the device is unsheathed by retracting the delivery sheath over the cable. Tension on the cable is then released, allowing the right atrial disk to reconfigure against the septum. This results in the left atrial disk being released from the LUPV and orienting correctly against the atrial septum. The unsheathing maneuver and the release of tension on the delivery cable must be performed sequentially and rapidly for the procedure to be successful. Proper deployment of the left atrial disk in the LUPV is paramount; if the left atrial disk is deployed too far into the LUPV, it will not be released from the vein. Conversely, if the left atrial disk is not deployed far enough in the LUPV, it will be released prematurely, and the technique will not be successful. The left bronchus is a useful fluoroscopic landmark for the ostium of the LUPV and should be used as a guide for placement.

Alternative sheath uses are described subsequently. The Hausdorf sheath (Cook, Bloomington, IN) has a double curve at the distal end, which facilitates appropriate alignment of the left atrial disk against the septum. This sheath is available in 10-, 11-, and 12-Fr sizes. Its use is particularly helpful in patients with deficient superior or anterosuperior rims.

A Mullins sheath may also be used. It has more of a curve compared with the standard 45-degree TorqVue delivery sheath and may help align the left atrial disk appropriately. Kutty and colleagues described the use of a Mullins sheath.[110] The sheath is modified by cutting off the distal curved portion of the sheath parallel to the shaft. This results in what they called a *straight side-hole sheath*.[110] The very sharp distal end of the modified sheath is then cut off to reduce the risk of perforation. This modification of the Mullins sheath results in the device exiting the tip of the delivery sheath at an angle that makes deployment of the left atrial disk parallel to the septum much easier.

For the balloon-assisted technique (Fig. 49-23 and Videos 49-16 through 49-18; see Video 49-14), Dalvi and associates reported a technique that uses a balloon as a buttress to prevent prolapse of the left atrial disk through the ASD during deployment. This technique is easy to learn and quite successful in our experience. To perform this procedure, a second venous line is inserted. The ASD is crossed in a standard fashion, and the defect is sized using the stop-flow technique. The appropriate device and delivery sheath are chosen and placed in the left atrium in the standard fashion. Through the second venous sheath, a catheter is placed in the LUPV, and a 0.035-inch guidewire is placed. The sizing balloon or a Meditech occlusion balloon can be placed over the guidewire. The balloon is inflated in the right atrium and placed against the right side of the atrial septum. The left atrial disk of the device is then deployed and pulled against the left side of the septum. The balloon helps prevent prolapse of the device at this time. The remainder of the device is deployed while the balloon remains in place against the septum. After the entire device is deployed, the sizing balloon is deflated.

TEE or ICE is used to assess the results. If the device has been correctly placed, the deflated balloon and guidewire are removed from across the septum. One disadvantage of this technique is that a second or third (if ICE is used) venous access is required.

Several other techniques have been described to assist in closure of large ASDs or those with deficient rims. They include the use of the dilator as a buttress similar to that described for the balloon-assisted technique, use of a right coronary guiding catheter, and use of a deflectable electrophysiology sheath.[111,112]

Multifenestrated Atrial Septal Defects

Fenestrations are frequently encountered with secundum ASDs. These additional defects are often found along the posteroinferior portion of the atrial septum. In many situations, closure of the primary defect within the fossa ovalis is enough to provide closure of the secondary defects. If the secondary fenestrated portion of the septum is fairly remote (>7 mm) from the primary defect, closure using multiple devices may be required (discussed later). If the fossa ovalis has multiple fenestrations, use of a non–self-centering device such as the Helex device or the Amplatzer cribriform device is appropriate.

The procedural details for closure of fenestrated ASDs are different from those for a standard secundum ASD in that the defect is *not* balloon sized. Instead, the distance from the central-most defect to the furthest reaches of the outer-most defect is measured under TEE or ICE guidance. It is important to measure this in multiple views and to use the largest diameter measured to choose a device. This measured dimension represents the radius of the device to be chosen. The device must have a diameter at least twice the measured radius to ensure that all the holes are covered with device material.

After the device is chosen, the central-most defect is crossed under ultrasound guidance. The operator must ensure that the central defect is crossed and not one of the satellite lesions. This may be difficult, especially in the setting of a septal aneurysm. A variety of catheters may be used for this purpose, but we have found that a multipurpose or Judkins right coronary catheter is often successful. Because the fenestrations are often small, the use of a non–J-tipped wire such as a Wholey wire or Terumo wire is necessary. The wire within the catheter makes identification of the catheter on ultrasound easier. As the catheter or wire crosses a very thin, floppy septum, the tissue is often moved out of plane on the echocardiogram, and it is important to look in several views to decide whether the appropriate hole has been crossed.

After the correct hole has been crossed, the guidewire is placed in the LUPV. If the Amplatzer cribriform device is chosen, the appropriate delivery sheath is advanced across the septum, and the device is deployed as previously described. If a Gore Helex device is chosen, the sheath should be advanced over the guidewire as mentioned in the procedural section earlier. After the Helex sheath is across the defect, the guidewire is removed and the device deployed in the standard fashion. A full TEE or ICE study should be repeated after device deployment to make certain that all the defects have been covered with the device.

Multiple Atrial Septal Defects

Multiple ASDs have been reported to occur in up to 7.3% of cases.[114] They can often be treated with a single device. If the secondary defect is not covered appropriately by a single device, deployment of a second device is necessary if the secondary defect is thought to be hemodynamically significant. Use of a second device may be anticipated if an Amplatzer septal occluder is chosen to close the primary defect and if the distance between the edges of the primary and secondary defects is 7 mm or more.

Several techniques have been used to close multiple defects, including simultaneous defect sizing and device deployment and sequential sizing and closure. We think either approach is acceptable. We typically perform sequential defect sizing and closure, in which one of the defects is crossed, sized, and then closed with an appropriate device. This is followed by crossing the secondary defect, sizing it, and closing it.

It does not matter which defect is addressed first. The relationship of the two devices to each other is likewise not critical. On some occasions, the larger device can sandwich the smaller device; at other times, the disks are intercalated. Either approach is acceptable. Smaller defects are often at the posteroinferior portion of the septum, and after they are closed, the two devices may orient themselves at almost 90 degrees to each other. This is to be expected because the atrial septum is a three-dimensional structure. On rare occasions, more than two devices are necessary to close additional defects. Meticulous attention to echocardiographic images is required to make certain that there is enough room in the left atrium to accommodate additional devices without impinging on adjacent structures.

Atrial Septal Defect Closure and Pulmonary Hypertension

Pulmonary hypertension (pulmonary artery systolic pressures >40 mm Hg) occurs in 6% to 50% of adults with ASDs.[115-120] This is a frequently encountered phenomenon when considering transcatheter ASD closure. Until recently, there were few data to guide the decision to perform transcatheter ASD closure in these patients. The availability of pulmonary vasodilator therapy such as sildenafil, bosentan, or prostacyclin has further clouded the issue.

Most studies use pulmonary artery systolic pressure (PASP) or right ventricular systolic pressure as assessed by echocardiography to divide patients into mild (PASP of 40 to 49 mm Hg), moderate (PASP of 50 to 59 mm Hg), or severe (PASP >60 mm Hg) groups. Pressure estimates are based on the modified Bernoulli equation using the tricuspid regurgitant velocity, v ($4v^2$ + right atrial pressure).

Yong and colleagues reported 215 consecutive adult patients undergoing transcatheter ASD closure with the ASO.[117] Of these patients, 108 (50.2%) had some elevation of pulmonary artery pressure as assessed on baseline echocardiography. Mild pulmonary hypertension was seen in 62 (28.8%), moderate in 27 (12.6%), and severe in 19 (8.8%). ASD closure was successful in 194 patients, and they were followed for a median duration of 15 months. A decrease in PASP of at least 5 mm Hg as assessed by echocardiography was found on follow-up in 33.7%, 73.9%, 79.2%, and 100% of patients with no, mild, moderate, or severe pulmonary hypertension, respectively. For patients with moderate or severe pulmonary hypertension, the median reduction in PASP was 18 mm Hg. PASP normalized in 141 patients (75.8%), which included 48.8% of those with moderate or severe pulmonary hypertension. Functional deterioration occurred in two patients who had a baseline PASP of 50 mm Hg or more and whose disease was categorized as New York Heart Association (NYHA) functional class II before ASD closure.

Multivariate analysis demonstrated that a higher baseline PASP, younger age, and smaller body size were independent factors associated with a reduction in PASP after transcatheter ASD closure. At the time of the cardiac catheterization in this study, all but three patients had a ratio of pulmonary artery to systemic pressure of 0.67 or less.

Balint and colleagues reviewed their experience with transcatheter closure of ASDs in patients with moderate or severe pulmonary hypertension undergoing closure between April 1999 and November 2004.[119] Of the patients referred for ASD closure, 11% (54 of 484) had moderate or severe pulmonary hypertension. There were 34 (63%) patients with moderate and 20 (37%) with severe pulmonary hypertension. Early follow-up was performed a mean of 2.3 months from device closure, and the right ventricular systolic pressure (RVSP) decreased from 57 to 51 mm Hg. The RVSP normalized in 26% (14 of 54) of patients, including 13 with moderate and 1 with severe pulmonary hypertension; however, 5 patients had an increase in RVSP greater than 10 mm Hg compared with baseline.

Late follow-up information was obtained for 45 patients (83%) an average of 31 months from implantation. Two patients died during follow-up, one from bowel obstruction and one from pulmonary thromboembolism. Two patients had pulmonary vasodilators started after closure, and one patient was receiving prostacyclin therapy before closure and bosentan therapy after closure. Late follow-up echocardiograms were available for 39 patients. In this group, the mean RVSP decreased from 58 mm Hg at baseline to 44 mm Hg. RVSP increased by more than 10 mm Hg in three patients. In patients with moderate pulmonary hypertension, the RVSP decreased from 51 to 38 mm Hg, and in those with severe pulmonary hypertension, the RVSP decreased from 70 to 48 mm Hg. Overall, 17 (44%) of 39 patients at late follow-up had normalization of RVSP, including 15 with moderate and 2 with severe pulmonary hypertension.

De Lezo and associates reviewed their experience with adults with pulmonary hypertension and transcatheter ASD closure.[120] Twenty-nine (28.7%) of a total of 101 patients undergoing percutaneous closure

had echocardiographic evidence of pulmonary hypertension. At cardiac catheterization, the PASP ranged from 41 to 147 mm Hg, with a mean of 64 mm Hg. The ratio of pulmonary to systemic pressure averaged 0.66, and the mean Qp/Qs ratio was 1:8. Three patients had systemic PASP and bidirectional shunts. They had further assessment with hyperoxia or balloon test occlusion of the ASD, or both, and underwent closure after a favorable test result. Immediately after the procedure, the mean PASP decreased to 54 mm Hg, and the pulmonary to systemic pressure ratio decreased to 0.54. All symptomatic patients improved, including those with systemic-level pulmonary hypertension. After a mean follow-up period of 21 months, the mean PASP as assessed by Doppler had decreased further to 34 mm Hg, and no clinical deterioration was identified.

On the basis of the results of these studies, we recommend ASD closure in patients with any level of pulmonary hypertension and a left-to-right shunt. Those with a bidirectional shunt and systemic desaturation (aortic saturation <92%) should undergo pulmonary vasodilator testing with test occlusion of the ASD. If the response is favorable, percutaneous ASD closure may be performed. A favorable response is defined as a fall in the mean pulmonary arterial pressures with oxygen and test occlusion, with no decrease in the cardiac output and no increase in the right atrial pressure. If the response is unfavorable, the patient should be started on pulmonary vasodilator therapy, and cardiac catheterization should be repeated after several months to reassess the hemodynamics. If there has been a favorable change, the ASD may be closed at that time with a fenestrated device designed for such cases (Fig 49-24).

Diastolic Left Ventricular Dysfunction and Atrial Septal Defect Closure

An increasing number of patients older than 60 years are being referred for transcatheter closure of ASDs. Up to 25% of these patients may have left ventricular restrictive physiology.[121] Closure of the ASD in this situation may result in an acute increase in left atrial pressure and precipitation of pulmonary edema and left heart failure.[122] Anticipation of this complication is important, and proper evaluation of the patient before ASD closure is necessary.

Ewert and coworkers described a group of 18 patients older than 60 years of age for whom transcatheter ASD closure was planned.[123] The patients underwent a baseline hemodynamic evaluation and TEE to assess the mitral valve inflow pattern. The ASD also was test occluded for 10 minutes with a sizing balloon, after which the left atrial pressure measurement and assessment of the mitral inflow Doppler were repeated. Eleven of the patients had no significant change in the left atrial pressure or the mitral Doppler findings, and of these, 10 underwent uneventful transcatheter ASD closure. In one patient, the defect was too large to be closed in the catheterization laboratory. The remaining 7 patients had a marked increase in the mean left atrial pressure from 14 to 23 mm Hg, with an increase in the *a* wave from 18 to 26 mm Hg and the *v* wave from 24 to 41 mm Hg. The mitral valve ratio of the early (E) to late (A) ventricular filling velocities (E/A ratio) also increased dramatically in this group of patients. Two patients had transcatheter ASD closure; one subsequently developed atrial flutter and biventricular heart failure, and the second developed pulmonary edema shortly after the procedure. In the study, all patients who had a mean left atrial pressure greater than 10 mm Hg before test occlusion developed significantly elevated left atrial pressure after occlusion.

Schubert and colleagues described a group of 59 consecutive patients older than 60 years who were admitted for transcatheter ASD closure.[121] They performed balloon test occlusion in all patients, who were considered to have restrictive left ventricular physiology if the mean left atrial pressure increased more than 10 mm Hg with test occlusion. Patients were divided into two groups based on whether the mean left atrial pressure increase was less than 10 mm Hg (group A) or greater than 10 mm Hg (group B) with test occlusion. Patients in group B underwent conditioning with dopamine, milrinone, and Lasix infusions for 48 to 60 hours before ASD closure, followed by stepwise discontinuation of the intravenous infusions and a change to oral Lasix 24 to 36 hours after the procedure.

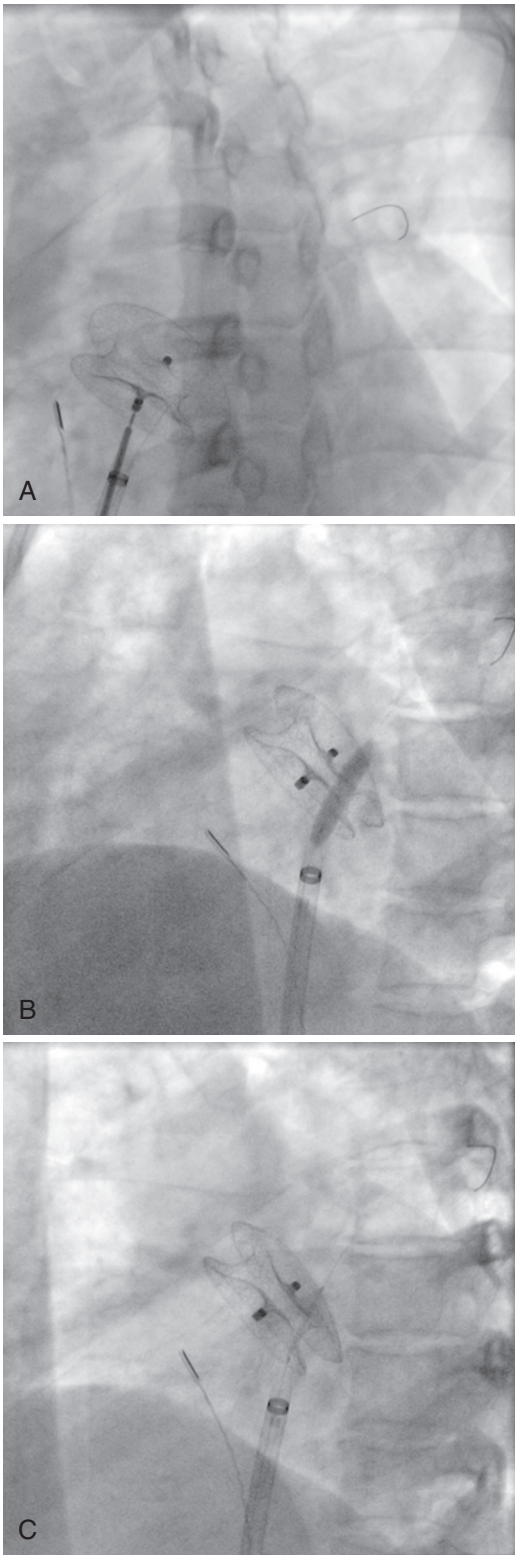

FIGURE 49-24 Cine images show the deployment of a fenestrated device for atrial septal defect closure in a patient with a bidirectional shunt and severe pulmonary hypertension responsive to pulmonary vasodilator therapy. After ex vivo creation of the fenestration, the fenestration is crossed with the use of an extra support wire before device loading. **A,** After it is deployed, the device is observed in a stable position. The extra support coronary wire tip is kept in the left upper pulmonary vein for support. **B,** After measurements, a coronary balloon is advanced over the wire and used to expand the fenestration. **C,** A bare-metal stent is then deployed across the fenestration.

Forty-four of 59 patients were in group A, and 15 patients (25%) were in group B. All patients in group A had an uncomplicated recovery after ASD closure. In group B, the mean left atrial pressure increased from 10 to 21 mm Hg with test occlusion before medical conditioning of the left ventricle. After 48 to 72 hours of conditioning, the mean left atrial pressure increased from 5 to only 7 mm Hg with test occlusion.

The ASD was successfully closed in 11 of 13 patients. In two patients, there was no reduction in left atrial pressure with medical conditioning, and they underwent ASD closure with fenestrated Amplatzer devices. Two other patients in group B had ASD closure, but it was performed without medical conditioning; one of the patients developed pulmonary edema and required mechanical ventilation, and the second developed pleural effusion 4 weeks after the procedure. Both patients were managed medically.

It is apparent from these and other studies that older adults are at high risk for restrictive physiology of the left heart, which may be unmasked by transcatheter ASD closure. Recognition of this phenomenon is important. We recommend a protocol similar to that described by Schubert and colleagues, in which patients have their left atrial pressure assessed with and without balloon occlusion.[121] If the left atrial pressure increases significantly (>10 mm Hg) with test occlusion, the patient should undergo medical conditioning with diuretics and a drug such as milrinone or nesiritide. A Swan-Ganz catheter can be placed in these patients to monitor wedge pressures. After 48 to 72 hours of medical therapy, the patient can then undergo a repeat catheterization, and if the left atrial pressure does not increase by more than 10 mm Hg, the ASD can be closed and the patient weaned from the medications over the next 48 hours. Diuretics are usually necessary on discharge.

CONCLUSIONS

Percutaneous closure of the secundum ASDs has changed the approach to congenital heart disease. Transcatheter secundum ASD closure is now considered the procedure of choice. This technique has moved beyond the spectrum of simple secundum ASDs and is applicable to large, multiple, or multifenestrated defects and to complex patients, such as those with pulmonary hypertension or restrictive left ventricular physiology. Many other devices are in development for ASD closure, and they may further expand the spectrum of defects that can be closed and improve the safety of the procedure.

REFERENCES

1. King TD, Thompson SL, Steiner C, et al: Secundum atrial septal defect: non-operative closure during cardiac catheterization. *JAMA* 235:2506–2509, 1976.
2. Mills NL, King TD: Late follow-up of nonoperative closure of secundum atrial septal defects using the King-Mills double umbrella device. *Am J Cardiol* 92:353–355, 2003.
3. Rashkind WJ: Transcatheter treatment of congenital heart disease. *Circulation* 67:711–716, 1983.
4. Rome JJ, Perry SB, Spevak PJ, et al: Double umbrella closure of atrial defects. Initial clinical applications. *Circulation* 82:751–758, 1990.
5. Moore KL, Persaud TUN: *Developing human: clinically oriented embryology*, Philadelphia, 1998, Saunders.
6. Meissner I, Whissant JP, Khandheria BK, et al: Prevalence of potential risk factors for stroke assessed by TEE and carotid ultrasonography: the SPARC Study. Stroke Prevention Assessment of Risk in a Community. *Mayo Clin Proc* 74:862–869, 1999.
7. Thompson T, Evans W: Paradoxical embolism. *Q J Med* 23:135–152, 1930.
8. Wu LA, Malouf JF, Dearani JA, et al: Patent foramen ovale in cryptogenic stroke. Current understanding and management options. *Arch Intern Med* 164:950–956, 2004.
9. Germonpre P, Hastir F, Dendale P, et al: Evidence for increasing patency of foramen ovale in divers. *Am J Cardiol* 95:912–915, 2005.
10. Rodriguez CJ, Homma S, Sacco RL, et al: Race-ethnic differences in patent foramen ovale, atrial septal aneurysm, and right atrial anatomy among ischemic stroke patients. *Stroke* 34:2097–2102, 2003.
11. Cohnheim J: *Thrombose und embolie: Vorlesung über allgemaine pathologie*, Berlin, 1877, Hirschwald, p 134.
12. Lechat PH, Mas MD, Lascault G, et al: Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 318:1148–1152, 1988.
13. Di Tullio M, Sacco RL, Gopal A, et al: Patent foramen ovale as a risk factor for cryptogenic stroke. *Ann Intern Med* 117:461–465, 1992.
14. Seward JB, Hayes DL, Smith HC, et al: Platypnea orthodeoxia: clinical profile, diagnostic work up, management, and report of seven cases. *Mayo Clin Proc* 59:221–231, 1984.
15. Godart F, Rey C, Prat A, et al: Atrial right to left shunting causing severe hypoxemia despite normal right sided pressures. *Eur Heart J* 21:483–489, 2000.
16. Bason R, Yacavone D: Decompression sickness: US navy altitude chamber experience 1 October 1981 to 30 September 1988. *Aviat Space Environ Med* 62:1180–1184, 1991.
17. Scherzmann M, Wiher S, Nedeltchev K, et al: Percutaneous closure of patent foramen ovale reduces the frequency of migraine attacks. *Neurology* 62:1399–1401, 2004.
18. Overell JR, Bone I, Lees KR: Interatrial septal abnormalities and stroke: a meta-analysis of case control studies. *Neurology* 55: 1172–1179, 2000.
19. Lamy C, Giannesini C, Zuber M, et al: Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale. The PFO-ASA study. *Stroke* 33:706–711, 2002.
20. Berthet K, Lavergne T, Cohen A, et al: Significant association of atrial vulnerability with atrial septal abnormalities in young patients with ischemic stroke of unknown cause. *Stroke* 31:298–403, 2000.
21. Thanigaraj S, Zajarias A, Lasala J, et al: Caught in the act: serial real time images of a thrombus traversing from the right to left atrium across a patent foramen ovale. *Eur J Echocardiogr* 7:179–181, 2006.
22. Sacco RL, Ellenberg JH, Mohr JP, et al: Infarcts of undetermined cause: the NINCDS Stroke Data Bank. *Ann Neurol* 25:382–390, 1989.
23. Cramer SC: Patent foramen ovale and its relationship to stroke. *Cardiol Clin* 23:7–11, 2005.
24. Cramer SC, Rordorf G, Maki JH, et al: Increased pelvic vein thrombi in cryptogenic stroke: Results of the paradoxical emboli from large veins in ischemic stroke (PELVIS) study. *Stroke* 35:46–50, 2004.
25. Konstantinides S, Geibel A, Kapser W, et al: Patent foramen ovale is an important predictor of adverse outcome in patients with major pulmonary embolism. *Circulation* 97:1946–1951, 1998.
26. Handke M, Harloff A, Olschewski M, et al: Patent foramen ovale and cryptogenic stroke in older patients. *N Engl J Med* 357:2262–2268, 2007.
27. Petty GW, Mayo K, Khandreia B, et al: Population based study of the relationship between patent foramen ovale and cerebrovascular ischemic events. *Mayo Clin Proc* 81:602–608, 2006.
28. Meissner I, Khandeira B, Heit JA, et al: Patent foramen ovale: Innocent or guilty? *J Am Coll Cardiol* 47:440–445, 2006.
29. Di Tullio MR, Sacco RL, Sciacca RR, et al: Patent foramen ovale and the risk of ischemic stroke in a multiethnic population. *J Am Coll Cardiol* 49(7):797–802, 2007.
30. Mas JL, Zuber M: Recurrent cerebrovascular events in patients with patent foramen ovale, atrial septal aneurysm or both and cryptogenic stroke or transient ischemic attack. *Am Heart J* 130:1083–1088, 1995.
31. De Castro S, Cartón D, Fiorelli M, et al: Morphological and functional characteristics of patent foramen ovale and their embolic complications. *Stroke* 31:2407–2413, 2000.
32. Cabanes L, Mas JL, Cohen A, et al: Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. *Stroke* 24:1865–1873, 1993.
33. Natanzon A, Goldman ME: Patent foramen ovale: Anatomy versus pathophysiology—which determines stroke risk. *J Am Soc Echocardiogr* 16:71–76, 2003.
34. Homma S, Di Tullio MR, Sacco RL, et al: Characteristics of patent foramen ovale associated with cryptogenic stroke: a biplane transesophageal echocardiographic study. *Stroke* 25: 582–586, 1994.
35. Schuchlenz HW, Saurer G, Wehis W, et al: Persisting eustachian valve in adults: relation to patent foramen ovale and cerebrovascular events. *J Am Soc Echocardiogr* 17:231–233, 2004.
36. Mas JL, Aruquizan C, Lamy C, et al: Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm or both. *N Engl J Med* 345:1740–1746, 2001.
37. Homma S, Sacco RL, Di Tullio M, et al: Effect of medical therapy in stroke patients with patent foramen ovale. Patent foramen ovale in cryptogenic stroke study. *Circulation* 105:2625–2631, 2002.
38. Bogousslavsky J, Garazi S, Jeanrenaud X, et al: Stroke recurrence in patients with patent foramen ovale. *Neurology* 46:1301–1305, 1996.
39. Khairy P, O'Donnell CP: Landzbergb MJ: Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical emboli. *Ann Intern Med* 139:753–760, 2003.
40. Messe SR, Silverman IE, Kizer JR, et al: Practice parameter: recurrent stroke with patent foramen ovale and atrial septal aneurysm: report of the quality standards subcommittee of the American Academy of Neurology. *Neurology* 62:1042–1050, 2004.
41. Dearani JA, Ugurlu BS, Danielson GK, et al: Surgical patent foramen ovale closure for prevention of paradoxical embolism-related cerebrovascular ischemic events. *Circulation* 100:II171–II175, 1999.
42. Windeker S, Wahl A, Chatterjee T, et al: Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long term risk of recurrent thromboembolic events. *Circulation* 101:893–898, 2000.
43. Wahl A, Meier B, Haxel B, et al: Prognosis after percutaneous closure of patent foramen ovale for paradoxical embolism. *Neurology* 57:1330–1332, 2001.
44. Braun M, Fassbender D, Schoen S, et al: Transcatheter closure of patent foramen ovale in patients with cerebral ischemia. *J Am Coll Cardiol* 39:2019–2025, 2002.
45. Windeker S, Wahl A, Nedeltchev K: Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. *J Am Coll Cardiol* 44:750–758, 2004.
46. Sacco RL, Adams R, Albers G, et al: Guidelines for the prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke* 37:598, 2006.
47. Carroll JD, Saver JL, Thaler DE, et al: Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med* 368:1092–1100, 2013.
48. Meier B, Kalesan B, Mattle HP, et al: Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med* 368:1083–1091, 2013.
49. Furlan AJ, Reisman M, Massaro J, et al: Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med* 366:991–999, 2012.
50. NCT00562289 trial. Patent foramen ovale closure or anticoagulants versus antiplatelet therapy to prevent stroke recurrence (CLOSE). Available at http://www.clinicaltrials.gov/ct2/show/NCT00562289?term=PFO+AND+stroke&rank=4 (accessed January 20, 2015).
51. NCT00738894 trial. Gore Helex septal occluder for patent foramen ovale closure in stroke patients (Gore REDUCE). Available at http://www.clinicaltrials.gov/ct2/show/NCT00738894?term=NCT&rank=1 (accessed January 20, 2014).
52. Riaz IB, Dhoble A, Mizyed A, et al: Transcatheter patent foramen ovale closure versus medical therapy for cryptogenic stroke: a meta-analysis of randomized clinical trials. *BMC Cardiovasc Disord* 13:116, 2013.
53. Stackhouse KA, Goel SS, Qureshi AM, et al: Off-label closure during CLOSURE study. *J Invasive Cardiol* 24:608–611, 2012.
54. Piechowski-Jozwiack A, Devuyst G, Bogousslavsky J: Migraine and patent foramen ovale: a residual coincidence or pathophysiological intrigue. *Cerebrovasc Dis* 22:91–100, 2006.
55. Kruit MC, van Buchen MA, Hofman PA, et al: Migraine as a risk factor for subclinical brain lesions. *JAMA* 291:427–434, 2004.
56. Milhaud D, Bogousslavsky J, van Melle G, et al: Ischemic stroke and active migraine. *Neurology* 57:1805–1811, 2001.

57. Anzola GP, Majuni M, Guindani M: Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. *Neurology* 52:1622–1625, 1999.
58. Scwerzmann M, Wiher S, Nedeltchev K, et al: Percutaneous closure of patent foramen ovale reduces the frequency of migraine attacks. *Neurology* 62:1399–1401, 2004.
59. Resiman M, Christofferson RD, Jesrum J, et al: Migraine headache relief after transcatheter closure of patent foramen ovale. *J Am Coll Cardiol* 45:233–299, 2005.
60. Anzola GP, Morad E, Casilli F, Onorato E: Shunt associated migraine responds favorable to atrial septal repair: a case control study. *Stroke* 37:430–434, 2006.
61. Reisman M, Christofferson RD, Jesrum J, et al: Migraine headache relief after transcatheter closure of patent foramen ovale. *J Am Coll Cardiol* 45:493–495, 2005.
62. Arzabal B, Tobis J, Suh W, et al: Association of interatrial shunts and migraine headaches: impact of transcatheter closure. *J Am Coll Cardiol* 45:489–492, 2005.
63. Giardini A, Donti A, Formigari R, et al: Transcatheter patent foramen ovale closure mitigates aura migraine headaches abolishing spontaneous right to left shunting. *Am Heart J* 151(922): E1–E5, 2006.
64. Dowson A, Mullen MJ, Peatfield R, et al: Migraine intervention with STARFlex technology (MIST) trial: a prospective multicenter, double blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headaches. *Circulation* 117:197–1404, 2008.
65. NCT00355056 trial. Prospective, randomized investigation to evaluate incidence of headache reduction in subjects with migraine and PFO using the Amplatzer PFO occluder to medical management (Premium Migraine Trial). Available at http://clinicaltrials.gov/ct2/show/NCT00355056 (accessed January 20, 2015).
66. Chen GPW, Goldberg S, Gill EA: Patent foramen ovale and the platypnea orthodeoxia syndrome. *Cardiol Clin* 2:85–89, 2005.
67. Ilkhanoff L, Naidu S, Rohatgi S, et al: Transcatheter device closure of interatrial septal defects in patients with hypoxia. *J Interv Cardiol* 18:227–232, 2005.
68. Waight DJ, Cao QL, Hijazi ZM: Closure of patent foramen oval in patients with orthodeoxia-platypnea using the Amplatzer devices. *Catheter Cardiovasc Interv* 50:195–198, 2000.
69. Roxas Timonera M, Larracas C, Gersony D, et al: Patent foramen ovale presenting as platypnea orthodeoxia: diagnosis by transesophageal echocardiography. *J Am Soc Echocardiogr* 14: 1039–1041, 2001.
70. Shanoudy H, Soliman A, Raggi P, et al: Prevalence of patent foramen ovale and its contribution to hypoxemia in patients with obstructive sleep apnea. *Chest* 113:91–96, 1998.
71. Germonpre P: Patent foramen ovale and diving. *Cardiol Clin* 23:97–104, 2005.
72. Germonpre P, Dendle P, Unger P, et al: Patent foramen ovale and decompression illness in sport divers. *J Appl Physiol* 84:1622–1626, 1998.
73. Schwerzmann M, Siller C, Lipp E, et al: Relation between directly detected patent foramen ovale and ischemic brain lesions in sport divers. *Ann Intern Med* 134:21–28, 2001.
74. Torti SR, Billager M, Schwerzmann M, et al: Risk of decompression among 230 divers in relation to the presence and size of PFO. *Eur Heart J* 25:1014–1020, 2004.
75. Kerut EK, Norfleet WT, Plotnick GD, et al: Patent foramen ovale: a review of associated condition and the impact of physiological size. *J Am Coll Cardiol* 38:613–623, 2001.
76. Hamman GF, Schatzer-Klotz D, Frohliq G, et al: Femoral infection of echo contrast medium may increase the sensitivity of testing for a patent foramen ovale. *Neurology* 50:1423–1428, 1998.
77. Daniels C, Weytjens C, Cosyns B, et al: Second harmonic transthoracic echocardiography: the new reference screening method for the detection of patent foramen ovale. *Eur J Echocardiogr* 5:449–452, 2004.
78. Thanigaraj S, Valika A, Zajarias A, et al: Comparison of transthoracic versus transesophageal echocardiography for the detection of right to left atrial shunting using agitated saline contrast. *Am J Cardiol* 96:1007–1010, 2005.
79. Anzola GP, Mornadi E, Casilli F, et al: Does transcatheter closure of patent foramen ovale really "shut the door?" A prospective study with transcranial Doppler. *Stroke* 35:2140–2144, 2004.
80. US Food and Drug Administration: *HDE #H99001*, Washington, DC, 2000, FDA.
81. Zajarias A, Thanigaraj S, Lasala J: Predictors and clinical outcomes of residual shunt in patients undergoing percutaneous transcatheter closure of patent foramen ovale. *J Invasive Cardiol* 18:533–537, 2006.
82. Alameddine F, Block PC: Transcatheter patent foramen ovale closure for secondary prevention of paradoxical embolic events: Acute results from the FORECAST Registry. *Catheter Cardiovasc Interv* 62:512–516, 2004.
83. Braun M, Gliech V, Boscheri A, et al: Transcatheter closure of patent foramen ovale (PFO) in patients with paradoxical embolism. Periprocedural safety and mid-term follow up results of three different device occluder systems. *Eur Heart J* 25:424–430, 2004.
84. Perloff JK: *Clinical recognition of congenital heart disease*, Philadelphia, 2003, Saunders, pp 493–495.
85. Van Praagh S, Carrera ME, Sanders SP, et al: Sinus venosus defects: unroofing of the right pulmonary veins—anatomic and echocardiographic findings and surgical treatment (abstract). *Am Heart J* 128:365, 1994.
86. Hunt CE, Lucas RV, Jr: Symptomatic atrial septal defect in infancy. *Circulation* 42:1042–1048, 1973.
87. Levin AR, Spach MS, Boineau JP, et al: Atrial pressure flow dynamics and atrial septal defects (secundum type). *Circulation* 37:476–488, 1968.
88. Clark EB, Kugler JD: Preoperative secundum atrial septal defect with coexisting sinus node and atrioventricular node dysfunction. *Circulation* 65:976–980, 1982.
89. Shub C, Tajik AJ, Seward JB, et al: Surgical repair of uncomplicated atrial septal defect without "routine" preoperative cardiac catheterization. *J Am Coll Cardiol* 6:49–54, 1985.
90. Freed MD, Nadas AS, Norwood WI, et al: Is routine preoperative cardiac catheterization necessary before repair of secundum and sinus venosus atrial septal defects? *J Am Coll Cardiol* 4:333–336, 1984.
91. Konstantinides S, Kasper W, Geibel A, et al: Detection of left-to-right shunt in atrial septal defect by negative contrast echocardiography: a comparison of transthoracic and transesophageal approach. *Am Heart J* 126:909–917, 1993.
92. Ishii M, Kato H, Inoue O, et al: Biplane transesophageal echo-Doppler studies of atrial septal defects: quantitative evaluation and monitoring for transcatheter closure (abstract). *Am Heart J* 125:1363, 1993.
93. Silverman NH, Schmidt KG: The current role of Doppler echocardiography in the diagnosis of heart disease in children. *Cardiol Clin* 7:265–297, 1989.
94. Taketa RM, Sahn DJ, Simon AL, et al: Catheter positions in congenital cardiac malformations. *Circulation* 51:749–757, 1975.
95. Du ZD, Hijazi ZM, Kleinman CS, et al: Comparison between transcatheter and surgical closure of secundum atrial septal defect in children and adults: results of a multicenter nonrandomized trial. *J Am Coll Cardiol* 39:1836–1844, 2002.
96. Jones TK, Latson LA, Zahn E, et al: Results of the US multicenter pivotal study of the Helex septal occluder for percutaneous closure of secundum atrial septal defects. *J Am Coll Cardiol* 49:2215–2221, 2007.
97. Amin Z, Hijazi ZM, Bass JL, et al: Erosion of Amplatzer septal occluder device after closure of secundum atrial septal defects: review of registry of complications and recommendations to minimize future risk. *Catheter Cardiovasc Interv* 63:496–502, 2004.
98. El-Said HG, Moore JW: Erosion of the Amplatzer septal occluder: experienced operator opinions at odds with manufacturer recommendations? *Catheter Cardiovasc Interv* 73:925–930, 2009.
99. FDA executive summary memorandum: transcatheter ASD occluders: clinical update and review of events. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM304924.pdf (accessed January 20, 2015).
100. St. Jude Medical: Structural heart and vascular products. Available at http://professional.sjm.com/professional/resources/ifu/sh/asd-closure (accessed January 20, 2015).
101. Levi DS, Moore JW: Embolization and retrieval of the Amplatzer septal occluder. *Catheter Cardiovasc Interv* 61:543–547, 2004.
102. Dibardino SJ, McElhinney DB, Kaza AK, et al: Analysis of the US food and drug administration manufacturer and user facility device experience database for adverse events involving Amplatzer septal occluder devices and comparison with the society of thoracic surgery congenital cardiac surgery database. *J Thorac Cardiovasc Surg* 137:1334–1339, 2009.
103. Fagan T, Dreher D, Cutright W, et al: Fracture of the Gore Helex septal occluder: Associated factors and clinical outcomes. *Catheter Cardiovasc Interv* 73:941–948, 2009.
104. Quershi AM, Mumtaz MA, Latson LA: Partial prolapse of a Helex device associated with early frame fracture and mitral valve perforation. *Catheter Cardiovasc Interv* 74:777–782, 2009.
105. Latson LA, Jones TK, Jacobson J, et al: Analysis of factors related to successful transcatheter closure of secundum atrial septal defects using the Helex septal occluder. *Am Heart J* 151:1129, e7-1129.e11, 2006.
106. Tan CA, Levi DS, Moore JW: Embolization and transcatheter retrieval of coils and devices. *Pediatr Cardiol* 26:267–274, 2005.
107. Peuster M, Reckers J, Fink C: Secondary embolization of a Helex occluder implanted into a secundum atrial septal defect. *Catheter Cardiovasc Interv* 59:77–82, 2003.
108. Kannan BR, Francis E, Sivakumar K, et al: Transcatheter closure of very large (>25 mm) atrial septal defects using the Amplatzer septal occluder. *Catheter Cardiovasc Interv* 59:522–527, 2003.
109. Varma C, Benson LN, Silversides C, et al: Outcomes and alternative techniques for device closure of the large secundum atrial septal defect. *Catheter Cardiovasc Interv* 61:131–139, 2004.
110. Kutty S, Asnes JD, Srinath G, et al: Use of a straight, side-hole delivery sheath for improved delivery of Amplatzer ASD occluder. *Catheter Cardiovasc Interv* 69:15–20, 2007.
111. Dalvi BV, Pinto RJ, Gupta A: New technique for device closure of large atrial septal defects. *Catheter Cardiovasc Interv* 64:102–107, 2005.
112. Wahab HA, Bairam AR, Cao QL, et al: Novel technique to prevent prolapse of the Amplatzer septal occluder through large atrial septal defect. *Catheter Cardiovasc Interv* 60:543–545, 2003.
113. Reference deleted in review
114. Podnar T, Martanovic P, Gavora P, et al: Morphological variations of secundum-type atrial septal defects: feasibility for percutaneous closure using Amplatzer septal occluders. *Catheter Cardiovasc Interv* 53:386–391, 2001.
115. Engelfriet PM, Duffels MG, Moller T, et al: Pulmonary arterial hypertension in adults born with a heart septal defect: the Euro Heart Survey on adult congenital heart disease. *Heart* 93:682–687, 2007.
116. Vogel M, Berger F, Kramer A, et al: Incidence of secondary pulmonary hypertension in adults with atrial septal or sinus venosus defects. *Heart* 82:30–33, 1999.
117. Yong G, Khairy P, De Guise P, et al: Pulmonary arterial hypertension in patients with transcatheter closure of secundum atrial septal defects: a longitudinal study. *Catheter Cardiovasc Interv* 2:455–462, 2009.
118. Steele PM, Fuster V, Cohen M, et al: Isolated atrial septal defect with pulmonary vascular obstructive disease-long-term follow-up and prediction of outcome after surgical correction. *Circulation* 76:1037–1042, 1987.
119. Balint OH, Samman A, Heberer K, et al: Outcomes in patients with pulmonary hypertension undergoing percutaneous atrial septal defect closure. *Heart* 94:1189–1193, 2008.
120. De Lezo JS, Medina A, Romero M, et al: Effectiveness of percutaneous device occlusion for atrial septal defect in adult patients with pulmonary hypertension. *Am Heart J* 144:877–880, 2002.
121. Schubert S, Peters B, Abdul-Khaliq H, et al: Left ventricular conditioning in the elderly patient to prevent congestive heart failure after transcatheter closure of atrial septal defect. *Catheter Cardiovasc Interv* 64:333–337, 2005.
122. Ewert P, Berger F, Nagdyman N, et al: Acute left heart failure after interventional occlusion of an atrial septal defect. *Z Kardiol* 90:362–366, 2001.
123. Ewert P, Berger F, Nagdyman N, et al: Masked left ventricular restriction in elderly patients with atrial septal defects: a contraindication for closure? *Catheter Cardiovasc Interv* 52:177–180, 2001.

Left Atrial Appendage Closure and Stroke: Local Device Therapy for Cardioembolic Stroke Protection

50

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KEY POINTS

- Atrial fibrillation (AF) is associated with substantial morbidity, primarily due to stroke and systemic embolism.
- The left atrial appendage (LAA) appears to be the primary source of thromboembolism in AF and therefore is a target for mechanical therapies for stroke reduction.
- Although concomitant LAA excision or exclusion is commonly performed during cardiac surgery in high-risk patients, insufficient resection or postoperative residual leaks occur frequently and may be associated with thrombus and neurologic events.
- Observational studies have provided conflicting results regarding the efficacy of surgical LAA closure for stroke reduction.
- Two randomized clinical trials that compared the Watchman LAA occluder with warfarin in oral anticoagulation–eligible patients have shown that closure with the device is an acceptable alternative to long-term warfarin in some patients for the prevention of cardiovascular death, stroke, and systemic embolism.
- The Amplatzer Cardiac Plug and the second-generation Amulet occlude the LAA using a mechanism different from that of the Watchman. Several small-scale, observational case series suggest that outcomes for the Amplatzer devices are similar to those for the Watchman device.
- The Lariat device, which is cleared by the U.S. Food and Drug Administration for soft tissue closure, has been applied clinically to percutaneously ligate the LAA using a combined transseptal and transpericardial approach.
- Evaluation of the patient with AF incorporates an assessment of thromboembolic and bleeding risk using well-validated risk schemes, such as the CHA_2DS_2VASc and HAS-BLED scores, which are based on individual comorbidity profiles.
- Appropriate patient selection for transcatheter LAA closure requires the assessment of the individual's risk of thromboembolism, long-term bleeding risk on oral anticoagulation, short-term procedural risk of device implantation, medication noncompliance, and patient preference.

Atrial fibrillation (AF) is associated with a significant risk of stroke and systemic embolism. The worldwide prevalence of this arrhythmia is increasing substantially as the global population ages. Although long-term treatment with oral anticoagulation (OAC) reduces thromboembolic risk, it is associated with an ongoing bleeding hazard and other limitations that deter its use.

The left atrial appendage (LAA) appears to be the dominant source of thromboembolism in patients with AF and has been described as "our most lethal human attachment."[1] Thrombus formation is normally prevented by vigorous blood flow in the appendage cavity, but LAA dysfunction can predispose to local thrombosis and systemic embolization. Local therapies that exclude the LAA from the systemic circulation offer a mechanical alternative to OAC for cardioembolic stroke protection in these patients, and several devices for transcatheter LAA closure have been developed.

This chapter summarizes the approaches to risk assessment for AF patients, describes the mechanistic basis for LAA closure, reviews the devices with the Conformité Européenne (CE) mark or U.S. Food and Drug Administration (FDA) clearance and their safety and efficacy datasets, and provides a framework for selecting the appropriate patient for device therapy.

ATRIAL FIBRILLATION AND STROKE

AF is caused by disorganized electrical activity in the atria. Instead of pumping in a coordinated manner, the heart contracts rapidly and irregularly, reducing the flow of blood to the body.

AF is the most common sustained arrhythmia. In 2010, the estimated prevalence of AF was between 2.7 and 6.1 million people in the United States and was approximately 33.5 million people worldwide.[2] The overall global burden of AF, its incidence, its prevalence, and its associated mortality have progressively increased over the past 2 decades,[3] and the prevalence of AF in the United States is expected to rise to between 5.6 and 12 million cases in 2050.[2]

Risk factors for AF include advancing age, male sex, diabetes mellitus, obesity, hypertension, and European ancestry. The cumulative risk of AF by 80 years of age in the Atherosclerosis Risk in Communities (ARIC) study was 21% among white men, 17% among white women, and 11% among African Americans.[4]

In addition to symptoms such as fatigue, palpitations, and shortness of breath, AF is associated with substantial morbidity, primarily due to stroke and thromboembolism. AF is associated with a fourfold to fivefold increased risk of ischemic stroke after adjusting for other risk factors,[5] and paroxysmal, persistent, or permanent forms of AF increase stroke risk to a similar degree.[6] Subclinical AF of more than 6 minutes' duration has been associated with an increased risk of ischemic stroke or systemic embolism.[7]

The relative contribution of AF to stroke is particularly large among the elderly. AF accounted for approximately 24% of strokes in those 80 to 89 years of age in the Framingham Heart Study.[5] AF-related ischemic strokes are more likely to be fatal than non-AF strokes, and among survivors, AF-related strokes are greater in severity and recur more frequently.[8]

ASSESSMENT OF THROMBOEMBOLIC AND BLEEDING RISK

An individualized assessment of thromboembolic risk is a critical part of therapeutic decision-making process. The $CHADS_2$ and CHA_2DS_2VASc scores are well-validated schemes for the risk stratification of ischemic stroke and systemic thromboembolism. Based on the individual comorbidities defined in Table 50-1, the scores are used to estimate the yearly risk of thromboembolic events and identify patients with AF who may derive clinical benefit from OAC (Table 50-2).[9,10] The CHA_2DS_2VASc score refines the $CHADS_2$ score by providing greater weight for elderly age (A_2) and incorporating the sex category (Sc) and vascular disease (V). The CHA_2DS_2VASc score can better identify patients who are at low risk (i.e., CHA_2DS_2VASc score = 0) and those who may not require OAC.[10] The CHA_2DS_2VASc score can also identify those at risk for stroke despite anticoagulation.[11]

TABLE 50-1 The $CHADS_2$ and CHA_2DS_2VASc Scoring for Thromboembolic Risk in Atrial Fibrillation

Characteristic	Points
$CHADS_2$	
C: congestive heart failure	1
H: hypertension	1
A: age ≥75 years	1
D: diabetes mellitus	1
S_2: prior stroke, transient ischemic attack, or thromboembolism	2
Maximum score	6
CHA_2DS_2VASc	
C: congestive heart failure	1
H: hypertension	1
A_2: age ≥75 years	2
D: diabetes mellitus	1
S_2: prior stroke, transient ischemic attack, or thromboembolism	2
V: vascular disease (i.e., prior MI, PAD, or aortic plaque)	1
A: age 65-74 years	1
Sc: sex category (e.g., female)	1
Maximum score	9

Modified from January CT, Wann LS, Alpert JS, et al: 2014 AHA/ACC/HRS guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society, *J Am Coll Cardiol* 64:e1-e76, 2014.
MI, Myocardial infarction; *PAD,* peripheral arterial disease.

TABLE 50-2 Yearly Risk of Stroke Based on $CHADS_2$ and CHA_2DS_2VASc Scores

Score	Adjusted Yearly Stroke Rate (%)
$CHADS_2$	
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2
CHA_2DS_2VASc	
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Modified from January CT, Wann LS, Alpert JS, et al: 2014 AHA/ACC/HRS guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society, *J Am Coll Cardiol* 64:e1-e76, 2014.

The 2014 American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (HRS) guidelines for the management of patients with AF recommend calculation of the CHA_2DS_2VASc score to assess stroke risk (class I, level B evidence) and the use of oral anticoagulants in patients with a CHA_2DS_2VASc score of 2 or greater (class I, level A evidence).[12] The European Society of Cardiology (ESC) guidelines also recommend OAC in patients with a CHA_2DS_2VASc score of 2 or greater (class I, level A evidence) and state that OAC should be considered in patients with a CHA_2DS_2VASc score of 1 (class IIa, level A evidence).[13]

The decision to treat a particular patient with OAC is often influenced by a real or perceived risk of bleeding. Several bleeding risk stratification schemes have been proposed. The HAS-BLED score, as defined in Table 50-3, provides better predictive capacity for bleeding events in OAC-treated patients compared with other scores and highlights risk factors that can be actively managed to reduce the bleeding risk.[14-16] The 2012 update of the ESC guidelines for the management of atrial fibrillation recommend that the HAS-BLED score should be used to assess bleeding risk. In that system, a score of 3 or higher indicates high risk, and some caution and regular review is needed after the initiation of antithrombotic therapy (class IIa, level A evidence). The guidelines further recommend that the HAS-BLED score be used to identify modifiable bleeding risks that need to be addressed, but they do not recommend that it be used on its own to exclude patients from OAC therapy (class IIa, level B evidence).[13]

The 2014 AHA/ACC/HRS guidelines make no formal recommendations regarding bleeding risk scores. However, it observes that a HAS-BLED score of 3 or higher indicates a high risk of bleeding that requires closer observation of a patient for adverse events, closer monitoring of international normalized ratios (INRs), and differential dose selections of oral anticoagulants or aspirin.[12]

TABLE 50-3 HAS-BLED Bleeding Risk Score for Hemorrhage Risk in Patients with Atrial Fibrillation

Characteristic	Points
H: hypertension (uncontrolled systolic blood pressure >160 mm Hg)	1
A: abnormal liver or renal function*	1 each, maximum 2
S: prior stroke	1
B: bleeding history or disposition (e.g., anemia)	1
L: labile INR (i.e., time in therapeutic range <60%)	1
E: elderly age (>65 yr)	1
D: drugs promoting bleeding or excess alcohol consumption (>7 units/wk)	1 each, maximum 2
Maximum score	9

Modified from Pisters R, Lane DA, Nieuwlaat R, et al: A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey, *Chest* 138:1093-1100, 2010.
INR, International normalized ratio.
*Abnormal liver function was defined as cirrhosis or biochemical evidence of significant hepatic derangement; abnormal renal function was defined as serum creatinine >200 µmol/L (2.26 mg/dL).

ORAL ANTICOAGULATION FOR STROKE PREVENTION

Oral anticoagulants reduce the risk of thromboembolism in patients with nonvalvular AF. Warfarin, a vitamin K antagonist, reduces the risk of ischemic stroke by approximately two thirds.[17] Successful therapy with warfarin, however, is challenging. Warfarin has a narrow therapeutic window. The pharmacokinetics and pharmacodynamics of warfarin vary considerably because they are influenced by genetics, diet, and numerous drug-drug interactions.[18] Regular laboratory monitoring and dose adjustment are required, and maintenance of anticoagulation in the therapeutic range can be difficult. Patients enrolled in clinical trials were in the therapeutic range 55% to 65% of the time.[19-22]

TABLE 50-4 Bleeding Outcomes in Randomized Trials of Non–Vitamin K Antagonist Oral Anticoagulants Compared with Warfarin in Patients with Atrial Fibrillation

		MAJOR BLEEDING* (% EVENTS/100 PT-YR)				GI BLEEDING (% EVENTS/100 PT-YR)			
Study	Study Drug	Interv.	Warf.	HR (95% CI)	*P* Value	Interv.	Warf.	HR (95% CI)	P Value
RE-LY[19]	Dabigatran†	3.11%	3.36%	0.93 (0.81-1.07)	.31	1.51%	1.02%	1.50 (1.19-1.89)	<.001
ARISTOTLE[20]	Apixaban	2.13%	3.09%	0.69 (0.60-0.80)	<.001	0.76%	0.86%	0.89 (0.70-1.15)	.37
ROCKET-AF[21]	Rivaroxaban	3.60%	3.4%	1.04 (0.90-1.20)	.58	3.15%	2.16%	NR	<.001
ENGAGE-AF[22]	Edoxaban†	2.75%	3.43%	0.80 (0.71-0.91)	<.001	1.23%	1.51%	1.23 (1.02-1.50)	.03

CI, Confidence interval; GI, gastrointestinal; HR, hazard ratio; Interv., intervention; NR, not reported; pt-yr, patient-years; Warf., warfarin.
*Definitions of major bleeding: *RE-LY,* clinically overt bleeding with decrease in hemoglobin of ≥2 g/dL, transfusion of ≥2 U of packed red blood cells (PRBCs), or symptomatic bleeding in a critical area or organ; *ARISTOTLE* and *ENGAGE-AF,* clinically overt bleeding with a decrease in hemoglobin of ≥2 g/dL or transfusion of ≥2 U of PRBCs, occurring at a critical site or resulting in death; *ROCKET-AF,* fatal outcome, involvement of a critical anatomic site, decrease in hemoglobin of ≥2 g/dL, transfusion of ≥2 U of PRBCs, or permanent disability.
†Event rates are listed for dabigatran (150 mg bid) and edoxaban (60 mg daily) dosages.

The novel (non–vitamin K antagonist) oral anticoagulants (NOACs) are noninferior or superior to warfarin for the prevention of stroke and systemic embolism, and they are more convenient because they do not require ongoing monitoring.[19-22] The efficacy of the NOACs compared with warfarin is driven primarily by reductions in hemorrhagic stroke; rates of ischemic strokes are similar or only modestly reduced. The NOACs are associated with a similar or lower rate of major hemorrhage than warfarin, with the exception of gastrointestinal bleeding, which is greater with all NOACs except apixaban, for which the risk of gastrointestinal bleeding is similar (see Table 50-3).[19-22]

Oral anticoagulants are underused despite their proven efficacy in reducing stroke and systemic embolism.[23-25] In the 2009 U.S. National Health and Wellness Survey, 36% of AF patients at high risk for thromboembolism were not being treated with an oral anticoagulant.[26] In a large study of commercially insured patients with AF, 47% were not receiving an oral anticoagulant despite being at moderate to high risk for stroke.[27] Patient characteristics associated with lower use of OAC include advancing age, perceived barriers to compliance, dementia, falls, hepatic or renal impairment, drug and alcohol abuse, gastrointestinal bleeding, and intracranial hemorrhage.[28] In the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT) study, patient refusal or preference, fall risk, and frailty were the factors associated with the lowest use of OAC among patients at high risk for stroke.[29]

Therapeutic challenges with the NOACs include cost, lack of widely available antidotes, side effects, and the need for long-term compliance. The overall bleeding hazard with the NOACs (Table 50-4) must be evaluated in the context of a therapy that needs to be administered for years. The safety and efficacy of NOACs for patients at higher risk for bleeding has not been defined because patients with prior bleeding events or those thought to be at high risk for bleeding were excluded or not well represented in the pivotal randomized trials.[19-22,30]

LEFT ATRIAL APPENDAGE CLOSURE

Rationale

The LAA is a multilobed, trabeculated, broad-shaped structure with a narrow neck. During AF, there is decreased LAA contractility and function, leading to dilation and remodeling and causing the appendage to function as a static pouch, predisposing patients to blood stagnation and thrombosis (Fig. 50-1).[31] Anatomic characteristics of the LAA, such as neck diameter, depth,[32] extent of trabeculations,[33] and cauliflower-type morphology,[34,35] have been associated with AF stroke risk (Fig. 50-2).

The LAA was the source of more than 90% of thrombi in cases of stroke in which the thrombus could be identified.[36] These data lend support to the hypothesis that elimination of the LAA may offer a preventive strategy for AF-related stroke.

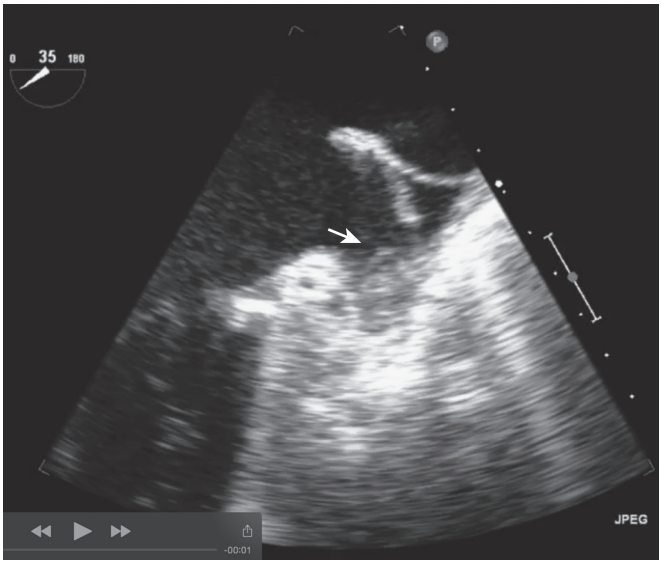


FIGURE 50-1 A left atrial appendage thrombus *(arrow)* in a patient with atrial fibrillation is identified by transesophageal echocardiography.

Surgical Approaches

More than 60 years ago, Madden suggested that surgical resection of the LAA in patients with AF could prevent recurrent arterial emboli,[37] and concomitant exclusion or removal of the LAA during cardiac surgery in high-risk AF patients has become commonplace. The heterogeneity of surgical techniques that are used and the lack of randomized data make it particularly challenging to assess whether this approach is effective in reducing the risk of thromboembolism in the absence of long-term OAC.

The two general approaches to surgical LAA closure are exclusion and excision. Exclusion can be performed with running or mattress sutures, with or without felt pledgets, from the endocardial or epicardial surface or with a stapler (Fig. 50-3). Excision can be performed by stapled excision or removal and oversewing.[38] However, postoperative residual leaks and insufficient resection occur frequently and can be associated with thrombus and neurologic events.[39,40] Incomplete or insufficient closure is more common with suture or staple exclusion than with excision.[38-41]

The results of observational studies that have examined the association between surgical LAA closure and stroke reduction are conflicting (Table 50-5).[38,41] The Left Atrial Appendage Occlusion Study III (LAAOS III) is recruiting participants and will randomly assign approximately 4500 patients with AF undergoing cardiac surgery to

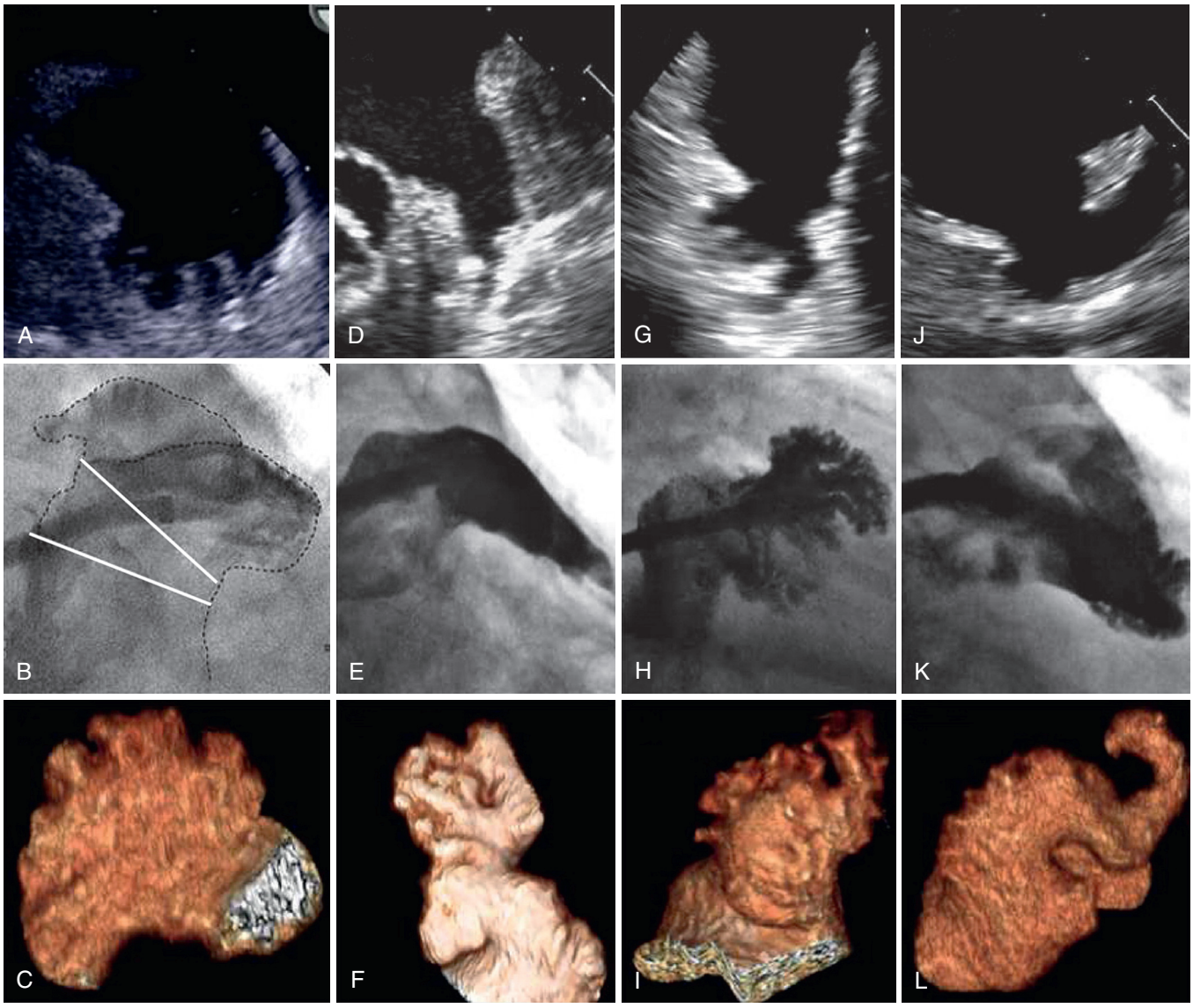


FIGURE 50-2 The four morphologic classifications of the left atrial appendage are shown by transesophageal echocardiography *(top)*, cine-angiography *(middle)*, and three-dimensional computed tomography *(bottom)*. **A** through **C,** Cauliflower morphology. **D** through **F,** Windsock morphology. **G** through **I,** Cactus morphology. **J** through **L,** Chicken wing morphology. (Modified from Beigel R, Wunderlich NC, Ho SY, et al: The left atrial appendage: anatomy, function, and noninvasive evaluation, *JACC Cardiovasc Imaging* 7:1251-1265, 2014.)

concomitant surgical LAA excision or exclusion or to conventional medical therapy. The primary end point is the first occurrence of stroke or systemic arterial embolism over a mean follow-up period of 4 years.[42] The results of this trial will help to define the efficacy of surgical approaches to stroke prevention.

Transcatheter Approaches

Percutaneous Left Atrial Appendage Transcatheter Occlusion System

The Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) system (ev3, Plymouth, MN) was the first percutaneous device to be prospectively evaluated for the purpose of LAA closure.[53] The device consisted of a self-expanding nitinol cage covered with an occlusive expanded polytetrafluoroethylene (ePTFE) membrane, with small anchors along the struts and passing through the membrane to help anchor the device in the LAA (Fig. 50-4). The device was delivered through a 14-Fr delivery sheath guided by transesophageal echocardiography (TEE) and fluoroscopy.

Device feasibility and long-term outcomes were evaluated in a prospective, nonrandomized, multicenter study of 64 AF patients in North America who were at high risk for thromboembolism ($CHADS_2$ score ≥2) but who were not candidates for warfarin.[54] Patients were treated after the procedure with indefinite aspirin and 4 to 6 weeks of clopidogrel. Anatomic closure at the time of the procedure (i.e., residual flow area ≤3 mm wide) was achieved in 98% of cases, and safety outcomes were excellent (i.e., only one major device-related adverse event within 1 month of the procedure). At the 5-year follow-up, the observed rate of stroke or transient ischemic attack was 3.8% per year, compared with an expected rate of 6.6% based on the $CHADS_2$ score of the study population.

The European prospective, multicenter, observational experience provided further insight into device feasibility and clinical efficacy over a relatively short-term clinical follow-up. In this registry, a total of 180

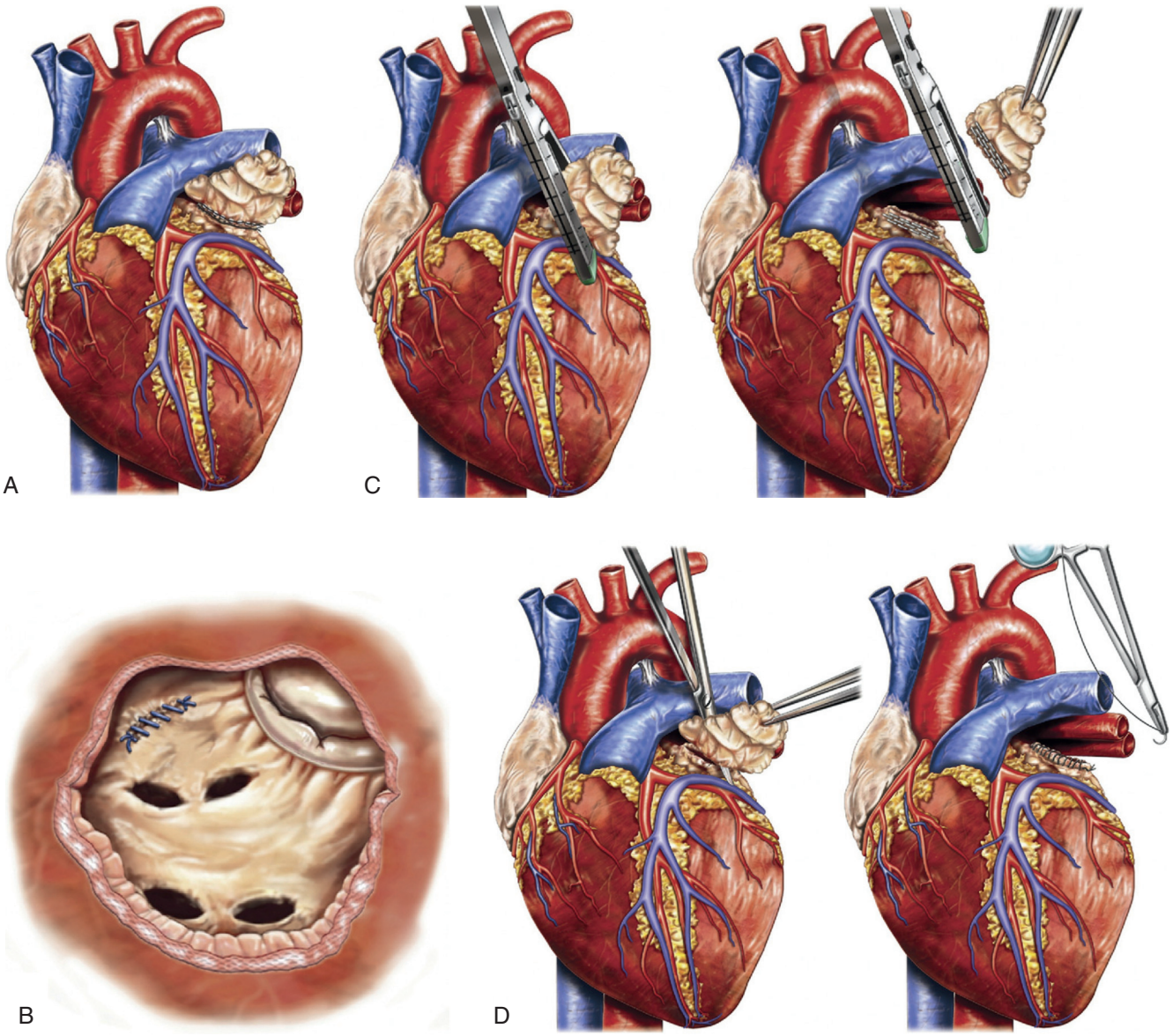


FIGURE 50-3 Surgical techniques used to close the left atrial appendage (LAA). **A,** Epicardial suture exclusion. **B,** Endocardial suture exclusion. **C,** Stapled excision, with the stapler positioned across the base of the LAA *(left)* and the LAA removed with an intact stump *(right)*. Thrombotic complications may occur if the residual stump is too large. **D,** Removal of the LAA by scissors or electrocautery *(left)*, followed by two-layer suture closure of the LAA stump flush with the heart surface. (Modified from Chatterjee S, Alexander JC, Pearson PJ, Feldman T: Left atrial appendage occlusion: lessons learned from surgical and transcatheter experiences, *Ann Thorac Surg* 92:2283-2292, 2011.)

high-risk AF patients were treated with the PLAATO device.[55] LAA occlusion was successful in 90%. The major periprocedural complication was cardiac tamponade, which occurred in 3.3% of cases. At 129 patient-years of follow-up, the observed incidence of stroke was 2.3% per year, compared with the expected 6.6%.[55] The device was not evaluated beyond these studies due to financial considerations. However, the PLAATO experience serves as proof of principle for transcatheter occlusion of the LAA for stroke prevention.

Watchman Occluder

Device Characteristics

The Watchman LAA closure device (Boston Scientific, Natick, MA) is parachute shaped and consists of a nitinol frame and a polyethylene terephthalate (PET) fabric membrane cap that faces the body of the left atrium (Fig. 50-5). Small tines that project toward the left atrium line the circumference of the distal portion of the device and help anchor the device in the LAA trabeculae. The device is connected to a delivery cable by a threaded insert in the proximal cap.

Device size corresponds to the diameter of the device measured at the proximal shoulders, which is its widest portion. The five sizes range from 21 to 33 mm. The manufacturer recommends oversizing the device by 8% to 20%. The Watchman device is used to occlude LAAs between approximately 17 and 33 mm in diameter, as long as there is sufficient depth to accommodate the device, whose length is approximately equal to its diameter. The device can be partially recaptured and redeployed before release from the delivery cable if the implant location is too deep, or it can be fully recaptured and removed if it is deployed too proximally or a different device size is required. This device is CE marked for sale within the European Economic Area and is under consideration by the FDA for approval in the United States.

TABLE 50-5 Comparisons of Surgical Left Atrial Appendage Closure Techniques

Study	Country	No. Studied	Closure Method	Closure Success Rate (%)*	Effect of LAA Closure on Stroke Prevention
Johnson et al, 2000[43]	United States	437	Excision	100	Positive
Katz et al, 2000[44]	United States	50	Endocardial suture	64	None
Garcia-Fernandez et al, 2003[45]	Spain	205	Endocardial suture	90	Positive
Bando et al, 2003[46]	Japan	812	Endocardial suture	Not measured	Negative
Blackshear et al, 2003[47]	United States	15	Thoracoscopic epicardial purse-string	93†	Positive
Pennec et al, 2003[48]	France	30	Endocardial Excision	70-80 100	Negative Positive
Schneider et al, 2005[49]	Germany	6	Endocardial suture	17	Negative
Healey et al, 2005[50]	Canada	77	Epicardial suture Stapler	45 72	Positive
Kanderian et al, 2008[51]	United States	137	Excision Suture exclusion Stapler	73 (20% stapler) 23 0	Positive trend
Bakhtiary et al, 2008[52]	Germany	259	Clamp and epicardial suture	100†	Positive

Adapted from Chatterjee S, Alexander JC, Pearson PJ, Feldman T: Left atrial appendage occlusion: lessons learned from surgical and transcatheter experiences, *Ann Thorac Surg* 92:2283-2292, 2011.
LAA, Left atrial appendage.
*Assessed by transesophageal echocardiography.
†Remnant size not measured.

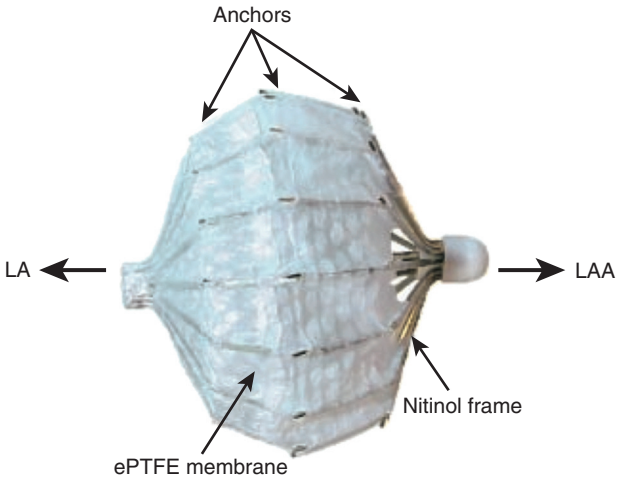


FIGURE 50-4 The Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) device was the first to be prospectively evaluated in patients with atrial fibrillation. It consists of a self-expanding nitinol cage covered with an occlusive expanded polytetrafluoroethylene (ePTFE) membrane, with small anchors along the struts and passing through the membrane to help anchor the device in the appendage. *LA,* Left atrium; *LAA,* left atrial appendage. (From Sievert H, Lesh MD, Trepels T, et al: Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience, *Circulation.* 105:1887-1889, 2002.)

FIGURE 50-5 The Watchman device is composed of a self-expanding nitinol frame with a polyethylene terephthalate fabric cap. Distal tines secure the device in the left atrial appendage trabeculae. The device length is approximately equal to its diameter. The device is fully retrievable before release from the delivery cable.

Implantation Procedure

Device selection is determined by LAA size, which is a combination of TEE and fluoroscopic measurements (Fig. 50-6). A 14-Fr double- or single-curved access sheath is introduced into the left atrium through a transseptal puncture in the inferoposterior aspect of the interatrial septum. The 14-Fr access sheath is carefully placed deep within the LAA and often telescoped over a diagnostic pigtail catheter to prevent laceration or perforation of the thin-walled, friable LAA.

The device, which is provided preloaded in a delivery system and attached to a delivery cable, is advanced to the tip of the access sheath, after which the sheath is withdrawn and the device deployed. Device implantation is guided by a combination of TEE and fluoroscopy, and TEE imaging plays a critical role in assessing the adequacy of device deployment (Figs. 50-7 and 50-8). The device is then released by counterclockwise rotation of the delivery cable if the appropriate TEE and fluoroscopic measurements are met.

Clinical Data

Clinical outcomes for the Watchman device have been evaluated in several studies (Table 50-6). Safety and clinical efficacy have been evaluated in two bayesian, randomized clinical trials that tested whether LAA occlusion was noninferior to warfarin therapy for the

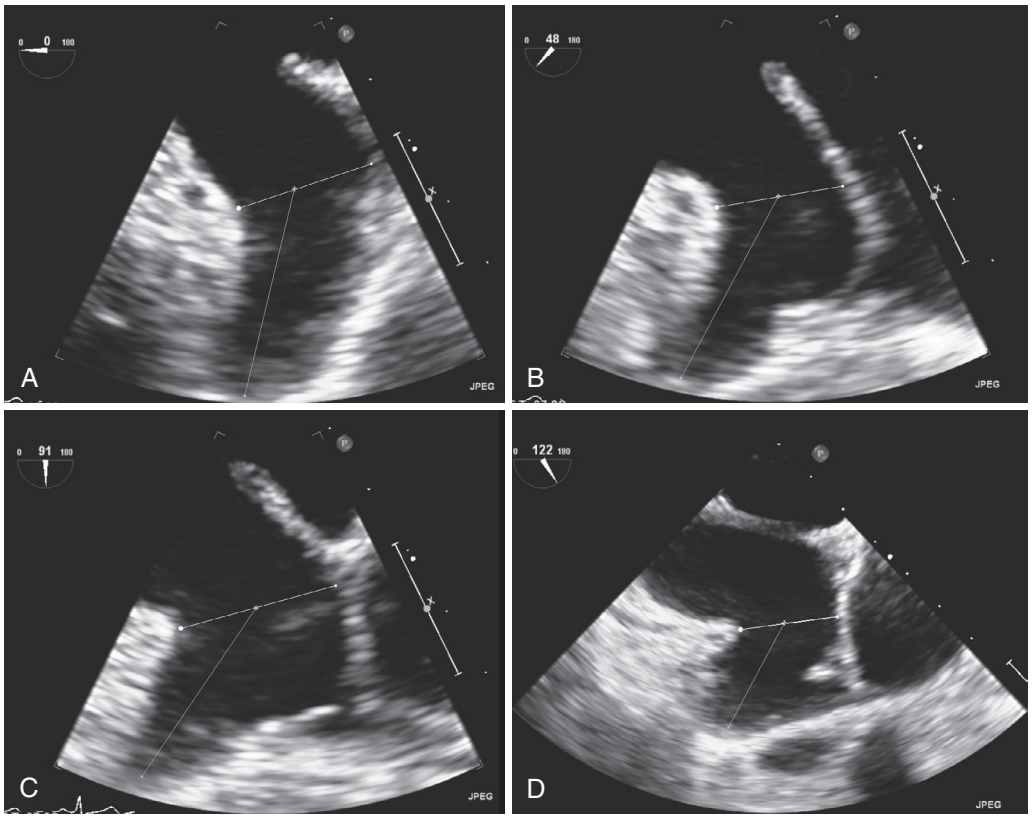


FIGURE 50-6 Preprocedural transesophageal echocardiographic assessment of the left atrial appendage (LAA) before Watchman occluder implantation. The diameter and depth of the LAA is measured at 0, 45, 90, and 135 degrees (**A, B, C,** and **D,** respectively). The diameter of the LAA is defined as the distance from a point just distal to the left circumflex artery (i.e., mitral valve annulus) to roughly 1 to 2 cm from the tip of the ridge of the left upper pulmonary vein. Alternatively, the LAA ostium can be measured by drawing a line from the mitral valve annulus across to the ridge of the left upper pulmonary vein perpendicular to the planned axis of the delivery sheath. The initially selected device size is often modified after the delivery sheath is introduced into the LAA because this may clarify the maximal implantation depth. (Copyright © MedReviews, LLC. Reprinted with permission of MedReviews, LLC. Price MJ: Left atrial appendage occlusion with the WATCHMAN™ for stroke prevention in atrial fibrillation, *Rev Cardiovasc Med* 15[2]:142-151, 2014. *Reviews in Cardiovascular Medicine* is a copyrighted publication of MedReviews, LLC. All rights reserved.)

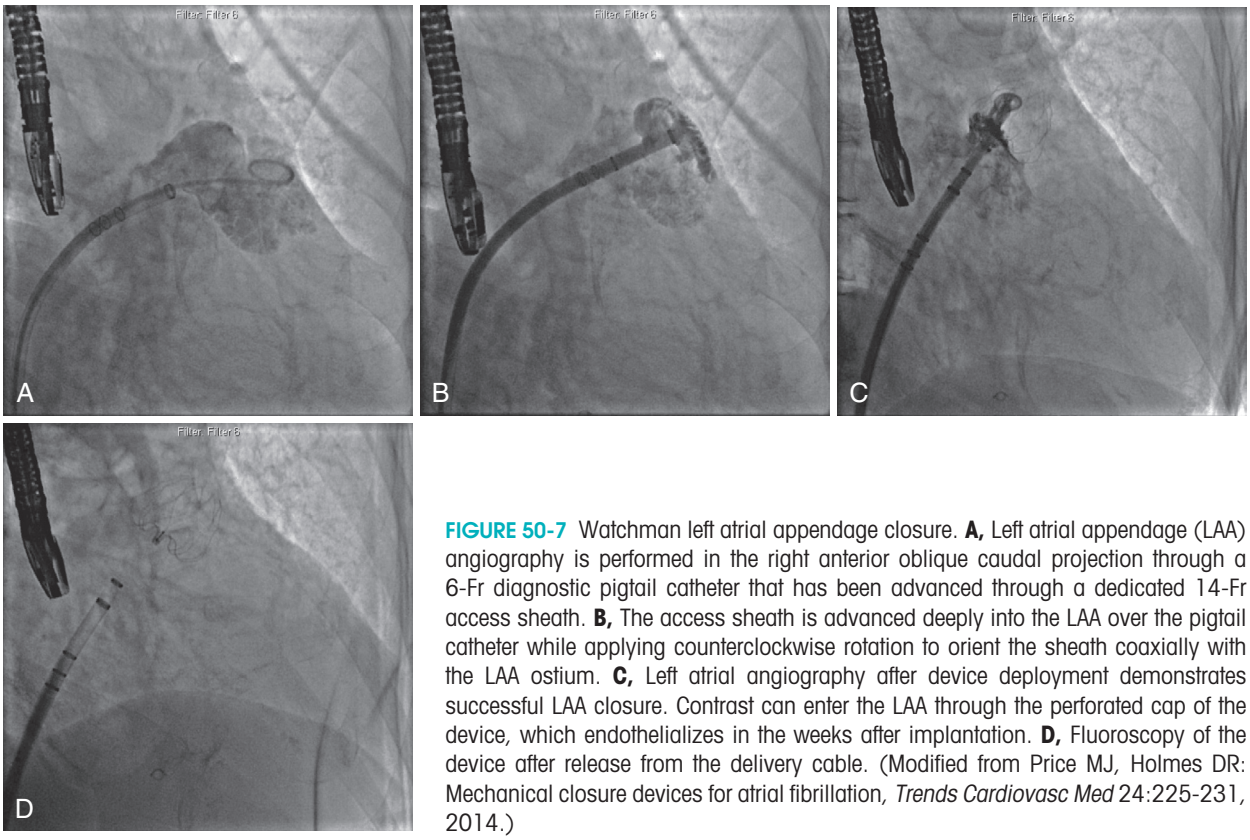


FIGURE 50-7 Watchman left atrial appendage closure. **A,** Left atrial appendage (LAA) angiography is performed in the right anterior oblique caudal projection through a 6-Fr diagnostic pigtail catheter that has been advanced through a dedicated 14-Fr access sheath. **B,** The access sheath is advanced deeply into the LAA over the pigtail catheter while applying counterclockwise rotation to orient the sheath coaxially with the LAA ostium. **C,** Left atrial angiography after device deployment demonstrates successful LAA closure. Contrast can enter the LAA through the perforated cap of the device, which endothelializes in the weeks after implantation. **D,** Fluoroscopy of the device after release from the delivery cable. (Modified from Price MJ, Holmes DR: Mechanical closure devices for atrial fibrillation, *Trends Cardiovasc Med* 24:225-231, 2014.)

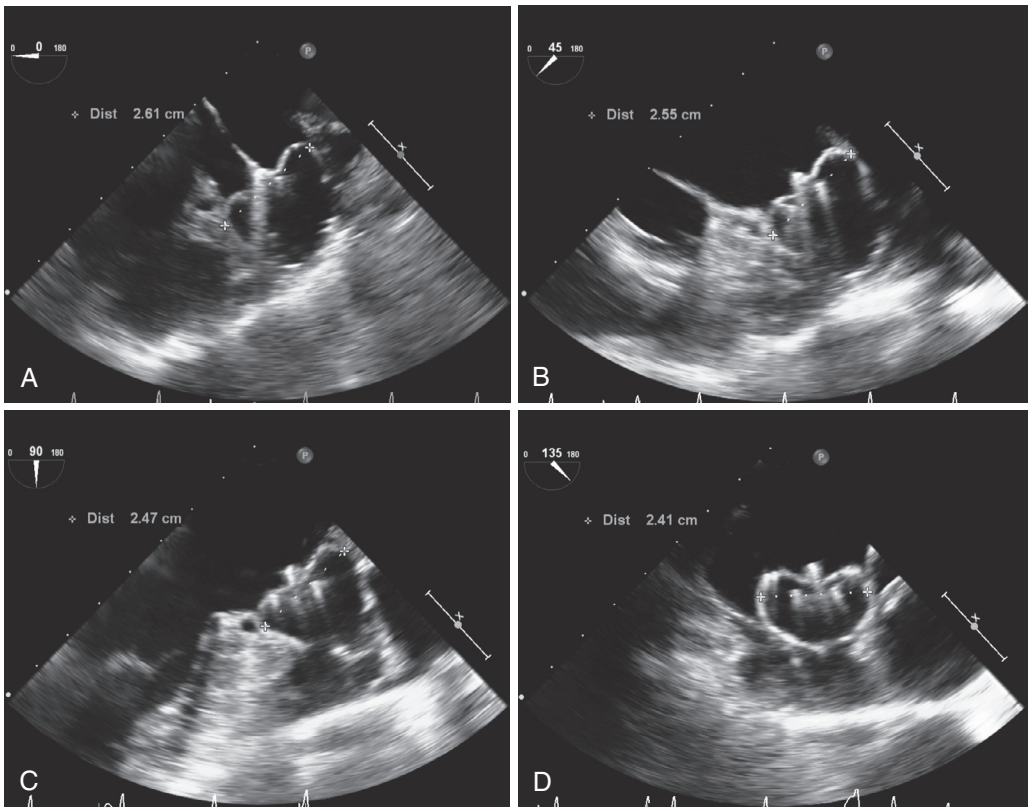


FIGURE 50-8 Transesophageal echocardiographic (TEE) assessment of Watchman occluder implantation. After deployment of a Watchman 30-mm left atrial appendage (LAA) occluder, the device is assessed at 0, 45, 90, and 135 degrees (**A, B, C,** and **D,** respectively). Compression is determined by measuring the distance across the shoulders of the device. The device is released if compression and position are adequate, the LAA is shown to be sealed by color Doppler and left atrial angiography, and the device is well anchored according to a tug test. In this case, the device is approximately 13% to 20% compressed and is well positioned, no color flow is seen around the device into the LAA, and the LAA moved with the device as a unit when the delivery cable was tugged gently. The device was therefore released from the cable with successful LAA occlusion. According to the protocol in research studies, the patient was treated with warfarin and aspirin for 6 weeks, when repeat TEE confirmed LAA closure without thrombus, and the warfarin was then discontinued. The patient was treated with aspirin and clopidogrel for 5 more months and then was continued on aspirin monotherapy. (Copyright © MedReviews, LLC. Reprinted with permission of MedReviews, LLC. Price MJ: Left atrial appendage occlusion with the WATCHMAN™ for stroke prevention in atrial fibrillation, *Rev Cardiovasc Med* 15[2]:142-151, 2014. *Reviews in Cardiovascular Medicine* is a copyrighted publication of MedReviews, LLC. All rights reserved.)

TABLE 50-6 Studies of Left Atrial Appendage Occlusion with the Watchman Device for Stroke Prevention in Nonvalvular Atrial Fibrillation

Study	Study Design	*N*	Patients
Pilot[57]	Prospective multicenter registry	66	OAC eligible
PROTECT AF[56,58]	Randomized clinical trial	707	OAC eligible
PREVAIL[59]	Randomized clinical trial	407	OAC eligible
CAP[60]	Continued access registry	460	OAC eligible
CAP2*	Continued access registry	579	OAC eligible
ASAP[61]	Prospective multicenter registry	150	OAC ineligible

ASAP, ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology; *CAP,* Continuing Access to PROTECT-AF; *CAP2,* Continued Access to PREVAIL; *OAC,* oral anticoagulation; *PREVAIL,* Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients with Atrial Fibrillation Versus Long-Term Warfarin Therapy; *PROTECT-AF,* Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation.
*Results not yet reported.

primary efficacy end point of stroke, systemic embolism, and cardiovascular or unexplained death in AF patients who were eligible for long-term OAC. The trials had different study sizes, entry criteria, and follow-up durations.

The Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF) trial randomly assigned 707 AF patients with a $CHADS_2$ score of 1 or greater who were eligible for long-term OAC to Watchman LAA closure or warfarin in a 2:1 ratio.[56] The Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device In Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) trial randomly assigned 407 AF patients with a $CHADS_2$ score of 2 or greater to Watchman LAA closure or warfarin in a 2:1 ratio. In these trials, patients who received the Watchman device were continued on warfarin therapy for approximately 6 weeks after the procedure, at which time they were transitioned to dual antiplatelet therapy with aspirin

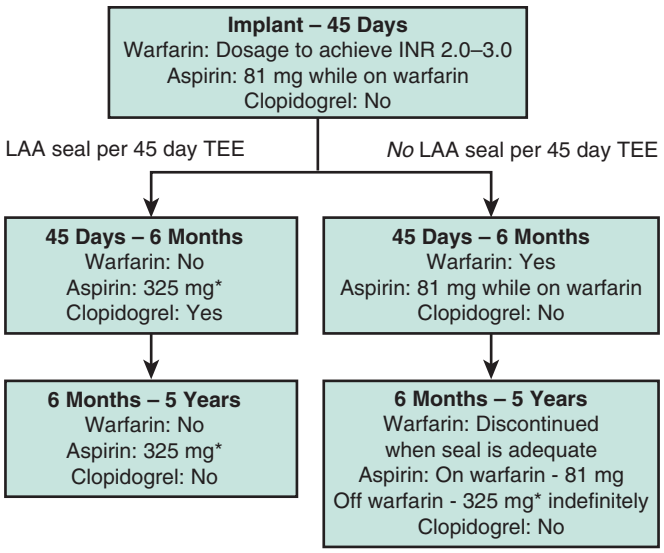


FIGURE 50-9 Anticoagulant and antiplatelet management strategy for patients receiving device therapy in the PROTECT-AF and PREVAIL randomized clinical trials of the Watchman left atrial appendage (LAA) occluder. After device implantation, patients were treated with a combination of warfarin and aspirin for approximately 6 weeks, at which time transesophageal echocardiography (TEE) was performed. If the LAA was sealed (i.e., residual leak <5 mm wide without evidence of thrombus), warfarin was discontinued, and the patient was treated with aspirin and clopidogrel until 6 months after the procedure, at which time the clopidogrel was discontinued and the patient continued on aspirin monotherapy. In the PROTECT-AF trial, patients could also receive clopidogrel at study entry if clinically indicated. *Asterisk,* Recommended dosage; *INR,* international normalized ratio; *PREVAIL,* Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy; *PROTECT-AF,* Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation. (Modified from Holmes DR Jr, Kar S, Price MJ, et al: Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial, *J Am Coll Cardiol* 64:1-12, 2014.)

and clopidogrel for 6 months, followed by indefinite aspirin monotherapy if LAA sealing was confirmed by TEE (Fig. 50-9).

In the PROTECT-AF trial, Watchman LAA closure was noninferior and superior to warfarin for the primary efficacy end point at a mean follow-up of 3.8 ± 1.7 years (2625 patient-years) (rate ratio = 0.60; 95% credible interval [CrI], 0.41 to 1.05; posterior probability of noninferiority >99.9%, posterior probability for superiority = 96%) (Fig. 50-10). LAA closure was also superior to warfarin therapy when the results were analyzed using traditional, frequentist statistical methods (hazard ratio [HR] = 0.61; 95% confidence interval [CI], 0.38 to 0.97; $P = .04$). The clinical efficacy of LAA closure was maintained after the completion of the protocol-mandated postprocedural adjunctive pharmacotherapy in the device group (i.e., warfarin and dual antiplatelet therapy) (HR = 0.32; 95% CI, 0.17 to 0.63; $P < .001$).

The rates of ischemic stroke did not differ between groups in the PROTECT-AF trial, although the rate of fatal and disabling stroke was lower in the device group (rate ratio = 0.37; 95% CrI, 0.15 to 1.00) (Fig. 50-11). Cardiovascular and all-cause mortality were also reduced with LAA closure (HR = 0.40; 95% CI, 0.21 to 0.75; $P = .005$ and HR = 0.66; 95% CI, 0.45 to 0.98; $P = .04$, respectively). Safety events were initially greater in device group and driven by procedural complications, although by the end of follow-up, the overall rate of safety events in both arms were similar due to bleeding events in the warfarin group (see Fig. 50-10). Peridevice flow on follow-up TEE was a common finding (41% and 32% of patients at 6 weeks and 1 year after the procedure, respectively). It was mostly less than 3 mm in diameter and did not appear to be associated with thromboembolic events.[62] Quality-of-life measurements were significantly improved for the patients randomly assigned to the device compared with those on warfarin.[63]

The aim of the smaller PREVAIL trial was to confirm procedural safety, particularly among newer operators, and to further explore clinical efficacy of LAA closure compared with warfarin.[59] Operators without prior Watchman experience implanted the device in approximately 40% of the enrolled patients. Three coprimary end points were examined: procedural safety, primary clinical efficacy (i.e., composite of stroke, systemic embolism, and cardiovascular or unexplained death), and late clinical efficacy (i.e., ischemic stroke and systemic embolism occurring >7 days after the procedure).

The Watchman met the performance goal for procedural and device safety prespecified by the sponsor and the FDA, with safety events occurring in 2.2% of patients. Implantation by new operators was not associated with reduced rates of implant success or an increased risk of major adverse events, indicating that the training program implemented during the trial mitigated any substantial learning curve with the device. The rate of procedural complications, including stroke and serious pericardial effusions, were significantly reduced in the PREVAIL trial compared with PROTECT-AF and were consistent with that of the prospective continued access registry that followed the PROTECT-AF trial (Table 50-7).[60]

At a mean follow-up of 11.8 ± 5.8 months, the primary efficacy end point of stroke, systemic embolism, or cardiovascular death was similar between study arms, but LAA closure did not achieve noninferiority due to wide 95% credible intervals (device event rate of 0.064 vs. warfarin event rate of 0.064; rate ratio = 1.07; 95% CrI, 0.57 to 1.89; rate ratio for noninferiority criterion: upper bound of 95% CrI <1.75). The rate of ischemic stroke or systemic embolism was noninferior to Watchman LAA closure. The clinical efficacy findings in the PREVAIL trial should be interpreted in the context of the relatively short follow-up and a much lower than expected rate of stroke and systemic embolism in the warfarin control group despite the baseline high-risk characteristics of the enrolled population.[59]

Although the PROTECT-AF and PREVAIL trials studied LAA closure in an OAC-eligible population, stroke prevention strategies are particularly challenging in patients who cannot tolerate anticoagulation or in whom anticoagulation is contraindicated. The ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology (ASAP) trial was a prospective, multicenter, nonrandomized study that examined the clinical efficacy of Watchman LAA closure in 150 AF patients who were ineligible for warfarin therapy.[11] After implantation, patients were treated with clopidogrel for 6 months and with aspirin indefinitely. The rate of stroke or systemic embolism was 2.3% per year at a mean follow-up of 14.4 ± 8.6 months, which was significantly less than the expected rate of 7.3% per year based on $CHADS_2$ scores. Further data are required to robustly define the early safety of the Watchman device with postprocedural dual antiplatelet therapy rather than a brief course of OAC. The WATCHMAN LAA occluder has been approved by the FDA for use within the United States. It is indicated to reduce the risk of thromboembolism from the LAA in patients with AF who are at increased risk for stroke or systemic embolism based on CHADS2 or CHA2DS2VASc and are recommended for anticoagulation; are deemed by their physicians to be suitable for warfarin; and have an appropriate rationale to seek a nonpharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared with warfarin.

Amplatzer Cardiac Plug and Amulet

Device Characteristics and Procedural Approach

The Amplatzer Cardiac Plug (ACP, St. Jude Medical, Minneapolis, MN) consists of a self-expanding nitinol mesh that forms a distal lobe and proximal disk, each with a sewn polyester patch, and they are

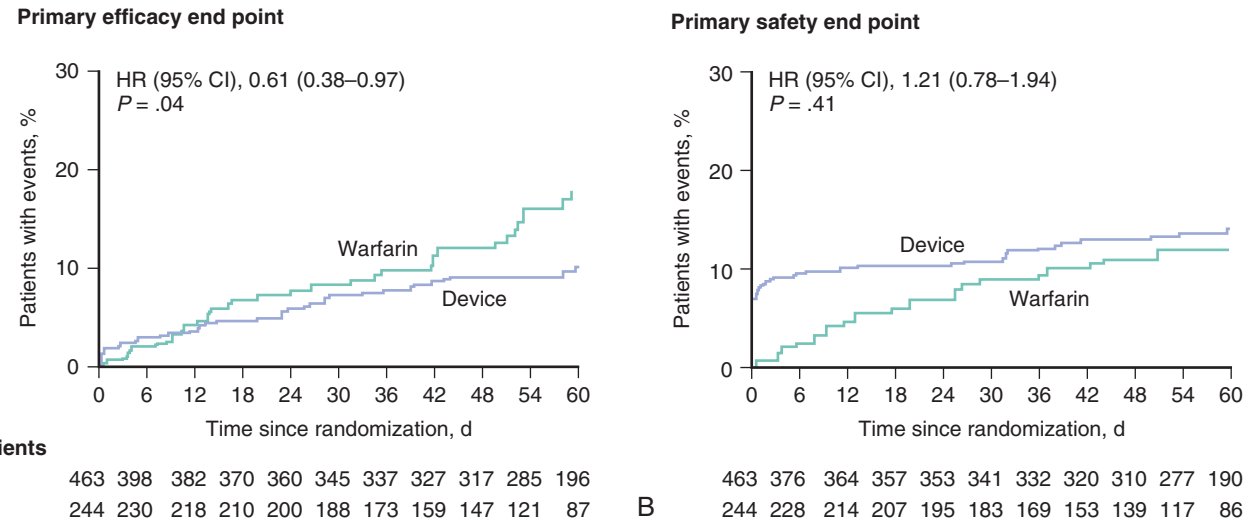
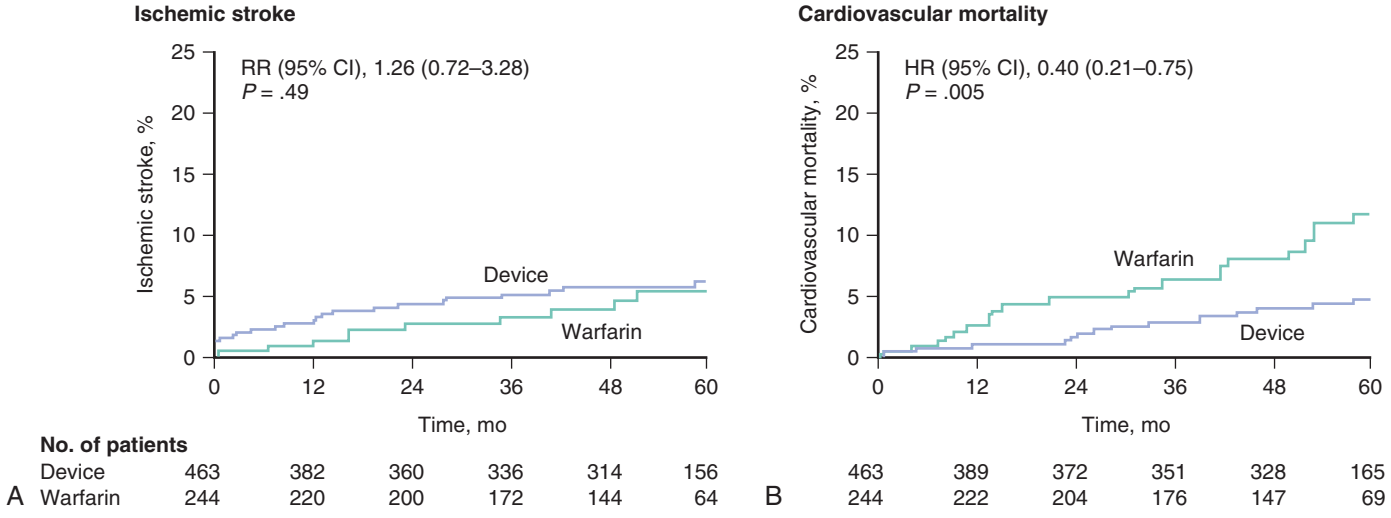


FIGURE 50-10 Long-term clinical and safety outcomes in the PROTECT-AF randomized clinical trial of the Watchman left atrial appendage (LAA) closure compared with warfarin therapy. **A,** Primary efficacy outcome of cardiovascular death, stroke, or systemic embolism. At a mean of 3.8 years (2621 patient-years) of follow-up, transcatheter LAA occlusion with the Watchman met prespecified criteria for noninferiority and superiority compared with warfarin. **B,** The primary safety outcome was a composite of major bleeding events and procedure-related complications. Although an early hazard was apparent in the periprocedural period with device therapy, the overall rate of safety events was similar in both groups, primarily due to ongoing bleeding events in the warfarin group. *PROTECT-AF,* Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation. (Modified from Reddy VY, Sievert H, Halperin J, et al: Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial, *JAMA* 312:1988-1998, 2012.)



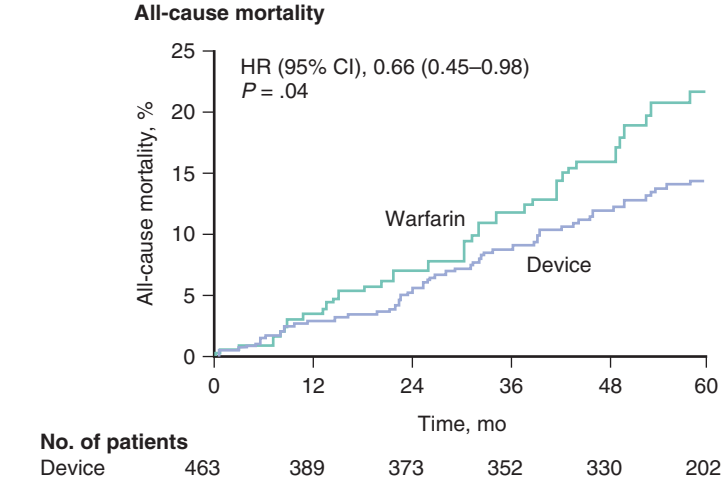


FIGURE 50-11 Ischemic stroke and mortality outcomes in the PROTECT-AF randomized clinical trial of Watchman left atrial appendage (LAA) closure compared with warfarin therapy. Ischemic stroke (**A**), cardiovascular mortality (**B**), and all-cause mortality (**C**) at a mean of 3.8 years (2621 patient-years) of follow-up. Compared with warfarin, transcatheter LAA occlusion resulted in a similar rate of ischemic stroke, and it significantly reduced the rates of cardiovascular and all-cause mortality. *PROTECT-AF,* Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation. (Modified from Reddy VY, Sievert H, Halperin J, et al: Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial, *JAMA* 312:1988-1998, 2012.)

TABLE 50-7 Safety Outcomes in Randomized Trials and Continued Access Registries of Left Atrial Appendage Occlusion with the Watchman Device Compared with Warfarin in Patients with Nonvalvular Atrial Fibrillation

Outcome	STUDY			*P* Value
	PROTECT-AF (*N* = 463)	CAP (*N* = 566)	PREVAIL (*N* = 269)	
Any complication within 7 days of procedure	8.7%	4.2%	4.5%	0.004
Procedure-related stroke	1.1%	0%	0.7%	0.02
Pericardial effusion requiring surgery	1.6%	0.2%	0.4%	0.03
Pericardial effusion requiring pericardiocentesis	2.4%	1.2%	1.5%	0.32
Device embolization	0.4%	0.2%	0.7%	0.37

Modified from Holmes DR Jr, Kar S, Price MJ, et al: Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial, *J Am Coll Cardiol* 64:1-12, 2014.
CAP, Continued Access to PROTECT-AF; *PREVAIL,* Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device In Patients with Atrial Fibrillation Versus Long-Term Warfarin Therapy; *PROTECT-AF,* Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation.

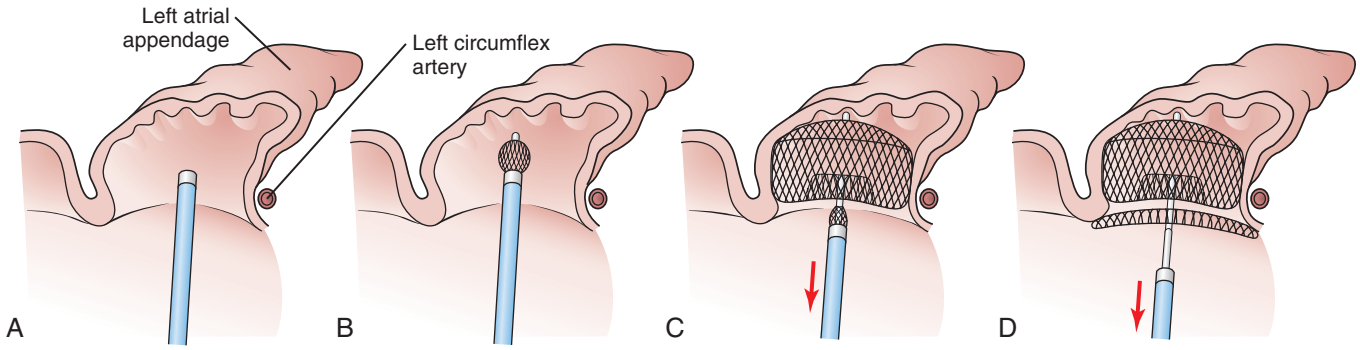


FIGURE 50-12 Amplatzer Cardiac Plug device deployment. **A,** Initial sheath position. **B,** Adjustment of the sheath position with a portion of the distal lobe extruded from the sheath to form a safe, ball-like tip. **C,** Device deployment by withdrawal of the sheath over the device delivery cable. **D,** Final device position, with the distal lobe acting as an anchor in the left atrial appendage (LAA) and the proximal disk forming an occlusive lid over the mouth of the LAA. (Modified from Meerkin D, Butnaru A, Dratva D, et al: Early safety of the Amplatzer Cardiac Plug for left atrial appendage occlusion, *Int J Cardiol* 168:3920-3925, 2013.)

connected by a short, central waist. The distal lobe has hooks around its circumference that anchors the device in the LAA, and the proximal disk covers the mouth of the LAA from within the left atrium, akin to a baby pacifier (Fig. 50-12).[64]

The mechanism of LAA occlusion is different from that of the Watchman, which occludes the LAA by filling the appendage itself. Device sizing is based on the maximal diameter of the distal lobe's landing zone, which is measured approximately 10 mm distal to the LAA orifice. The second-generation ACP, the Amulet, has a slightly longer distal lobe, more stabilizing hooks, a longer central waist, and a larger-diameter proximal disk with a recessed threaded insert (Fig. 50-13).[65] These modifications improve device stability, position, residual leak, and the incidence of device-associated thrombi.[66]

For the ACP or Amulet, the landing zone is measured approximately 12 to 15 mm from the LAA orifice.[67] The device is delivered through a 12- to 14-Fr double-curved sheath that is introduced into the LAA from the right femoral vein through a transseptal puncture. The ACP and Amulet have the CE mark but are not approved for use in the United States.

Clinical Data

The safety and clinical efficacy of the ACP and Amulet devices for stroke prevention in AF have been examined in several nonrandomized, retrospective and prospective, observational studies, many of which were single-center experiences (Table 50-8). Most studies evaluated the device in patients with intolerance or contraindications to OAC, and patients were usually treated with a limited course of antiplatelet therapy after device implantation.

Several tentative conclusions can be gleaned from the reported experience with the ACP and the Amulet. The rates of successful LAA

FIGURE 50-13 The Amulet left atrial appendage occluder consists of a self-expanding nitinol mesh that forms a distal lobe and proximal disk, each with a sewn-in polyester patch. The distal lobe and proximal disk are connected by a short, central waist. The distal lobe has hooks around its circumference that anchor the device in the left atrial appendage (LAA), and the proximal disk covers the mouth of the LAA from within the left atrium. (Courtesy St. Jude Medical, Minneapolis, MN. AMPLATZER, Amulet, and St. Jude Medical are trademarks of the St. Jude Medical, Inc. Or its related companies. Reprinted with permission of St. Jude Medical, © 2015. All rights reserved.)

closure are excellent. The most frequent procedural complication appears to be pericardial effusion, occurring at rates similar to those seen in the randomized Watchman experience, and clinical efficacy appears acceptable, with the important caveat that the dataset is substantially limited by the study designs.

A large, randomized clinical trial of the ACP compared with long-term OAC (NCT01118299) was halted, likely due to the anticipated FDA approval of the Watchman. Trial reinitiation with the Amulet and a revised study design are planned.

Transcatheter Left Atrial Appendage Ligation with the Lariat Device

Device Characteristics and Procedural Approach

The Lariat (SentreHeart, Redwood City, CA) is 510(k) cleared by the FDA (i.e., safety and effectiveness information in the premarketing notification has been reviewed) for the approximation of soft tissue. It enables percutaneous delivery of a pretied surgical suture to ligate the LAA.[78] This is accomplished through a combined subxyphoid (i.e., transpericardial) and transseptal approach (Fig. 50-14).

TABLE 50-8 Studies of Left Atrial Appendage Occlusion Using the First- and Second-Generation Amplatzer Cardiac Plug

Study	Study Design	*N*	Patient Population	Duration of Follow-up	Postprocedure Medical Regimen	Safety Outcomes (%)†	Efficacy Outcomes (%)
Park et al, 2011[64]	Retrospective, multicenter, observational	143	NR	24 hr	NA	PRCs: 7.0 SPE: 3.5 DE: 1.4 Stroke: 2.1	NA
Ueno et al, 2013[68]	Prospective, multicenter, observational	52	OAC ineligible	20 ± 5 mo	ASA/clopidogrel for 1-6 mo, then ASA monotherapy	PRCs: 5.8 SPE: 0 DE: 1.9% Stroke: 0	CV death: 1.9% Stroke: 1.9%
Meerkin et al, 2013[69]	Retrospective, single operator, observational	100	OAC ineligible	In hospital	NA	PRCs: 1.0% SPE: 1.0% DE: 0 Stroke: 0	NA
Lam et al, 2012[70]	Prospective, two-center, observational	20	OAC ineligible	12.7 ± 3.1 mo	ASA/clopidogrel for 1 mo	PRCs: 10 SPE: 0 DE: 0 Stroke: 0	Stroke: 0
Chun et al, 2013[71]	Prospective, single-center, observational	40	OAC ineligible	1 yr	ASA/clopidogrel for 6 wk (76%)	PRC: 5% SPE: 2.5 DE: 2.5 (late) Stroke: 0	Death: 5 Stroke: 0
Guérios et al, 2012[72]	Single-center, observational	86	OAC ineligible	25.9 pt-yr	ASA/clopidogrel for 1 mo, then ASA for 3-4 mo	PRCs: 5.6 SPE: 2.2 DE: 1.1 Stroke: 2.3	Death: 3.5 Stroke: 0
Danna et al, 2013[73]	Single-center, observational	37	OAC ineligible	1 yr	ASA/clopidogrel for 1 mo, then ASA for at least for 5 mo	PRCs: NR SPE: 2.7 DE: 5.9 Stroke: 0	Death: 5 Stroke: 2.9
Horstmann et al, 2014[74]	Single-center, observational	20	OAC ineligible (prior ICH)	13.6 ± 8.2 mo	ASA and clopidogrel for 3 mo, then ASA monotherapy	PRCs: 0 SPE: 0 DE: 0 Stroke: 0	Stroke: 0
Santoro et al, 2014[75]	Retrospective, multicenter, observational	134	OAC unsuitable	680 ± 351 days 238 pt-yr	ASA and clopidogrel for 1-3 mo, then ASA monotherapy	PRCs: 2.2 SPE: 2.2 DE: 0 Stroke: 0	Stroke 0.8 TE: 2.5
Wiebe et al, 2014[76]	Single-center, observational	60	OAC unsuitable	1.8 yr	ASA and clopidogrel for 3 mo, then ASA monotherapy	PRCs: 11.7 SPE: 1.6 DE: 3.3 Stroke: 0	Death: 4.8 Stroke: 0
Freixa et al, 2014[77]*	Single-center, observational	25	OAC ineligible or stroke with labile INR	1 to 3 mo	NR	PRCs: 0 SPE: 0 DE: 0 Stroke: 0	Stroke: 0
Lam et al, 2015[66]*	Single-center, observational	17	OAC unsuitable	90 days	ASA and clopidogrel for 3 mo, then ASA monotherapy	PRCs 5.8 SPE: 5.8 DE: 0 Stroke: 0	Stroke: 0

ASA, Aspirin; *CV,* cardiovascular; *DE,* device embolization; *ICH,* intracranial hemorrhage; *INR,* international normalized ratio; *NA,* not applicable; *NR,* not reported; *OAC,* oral anticoagulation; *PRCs,* procedure-related complications; *pt-yr,* patient-years; *SPE,* significant pericardial effusion; *TE,* thromboembolism.

*Case series using the second-generation Amulet device.

†Definitions of procedure-related complications and significant pericardial effusion varied across studies.

Anatomic eligibility for the procedure is determined by cardiac computed tomography (CT). Appendages with a diameter greater than 40 mm, lobes behind the pulmonary artery, or a posterior orientation should be avoided. A larger, second-generation device will allow closure of appendages as large as 45 mm in diameter. The procedure cannot be performed in patients with prior cardiac surgery because it requires an intact pericardium. The procedure should also be avoided in patients with prior pericarditis because pericardial adhesions can prevent manipulation in the pericardial space and hinder procedural success.

A 14-Fr, slightly curved, and soft-tipped sheath is introduced into the anterior pericardial space using an epidural or micropuncture needle under fluoroscopic guidance. After pericardial access is established, an 8.5-Fr, transseptal sheath is introduced into the left atrium from the right femoral vein using the standard technique; an inferoposterior location in the interatrial septum is preferred. A magnet-tipped guidewire is advanced through the transseptal sheath into the anterior aspect of the LAA, and a complementary magnet-tipped guidewire advanced through the pericardial sheath and connected with the magnet-tipped wire in the LAA, forming a rail over which the Lariat snare is delivered.

The Lariat snare is advanced through the pericardial sheath and over the LAA and then closed at the LAA ostium using TEE and fluoroscopic guidance. The snare contains a preloaded and tied surgical suture. The operator releases the suture with a proximal actuator and then tightens the pretied knot using a suture-tensioning device, after which the snare is removed and the suture cut using a suture cutter. The pericardial sheath is exchanged for a drain, which is left in place for at least 4 to 6 hours.

Clinical Outcomes

The dataset for the safety and efficacy of LAA closure with the Lariat has been limited to a few small, observational studies.[79,80] The studies suggest that the major complications associated with the procedure are significant pericardial effusions and postprocedural pericarditis. Results are insufficient to determine the clinical efficacy of the device for stroke prevention.

Bartus and colleagues conducted a single-center, nonrandomized study that enrolled 92 patients who had adequate anatomy for Lariat ligation according to CT imaging.[79] The procedure was aborted in three patients (3.2%) due to unexpected pericardial adhesions. Successful closure, defined as a residual leak of less than 1 mm in diameter, was

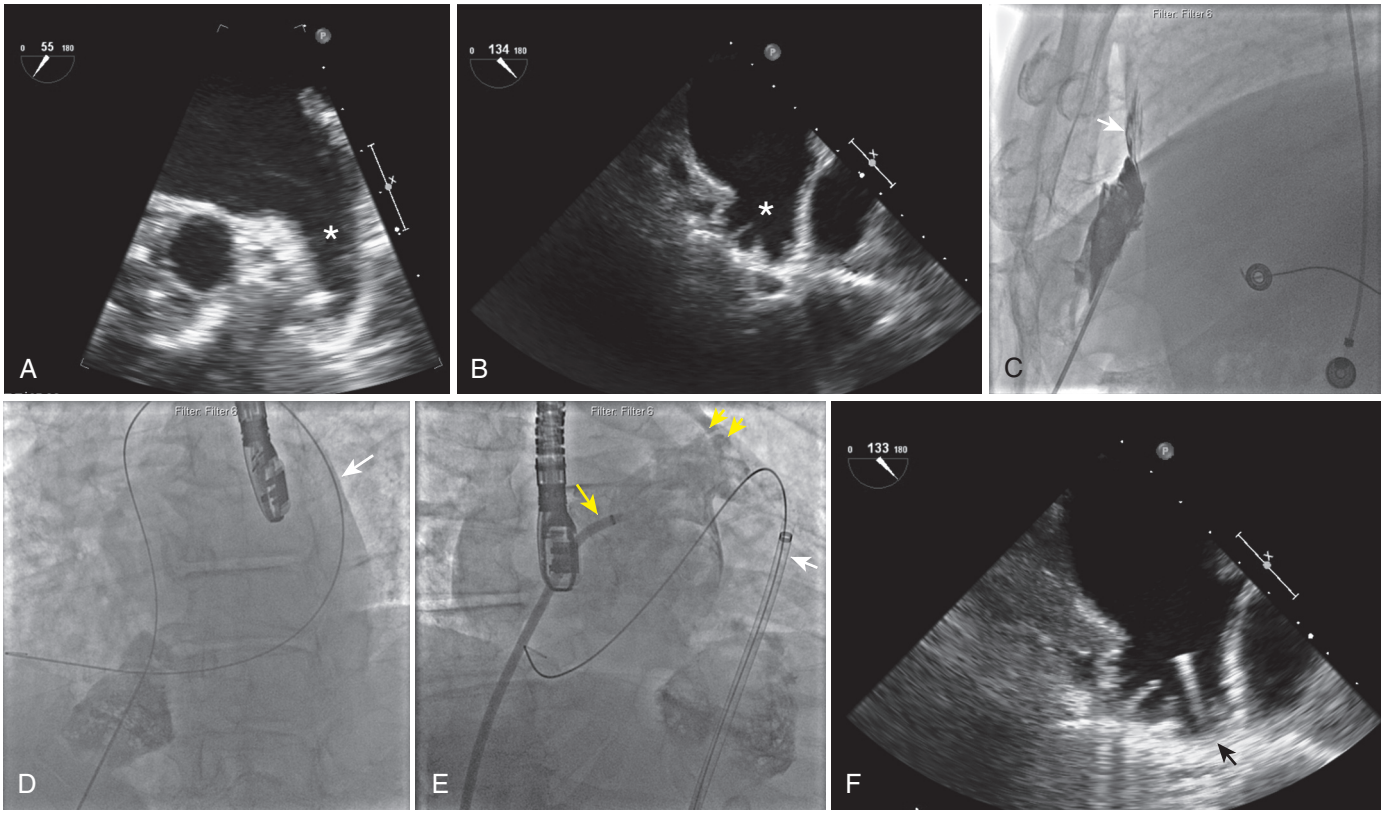


FIGURE 50-14 Transcatheter ligation of the left atrial appendage (LAA) with the Lariat. **A,** Baseline transesophageal echocardiography (TEE) of the LAA *(asterisk)* at approximately 45 degrees. **B,** Baseline TEE of the LAA *(asterisk)* at approximately 135 degrees. **C,** Dry pericardial access is obtained by carefully advancing a 17-gauge, 150-mm Tuohy (Pajunk) needle just below the xyphoid process and directed slightly laterally using fluoroscopy in the 90-degree lateral position. Dilute contrast can be injected through the needle lumen to confirm the position, identify tenting of the parietal pericardium, and visualize contrast filling the pericardial space *(arrow)*. A micropuncture needle can also be used. **D,** A 0.035-inch wire is advanced through the needle into the pericardium. In the shallow left anterior oblique projection, the wire should lie along the lateral border of the heart *(arrow)*, confirming the pericardial location. **E,** A soft-tipped, slightly curved 14-Fr sheath is advanced over the wire into the pericardium *(white arrow)*, and a 8.5-Fr transseptal sheath *(yellow arrow)* is advanced into the left atrium using the standard technique. Left atrial angiography demonstrates the left atrial appendage *(double yellow arrows)*. **F,** The magnet-tipped endocardial wire is advanced through the transseptal sheath into the anterior lobe of the LAA and confirmed by TEE *(arrow)*.

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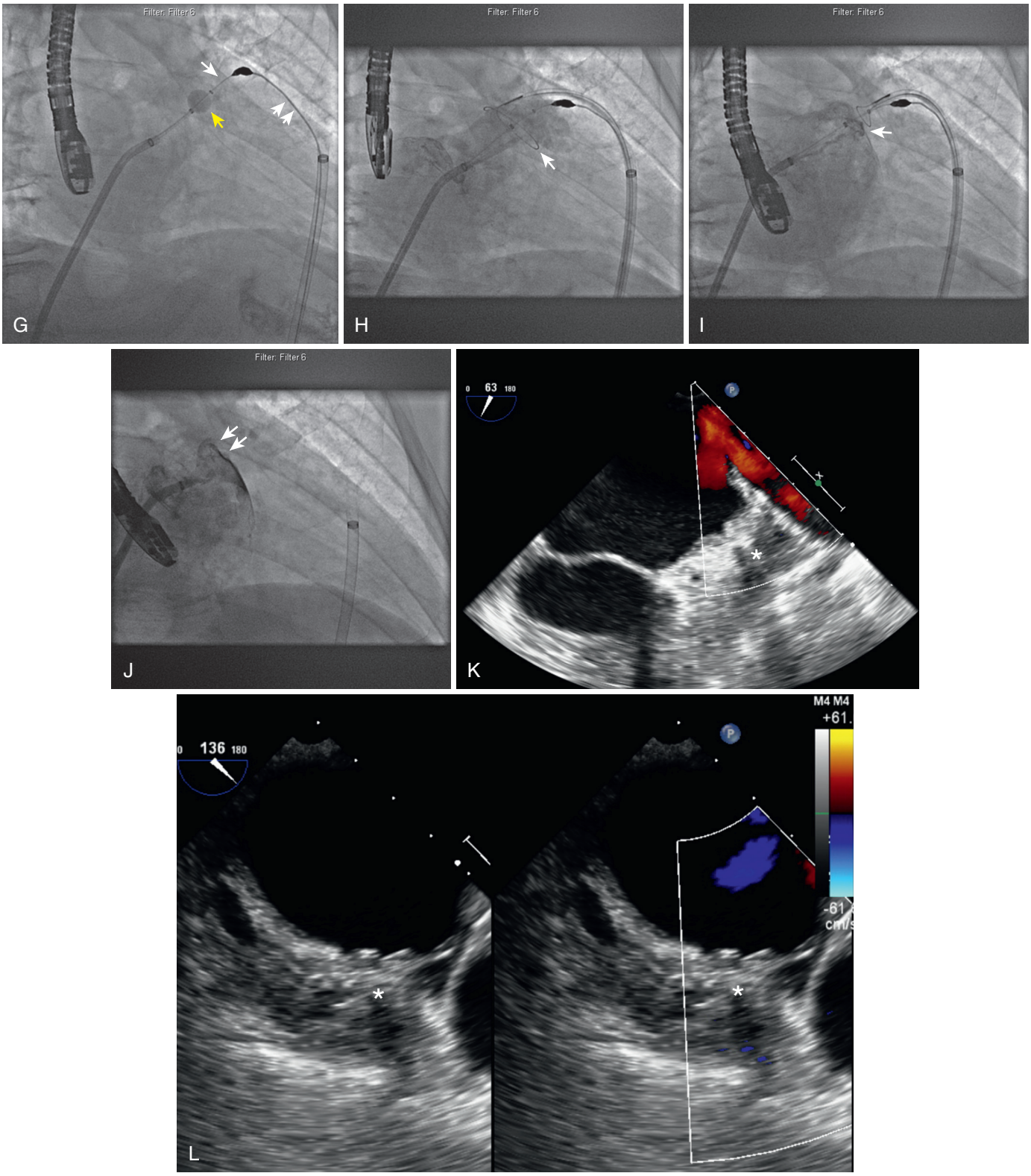

FIGURE 50-14, cont'd **G,** The magnet-tipped epicardial wire *(double arrows)* is advanced through the pericardial sheath and connected, preferably end to end, with the epicardial wire *(single white arrow)*. The over-the-wire balloon catheter is advanced, and the compliant balloon is inflated with dilute contrast *(yellow arrow)* to coregister the location of mouth of the LAA on fluoroscopy with TEE. **H,** The Lariat snare *(arrow)* is introduced into the pericardium over the epicardial wire and then opened and advanced over the LAA. **I,** The Lariat snare is closed over the LAA, and the operator delivers a pretied surgical knot by means of an actuator at the proximal end of the device. Left atrial angiography through the transseptal sheath confirms LAA closure *(arrow)*. **J,** The suture is tightened with a tensioning device, the Lariat snare and wires are removed, and the suture is cut with a specialized cutter. LAA angiogram demonstrates complete ligation of the LAA without residual leak *(double arrows)*. **K,** TEE with color Doppler of the LAA at 60 degrees after Lariat ligation shows complete closure without residual flow. An *asterisk* indicates the remnant LAA. **L,** TEE with color Doppler of the LAA at 135 degrees after Lariat ligation shows complete closure without residual flow. An *asterisk* indicates the remnant LAA.

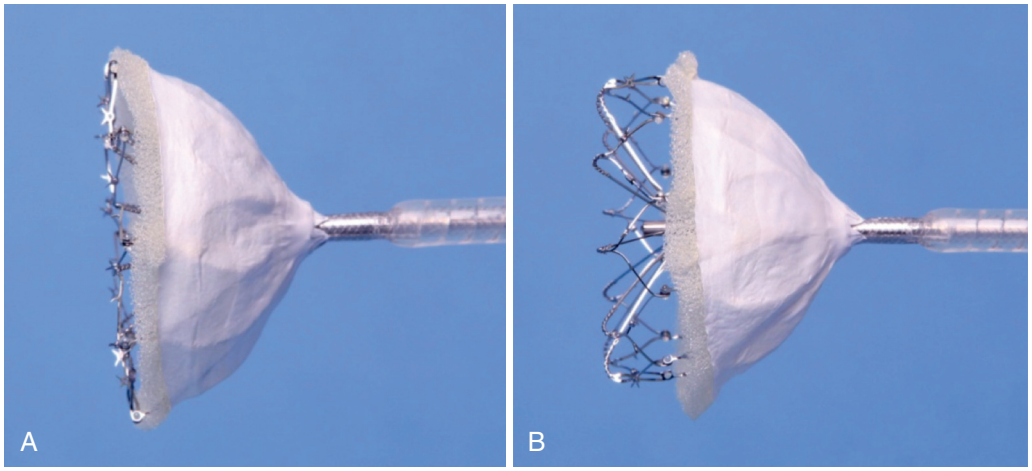

FIGURE 50-15 The WaveCrest left atrial appendage (LAA) occlusion system. **A,** The occluder has an expanded polytetrafluoroethylene cap and tines in the withdrawn position. **B,** The occluder has tines rolled forward to anchor the device in the LAA. The tines can be withdrawn if required for device repositioning or recapture. (Courtesy Coherex Medical, Salt Lake City, UT.)

achieved in 96% of cases. Procedural complications, all of which were significant pericardial effusions, occurred in three patients (3.2%), and pericarditis occurred in two patients (2.2%). At the 1-year follow-up assessment, slightly more than one half of the patients remained on warfarin therapy. There was no evidence of late leaks on follow-up TEE, and there were no thromboembolic events.

In a single-center study of 21 patients undergoing Lariat ligation, successful closure was achieved in 20 patients, complicated by a significant pericardial effusion in 2 patients (10%) and pericarditis in 3 patients (15%).[80a] There were no thromboembolic events over 352 ± 143 days of follow-up.

A multicenter, retrospective study examined the early safety and efficacy of LAA closure with the Lariat device in 154 patients undergoing the procedure in the United States.[80b] Enrolled patients were at high risk of thromboembolic and bleeding, with mean CHA_2DS_2VASc score of 4.1 ± 1.6 and a mean HAS-BLED score of 3.2 ± 1.2. Device success (i.e., suture deployment and a less than 5 mm leak by postprocedure TEE) was 94%. Similar to the Bartus experience,[79] 3% of cases were aborted due to unanticipated pericardial adhesions. Procedure-related major bleeding (i.e., Bleeding Academic Research Consortium type 3 bleeding or greater) occurred in 9.1%, and significant pericardial effusion occurred in 10.4% of patients. The incidence of pericarditis was not investigated. Among the 63 patients with immediate closure and on TEE follow-up, 3 patients had LAA stump thrombus (4.8%), and 13 (20%) had residual leaks, approximately one third of which were 5 mm or greater in diameter.

Another multicenter, observational study of 41 patients reported relatively frequent safety events after Lariat LAA ligation.[81] Pericardial effusions that required pericardiocentesis occurred in eight patients (20%), LAA perforation occurred in four patients (9%), and late LAA leaks seen on follow-up imaging occurred in 24%.[81]

The consequences of residual leaks after the Lariat procedure are unknown, although incomplete surgical LAA ligation has been associated with subsequent thrombus formation and clinical events.[40] Residual leaks after the Lariat procedure can be treated successfully with percutaneous approaches.[82-84]

LAA ligation can have an antiarrhythmic effect in selected patients because the LAA can be a source of AF. The Lariat procedure appears to isolate LAA electrical activity,[85] and in an observational study, the AF burden in patients with known AF triggers in the LAA was significantly reduced at 12 months after the Lariat procedure compared with baseline AF activity.[86]

The Lariat appears to provide high rates of immediate anatomic closure of the LAA, although procedural morbidity is not uncommon. Bleeding events and pericardial effusions drive procedural complications. Several questions regarding the Lariat remain unanswered, including whether safety events can be reduced with increased operator experience, what amount or type of postprocedure medical therapy is required (i.e., brief duration of antiplatelet or anticoagulation therapy), what are the rates and clinical consequences of late residual leaks, and whether the Lariat is effective in reducing thromboembolic events in the absence of long-term oral anticoagulant therapy.

WaveCrest Occluder

Device Characteristics and Procedural Approach

The WaveCrest LAA occlusion system (Coherex Medical, Salt Lake City, UT) has CE mark, and initiation of a pivotal trial in the United States is planned. The occluder consists of a self-expanding nitinol cage with a proximal ePTFE cap (Fig. 50-15). A foam skirt is incorporated through the distal portion of the occluder cap, which could potentially enhance LAA sealing. The system separates the act of LAA occlusion from device anchoring.

When the device is implanted, the occluder is positioned to occlude the LAA, and a set of anchors or tines are then deployed in a separate step to anchor the device in the LAA. Potential advantages of this device include less traumatic deployment and more flexibility in closing the LAA irrespective of its depth. There are no peer-reviewed publications regarding the safety and efficacy of LAA closure with the WaveCrest.

PATIENT SELECTION

Appropriate patient selection for transcatheter LAA closure incorporates a particular individual's risk of thromboembolism, long-term bleeding risk on OAC, and the short-term procedural risk of device implantation. Other factors include patient compliance, personal preference, and relative or absolute contraindications to chronic OAC. Thromboembolic risk can be assessed using the $CHADS_2$ and CHA_2DS_2-VASc scores (see Tables 50-1 and 50-2), and bleeding risk can be assessed using schemes such as HAS-BLED (see Table 50-3).

Not all strokes can be prevented by LAA-targeted strategies, and OAC can reduce the risk of stroke in AF patients independent of its role in preventing LAA thrombus. For example, as many as 25% of strokes in AF patients are linked to intrinsic cerebrovascular disease.[87] The mechanistic connections between the LAA and many risk factors that predict stroke in AF, including several components of the CHA_2DS_2VASc score, have not been fully elucidated. AF also is associated with platelet activation and a hypercoagulable state.[88] For these

TABLE 50-9 Recommendations for Left Atrial Appendage Closure

Society Guidelines	Classification	Level of Evidence	Recommendation
American Heart Association/American College of Cardiology/Heart Rhythm Society 2014 guidelines for management of patients with atrial fibrillation[12]	IIb	C	Surgical excision of the left atrial appendage may be considered in patients undergoing cardiac surgery.
European Society of Cardiology 2012 guidelines for management of atrial fibrillation[13]	IIb	C	Surgical excision of the left atrial appendage may be considered in patients undergoing open heart surgery.
	IIb	B	Interventional, percutaneous left atrial appendage closure may be considered in patients with a high stroke risk and contraindications for long- term oral anticoagulation.

reasons, LAA closure should not be considered a panacea for stroke prevention in the AF patient who is not an optimal candidate for OAC.

Society recommendations for LAA occlusion are listed in Table 50-9. In brief, the AHA/ACC/HRS guidelines state that surgical excision of the LAA during concomitant cardiac surgery may be considered, but its efficacy is uncertain (class IIb, level C evidence).[12] The ESC guidelines state that surgical excision may be considered during concomitant cardiac surgery (class IIb, level C evidence) and that transcatheter LAA closure may be considered in patients with a high stroke risk and contraindications to long-term OAC (class IIb, level B evidence).[13]

CONCLUSIONS

Atrial fibrillation is associated with increased risk of stroke and systemic embolism, and its prevalence is growing significantly due to aging of the global population. Although chronic anticoagulation with vitamin K antagonists and the NOACs reduce the risk of stroke, they are substantially underused, in large part because of therapeutic challenges such as long-term bleeding risk.

The LAA appears to be the primary source of thromboembolism in AF, and it is therefore an attractive target for mechanical approaches to stroke prevention in this patient population. Several devices have been developed to percutaneously occlude or ligate the LAA. Robust safety and efficacy data are limited for most devices. The totality of the clinical trial data suggests that the Watchman LAA occluder is an acceptable alternative to warfarin therapy in many patients. Studies of larger cohorts are needed to determine the safety and clinical efficacy of the other devices beyond their ability to provide immediate anatomic LAA closure. Patient selection for LAA closure must consider the risk of procedural complications, baseline thromboembolic risk, the risk and suitability of OAC, and patient preference.

REFERENCES

1. Johnson WD, Ganjoo AK, Stone CD, et al: The left atrial appendage: our most lethal human attachment! Surgical implications. *Eur J Cardiothorac Surg* 17:718–722, 2000.
2. Mozaffarian D, Benjamin EJ, Go AS, et al: Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation* 131:e29–e322, 2015.
3. Chugh SS, Havmoeller R, Narayanan K, et al: Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation* 129:837–847, 2014.
4. Alonso A, Agarwal SK, Soliman EZ, et al: Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J* 158:111–117, 2009.
5. Wolf PA, Abbott RD, Kannel WB: Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 22:983–988, 1991.
6. Hart RG, Pearce LA, Rothbart RM, et al: Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy, Stroke Prevention in Atrial Fibrillation investigators. *J Am Coll Cardiol* 35:183–187, 2000.
7. Healey JS, Connolly SJ, Gold MR, et al: Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 366:120–129, 2012.
8. Lin HJ, Wolf PA, Kelly-Hayes M, et al: Stroke severity in atrial fibrillation: the Framingham Study. *Stroke* 27:1760–1764, 1996.
9. Gage BF, Waterman AD, Shannon W, et al: Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 285:2864–2870, 2001.
10. Lip GY, Nieuwlaat R, Pisters R, et al: Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 137:263–272, 2010.
11. Lip GY, Frison L, Halperin JL, Lane DA: Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke* 41:2731–2738, 2010.
12. January CT, Wann LS, Alpert JS, et al: 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 64:e1–e76, 2014.
13. Camm AJ, Lip GY, De Caterina R, et al: 2012 Focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 33:2719–2747, 2012.
14. Pisters R, Lane DA, Nieuwlaat R, et al: A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 138:1093–1100, 2010.
15. Lip GY, Frison L, Halperin JL, Lane DA: Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol* 57:173–180, 2011.
16. Roldan V, Marin F, Manzano-Fernandez S, et al: The HAS-BLED score has better prediction accuracy for major bleeding than CHADS2 or CHA2DS2-VASc scores in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol* 62:2199–2204, 2013.
17. Hart RG, Benavente O, McBride R, Pearce LA: Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 131:492–501, 1999.
18. Wittkowsky AK: Warfarin and other coumarin derivatives: pharmacokinetics, pharmacodynamics, and drug interactions. *Semin Vasc Med* 3:221–230, 2003.
19. Connolly SJ, Ezekowitz MD, Yusuf S, et al: Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 361:1139–1151, 2009.
20. Granger CB, Alexander JH, McMurray JJ, et al: Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 365:981–992, 2011.
21. Patel MR, Mahaffey KW, Garg J, et al: Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 365:883–891, 2011.
22. Giugliano RP, Ruff CT, Braunwald E, et al: Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 369:2093–2104, 2013.
23. Waldo AL, Becker RC, Tapson VF, et al: Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. *J Am Coll Cardiol* 46:1729–1736, 2005.
24. Samsa GP, Matchar DB, Goldstein LB, et al: Quality of anticoagulation management among patients with atrial fibrillation: results of a review of medical records from 2 communities. *Arch Intern Med* 160:967–973, 2000.
25. Gladstone DJ, Bui E, Fang J, et al: Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke* 40:235–240, 2009.
26. Goren A, Liu X, Gupta S: Warfarin and aspirin use for stroke prevention among patients with atrial fibrillation: the US National Health and Wellness Survey. *Am J Ther* 2013. [Epub ahead of print].
27. Casciano JP, Dotiwala ZJ, Martin BC, Kwong WJ: The costs of warfarin underuse and nonadherence in patients with atrial fibrillation: a commercial insurer perspective. *J Manag Care Pharm* 19:302–316, 2013.
28. Baczek VL, Chen WT, Kluger J, Coleman CI: Predictors of warfarin use in atrial fibrillation in the United States: a systematic review and meta-analysis. *BMC Fam Pract* 13:5, 2012.
29. O'Brien EC, Holmes DN, Ansell JE, et al: Physician practices regarding contraindications to oral anticoagulation in atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *Am Heart J* 167:601.e1–609.e1, 2014.
30. Connolly SJ, Eikelboom J, Joyner C, et al: Apixaban in patients with atrial fibrillation. *N Engl J Med* 364:806–817, 2011.
31. Beigel R, Wunderlich NC, Ho SY, et al: The left atrial appendage: anatomy, function, and noninvasive evaluation. *JACC Cardiovasc Imaging* 7:1251–1265, 2014.
32. Beinart R, Heist EK, Newell JB, et al: Left atrial appendage dimensions predict the risk of stroke/TIA in patients with atrial fibrillation. *J Cardiovasc Electrophysiol* 22:10–15, 2011.
33. Khurram IM, Dewire J, Mager M, et al: Relationship between left atrial appendage morphology and stroke in patients with atrial fibrillation. *Heart Rhythm* 10:1843–1849, 2013.
34. Di Biase L, Santangeli P, Anselmino M, et al: Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. *J Am Coll Cardiol* 60:531–538, 2012.
35. Kimura T, Takatsuki S, Inagawa K, et al: Anatomical characteristics of the left atrial appendage in cardiogenic stroke with low CHADS2 scores. *Heart Rhythm* 10:921–925, 2013.
36. Blackshear JL, Odell JA: Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 61:755–759, 1996.
37. Madden JL: Resection of the left auricular appendix; a prophylaxis for recurrent arterial emboli. *JAMA* 140:769–772, 1949.
38. Chatterjee S, Alexander JC, Pearson PJ, Feldman T: Left atrial appendage occlusion: lessons learned from surgical and transcatheter experiences. *Ann Thorac Surg* 92:2283–2292, 2011.
39. Katz ES, Tsiamtsiouris T, Applebaum RM, et al: Surgical left atrial appendage ligation is frequently incomplete: a transesophageal echocardiograhic study. *J Am Coll Cardiol* 36:468–471, 2000.
40. Kanderian AS, Gillinov AM, Pettersson GB, et al: Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. *J Am Coll Cardiol* 52:924–929, 2008.
41. Dawson AG, Asopa S, Dunning J: Should patients undergoing cardiac surgery with atrial fibrillation have left atrial appendage exclusion? *Interact Cardiovasc Thorac Surg* 10:306–311, 2010.

42. Whitlock R, Healey J, Vincent J, et al: Rationale and design of the Left Atrial Appendage Occlusion Study (LAAOS) III. *Ann Cardiothorac Surg* 3:45–54, 2014.
43. Johnson WJ, Ganjoo AK, Stone CD: The left atrial appendage: our most lethal human attachment! Surgical implications. *Eur J Cardiothorac Surg* 17:718–722, 2000.
44. Katz ES, Tsiamtsiouris T, Applebaum RM: Surgical left atrial appendage ligation is frequently incomplete: a transesophageal echocardiographic study. *J Am Coll Cardiol* 36:468–471, 2000.
45. Garcia-Fernandez MA, Perez-David E, Quiles J, et al: Role of left atrial appendage obliteration in patients with mitral valve prosthesis. *J Am Coll Cardiol* 42:1253–1258, 2000.
46. Bando K, Kobayashi J, Hirata M, et al: Early and late stroke after mitral valve replacement with a mechanical prosthesis: risk factor analysis of a 24-year experience. *J Thorac Cardiovasc Surg* 126:358–364, 2003.
47. Blackshear JL, Johnson WD, Odell JA, et al: Thoracoscopic extracardiac obliteration of the left atrial appendage for stroke risk reduction in atrial fibrillation. *J Am Coll Cardiol* 42:1249–1252, 2003.
48. Pennec PY, Jobic Y, Blanc JJ, et al: Assessment of different procedures for surgical left atrial appendage exclusion. *Ann Thorac Surg* 76:2168–2169, 2003.
49. Schneider B, Stollberger C, Sievers HH: Surgical closure of the left atrial appendage—a beneficial procedure? *Cardiology* 104:127–132, 2005.
50. Healey JS, Crystal E, Lamy A, et al: Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. *Am Heart J* 150:288–293, 2005.
51. Kanderian AS, Gillinov AM, Pettersson GB, et al: Success of surgical left atrial appendage closure. *J Am Coll Cardiol* 52:924–929, 2008.
52. Bakhtiary F, Kleine P, Martens S, et al: Simplified technique for surgical ligation of the left atrial appendage in high-risk patients. *J Thorac Cardiovasc Surg* 135:430–431, 2008.
53. Sievert H, Lesh MD, Trepels T, et al: Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience. *Circulation* 105:1887–1889, 2002.
54. Block PC, Burstein S, Casale PN, et al: Percutaneous left atrial appendage occlusion for patients in atrial fibrillation suboptimal for warfarin therapy: 5-year results of the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) study. *JACC Cardiovasc Interv* 2:594–600, 2009.
55. Bayard YL, Omran H, Neuzil P, et al: PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) for prevention of cardioembolic stroke in non-anticoagulation eligible atrial fibrillation patients: results from the European PLAATO study. *EuroIntervention* 6:220–226, 2010.
56. Reddy VY, Sievert H, Halperin J, et al: Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA* 312:1988–1998, 2012.
57. Sick PB, Schuler G, Hauptmann KE, et al: Initial worldwide experience with the Watchman left atrial appendage system for stroke prevention in atrial fibrillation. *J Am Coll Cardiol* 49:1490–1495, 2007.
58. Holmes DR, Reddy VY, Turi ZG, et al: Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 374:534–542, 2009.
59. Holmes DR, Jr, Kar S, Price MJ, et al: Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 64:1–12, 2014.
60. Reddy VY, Holmes D, Doshi SK, et al: Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System For Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. *Circulation* 123:417–424, 2011.
61. Reddy VY, Mobius-Winkler S, Miller MA, et al: Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study with Watchman left atrial appendage closure technology). *J Am Coll Cardiol* 61:2551–2556, 2013.
62. Viles-Gonzalez JF, Kar S, Douglas P, et al: The clinical impact of incomplete left atrial appendage closure with the Watchman Device in patients with atrial fibrillation: a PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation) substudy. *J Am Coll Cardiol* 59:923–929, 2012.
63. Alli O, Doshi S, Kar S, et al: Quality of life assessment in the randomized PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation) trial of patients at risk for stroke with nonvalvular atrial fibrillation. *J Am Coll Cardiol* 61:1790–1798, 2013.
64. Park JW, Bethencourt A, Sievert H, et al: Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. *Catheter Cardiovasc Interv* 77:700–706, 2011.
65. Freixa X, Chan JL, Tzikas A, et al: The Amplatzer Cardiac Plug 2 for left atrial appendage occlusion: novel features and first-in-man experience. *EuroIntervention* 8:1094–1098, 2013.
66. Lam SC, Bertog S, Gafoor S, et al: Left atrial appendage closure using the amulet device: an initial experience with the second generation amplatzer cardiac plug. *Catheter Cardiovasc Interv* 1(85):297–303, 2015.
67. Saw J, Lempereur M: Percutaneous left atrial appendage closure: procedural techniques and outcomes. *JACC Cardiovasc Interv* 7:1205–1220, 2014.
68. Urena M, Rodes-Cabau J, Freixa X, et al: Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. *J Am Coll Cardiol* 62:96–102, 2013.
69. Meerkin D, Butnaru A, Dratva D, et al: Early safety of the Amplatzer Cardiac Plug for left atrial appendage occlusion. *Int J Cardiol* 168:3920–3925, 2013.
70. Lam YY, Yip GW, Yu CM, et al: Left atrial appendage closure with AMPLATZER cardiac plug for stroke prevention in atrial fibrillation: initial Asia-Pacific experience. *Catheter Cardiovasc Interv* 79:794–800, 2012.
71. Chun KR, Bordignon S, Urban V, et al: Left atrial appendage closure followed by 6 weeks of antithrombotic therapy: a prospective single-center experience. *Heart Rhythm* 10:1792–1799, 2013.
72. Guérios EE, Schmid M, Gloekler S, et al: Left atrial appendage closure with the Amplatzer cardiac plug in patients with atrial fibrillation. *Arq Bras Cardiol* 98:528–536, 2012.
73. Danna P, Proietti R, Sagone A, et al: Does left atrial appendage closure with a cardiac plug system reduce the stroke risk in nonvalvular atrial fibrillation patients? A single-center case series. *Pacing Clin Electrophysiol* 36:347–353, 2013.
74. Horstmann S, Zugck C, Krumsdorf U, et al: Left atrial appendage occlusion in atrial fibrillation after intracranial hemorrhage. *Neurology* 82:135–138, 2014.
75. Santoro G, Meucci F, Stolcova M, et al: Percutaneous left atrial appendage occlusion in patients with non-valvular atrial fibrillation: implantation and up to four years follow-up of the AMPLATZER Cardiac Plug. *EuroIntervention* 2014. [Epub ahead of print].
76. Wiebe J, Bertog S, Franke J, et al: Safety of percutaneous left atrial appendage closure with the Amplatzer cardiac plug in patients with atrial fibrillation and contraindications to anticoagulation. *Catheter Cardiovasc Interv* 83:796–802, 2014.
77. Freixa X, Abualsaud A, Chan J, et al: Left atrial appendage occlusion: initial experience with the Amplatzer Amulet. *Int J Cardiol* 174:492–496, 2014.
78. Lee RJ, Bartus K, Yakubov SJ: Catheter-based left atrial appendage (LAA) ligation for the prevention of embolic events arising from the LAA: initial experience in a canine model. *Circ Cardiovasc Interv* 3:224–229, 2010.
79. Bartus K, Han FT, Bednarek J, et al: Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. *J Am Coll Cardiol* 62:108–118, 2013.
80. Massumi A, Chelu MG, Nazeri A, et al: Initial experience with a novel percutaneous left atrial appendage exclusion device in patients with atrial fibrillation, increased stroke risk, and contraindications to anticoagulation. *Am J Cardiol* 111:869–873, 2013.
80a. Massumi A, Chelu MG, Nazeri A, et al: Initial experience with a novel percutaneous left atrial appendage exclusion device in patients with atrial fibrillation, increased stroke risk, and contraindications to anticoagulation. *Am J Cardiol* 111:869–873, 2013.
80b. Price MJ, Gibson DN, Yakubov SJ, et al: Early Safety and Efficacy of Percutaneous Left Atrial Appendage Suture Ligation: Results From the U.S. Transcatheter LAA Ligation Consortium. *J Am Coll Cardiol* 64:565–572, 2014.
81. Miller MA, Gangireddy SR, Doshi SK, et al: Multicenter study on acute and long-term safety and efficacy of percutaneous left atrial appendage closure using an epicardial suture snaring device. *Heart Rhythm* 11:1853–1859, 2014.
82. Mosley WJ, 2nd, Smith MR, Price MJ: Percutaneous management of late leak after lariat transcatheter ligation of the left atrial appendage in patients with atrial fibrillation at high risk for stroke. *Catheter Cardiovasc Interv* 83:664–669, 2014.
83. Yeow WL, Matsumoto T, Kar S: Successful closure of residual leak following LARIAT procedure in a patient with high risk of stroke and hemorrhage. *Catheter Cardiovasc Interv* 83:661–663, 2014.
84. Pillai AM, Kanmanthareddy A, Earnest M, et al: Initial experience with post Lariat left atrial appendage leak closure with Amplatzer septal occluder device and repeat Lariat application. *Heart Rhythm* 11:1877–1883, 2014.
85. Han FT, Bartus K, Lakkireddy D, et al: The effects of LAA ligation on LAA electrical activity. *Heart Rhythm* 11:864–870, 2014.
86. Afzal MR, Kanmanthareddy A, Earnest M, et al: Impact of left atrial appendage exclusion using an epicardial ligation system (LARIAT) on atrial fibrillation burden in patients with cardiac implantable electronic devices. *Heart Rhythm* 12:52–59, 2015.
87. Miller VT, Rothrock JF, Pearce LA, et al: Ischemic stroke in patients with atrial fibrillation: effect of aspirin according to stroke mechanism. Stroke Prevention in Atrial Fibrillation Investigators. *Neurology* 43:32–36, 1993.
88. Watson T, Shantsila E, Lip GY: Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet* 373:155–166, 2009.

51 Mitral Valvuloplasty

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KEY POINTS

- The efficacy, safety, and applicability of the Inoue balloon technique are established worldwide. The technique is the point of reference for percutaneous mitral commissurotomy (PMC).
- Transesophageal echocardiography is essential for monitoring the procedure and for assessing the immediate results.
- Technical experience is essential for the safety of the procedure and the selection of patients.
- PMC provides good immediate and long-term clinical results and carries a low risk when performed by experienced teams.
- Patient selection is based on anatomy and other predictors of outcome.
- PMC is the treatment of choice for patients with favorable characteristics.
- The decision must be individualized for other patients, and PMC and valve replacement should be considered complementary techniques.

Until the first publication by Inoue and coworkers describing percutaneous mitral commissurotomy (PMC) in 1984, surgery was the only treatment for patients with mitral stenosis.[1] Since then, the technique has evolved considerably. Many patients with a wide range of clinical conditions have been treated, enabling efficacy and risk to be assessed. These long-term results allow selection of the most appropriate candidates for PMC.[2,3]

DEVICES AND TECHNIQUES

Acting in the same way as surgical commissurotomy, PMC opens the fused commissures (Fig. 51-1). PMC is of little or no help in cases of restricted valvular mobility caused by valve fibrosis or severe subvalvular disease or in cases of degenerative calcified mitral annulus. The techniques and devices used for PMC have varied over time and from group to group. Currently, the transvenous or transseptal approach using the Inoue balloon is largely predominant.

Transseptal Approach

The transvenous, or antegrade, approach is performed through the femoral vein. Transseptal catheterization is the crucial first step of the procedure. Usually, transseptal catheterization is performed under fluoroscopic guidance with use of several views. Continuous pressure monitoring is recommended. Echocardiography is not used systematically during transseptal catheterization, but it can enhance its safety, especially for less experienced operators and when technical difficulties are encountered (e.g., severe anatomic distortion).

The procedure has been done primarily with transesophageal echocardiography (TEE), which is superior to transthoracic echocardiography (TTE) for imaging the interatrial septum (IAS) (Video 51-1). Intracardiac echocardiography (ICE) is considered the imaging tool of choice in several catheterization centers to guide transseptal puncture because it may be used without additional operators or general anesthesia, although the price of the device seriously limits its use in most places.[4]

In experienced centers, the whole procedure can be performed using a single venous approach and noninvasive monitoring, which reduces the risk of vascular complications, discomfort, and cost. The retrograde transatrial approach has been abandoned due to its complexity.

Inoue Technique

The Inoue technique was the first to be described, and extensive experience has been acquired by many groups worldwide. The Inoue balloon, composed of nylon and rubber micromesh, is self-positioning and pressure extensible. It is large (24 to 30 mm in maximal diameter) and has a low profile (4.5 mm balloon diameter). The balloon has three distinct parts, each with a specific elasticity, enabling the parts to be inflated sequentially. This sequence allows fast, stable positioning across the valve. Each of the four balloon sizes (i.e., 24, 26, 28, and 30 mm) is pressure dependent, and its diameter can be varied by up to 4 mm, as required by circumstances.

The main steps are as follows: After transseptal catheterization, a stiff guidewire is introduced into the left atrium. The femoral entry site and the atrial septum are dilated with a rigid dilator (14 Fr), and the balloon is introduced into the left atrium. Inoue recommended the use of a stepwise dilation technique under echocardiographic guidance.

Balloon size is chosen in accordance with the patient's height: 26 mm for very small patients or infants, 28 mm for patients shorter than 1.6 m, and 30 mm for patients taller than 1.6 m. The balloon is inflated sequentially. First, the distal portion is inflated with 1 or 2 mL of diluted contrast; it acts as a floating balloon catheter when crossing the mitral valve. Second, the distal part is further inflated, and the balloon is pulled back into the mitral orifice. Inflation next occurs at the level of the proximal part and then in the central portion, with the disappearance of the central waist at full inflation (Fig. 51-2 and Videos 51-2 and 51-3).

The first inflation is performed 4 mm below the maximal balloon size, and the balloon size is increased in 1-mm increments. The balloon is then deflated and withdrawn into the left atrium. If mitral regurgitation (assessed by color Doppler echocardiography) has not increased by more than one grade and the valve area is less than 1 cm^2/m^2 of body surface area, the balloon is advanced again across the valve, and PMC is repeated with a balloon diameter increased by 1 mm (Fig. 51-3).[1] The criterion for ending the procedure is an adequate valve area or an increase in the degree of mitral regurgitation.

Other Techniques

The double-balloon technique has been described extensively.[5] The multitrack system, which is a refinement of the double-balloon technique that uses a monorail system and the metallic commissurotome, has a limited or no current use.

MONITORING THE PROCEDURE AND EVALUATING RESULTS

There are two ways to monitor the procedure and assess immediate results in the catheterization laboratory: hemodynamics and echocardiography. Echocardiography provides essential information. Besides

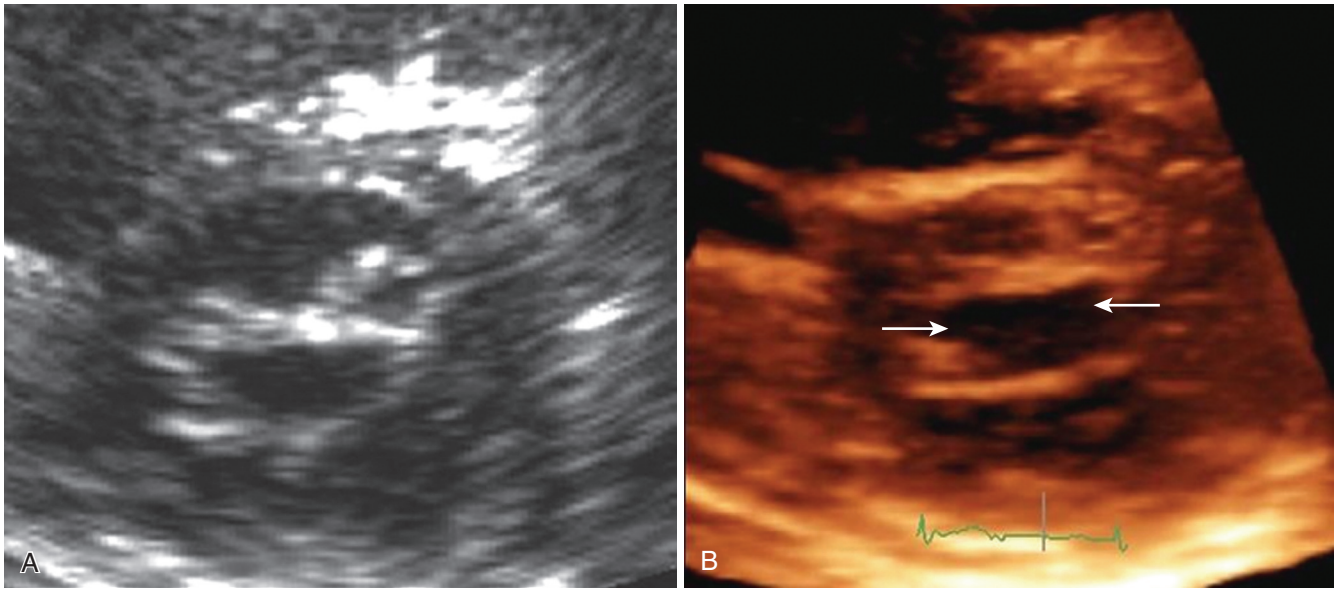


FIGURE 51-1 Transthoracic two-dimensional echocardiography before (**A**) and three-dimensional echocardiography after (**B**) percutaneous mitral commissurotomy (PMC). The *arrows* show the bilateral commissural opening after PMC.

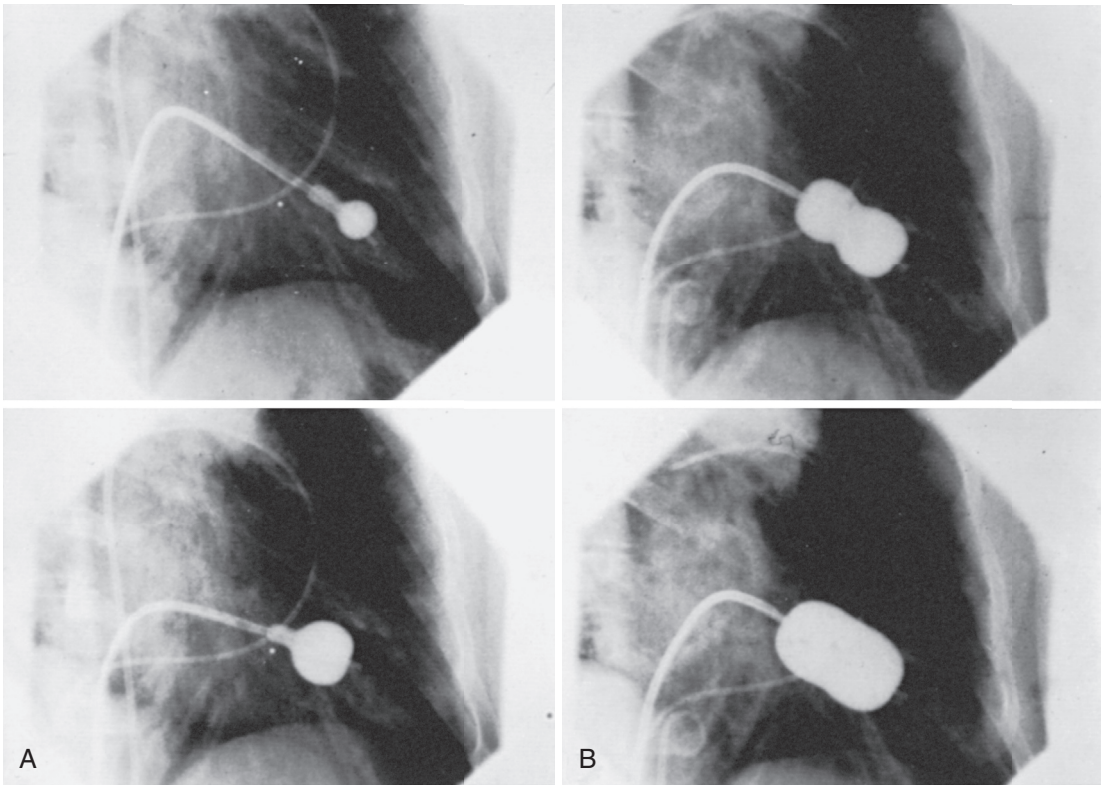


FIGURE 51-2 Inoue's percutaneous mitral commissurotomy technique. **A,** Inflation of the distal portion of the balloon, which is then pulled back and anchored at the mitral valve. **B,** Subsequent inflation of the proximal and middle portions of the balloon. At full inflation, the waist of the balloon in its midportion has disappeared.

its usefulness in guiding transseptal catheterization, echocardiography provides information on the course of the mitral opening, which is essential when using the stepwise Inoue technique. Echocardiography enables detection of early complications such as pericardial hemorrhage and severe mitral regurgitation.

Monitoring the Procedure

Because the accuracy of Doppler measurements during valvuloplasty is low, planimetry using two-dimensional echocardiography is the method of choice if it is technically feasible. Color Doppler assessment is preferred for sequential evaluation of the changes in the degree of

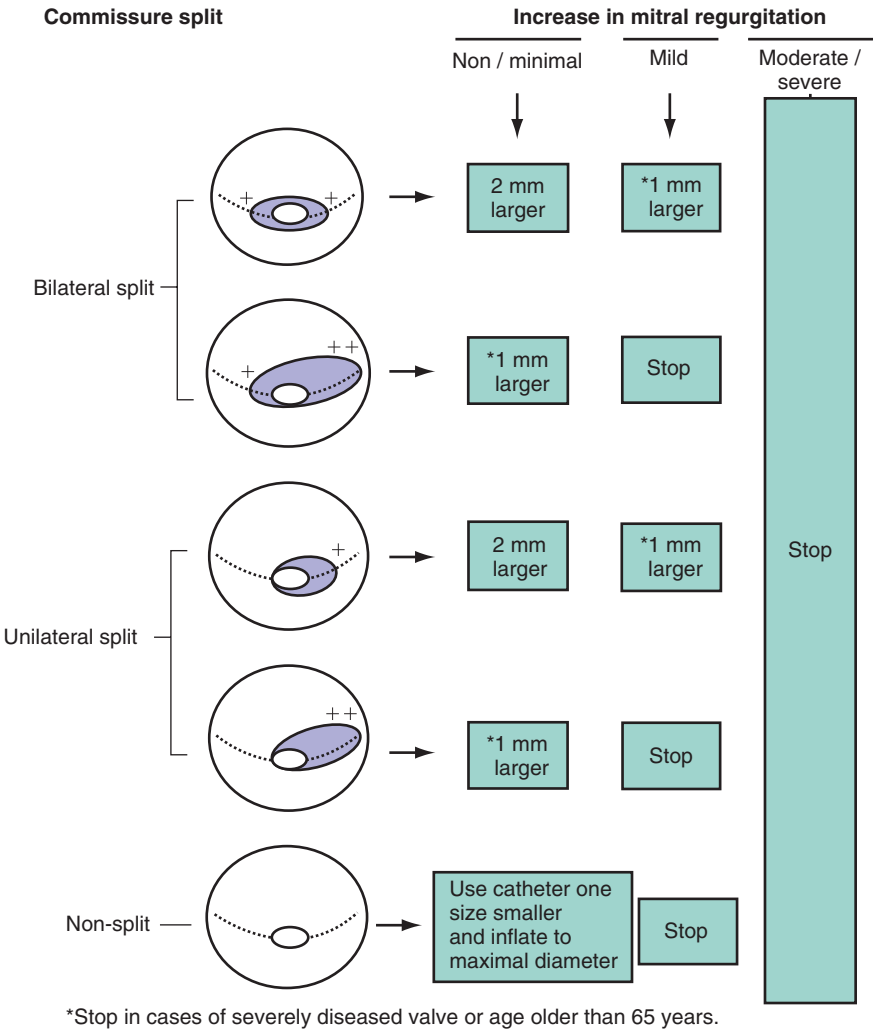


FIGURE 51-3 Decision making during the stepwise dilation technique is based on echocardiographic findings after each balloon dilation. +, Incomplete split; ++, complete split. (Modified from Inoue K, Owaki T, Nakamura T, et al: Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg* 87:394-402, 1984.)

regurgitation. The commissural opening, which is the main parameter, is usually assessed in the parasternal short-axis view during TTE. When available, real-time three-dimensional echocardiography is the most accurate method for assessing the degree of commissural opening using short-axis views (Video 51-4).[6]

An integrative assessment using the following criteria has been proposed for the desired end point of the procedure: mitral valve area of more than 1 cm^2/m^2 of the body surface area; complete opening of at least one commissure; or appearance or increment of regurgitation greater than grade 1 in the Sellers 0 to 4 classification. The strategy must be tailored to individual circumstances, taking into account clinical and anatomic factors and the cumulative data of periprocedural monitoring. For example, balloon size, increments of size, and expected final valve area are smaller in older or pregnant patients, in whom the need for emergency surgery is a concern, and in cases of tight mitral stenosis, extensive valve or subvalvular disease, and nodular commissural calcification.

After the procedure, the most accurate evaluation of the valve area is achieved by echocardiography. Color Doppler flow is the most sensitive method for assessing the degree of regurgitation and interatrial shunting.

Immediate Results

Failures

The failure rate for PMC ranges from 1% to 17%.[3,5,7-9] Failure is often caused by an inability to puncture the atrial septum or position the balloon correctly across the valve. Most failures occur early in the operator's experience. Failures can also result from unfavorable anatomy such as severe atrial stenosis or predominant subvalvular stenosis.

Hemodynamics

PMC usually provides an increase of more than 100% in the valve area, with final valve areas ranging from 1.5 to more than 2 cm^2. Improvement in valve function immediately decreases left atrial pressure (Fig. 51-4) and slightly increases the cardiac index. Pulmonary arterial pressure and pulmonary vascular resistance gradually decrease. High pulmonary vascular resistance continues to decrease in the absence of restenosis.

PMC has a beneficial effect on exercise capacity. PMC improves the pump function of the left atrium and the left atrial appendage and decreases left atrial stiffness. It also decreases the intensity of spontaneous echocardiographic contrast in the left atrium.

Complications

Large series have enabled assessment of the risks of the technique [3,5-12] The procedural mortality rate has ranged from 0% to 3% in most series. The main causes of death are left ventricular perforation and poor general condition of the patient.

The incidence of hemopericardium is between 0.5% and 12%. Pericardial hemorrhage may be related to transseptal catheterization or to apex perforation by guidewires or the balloon itself when exaggerated movement occurs when using over-the-wire techniques. However, this

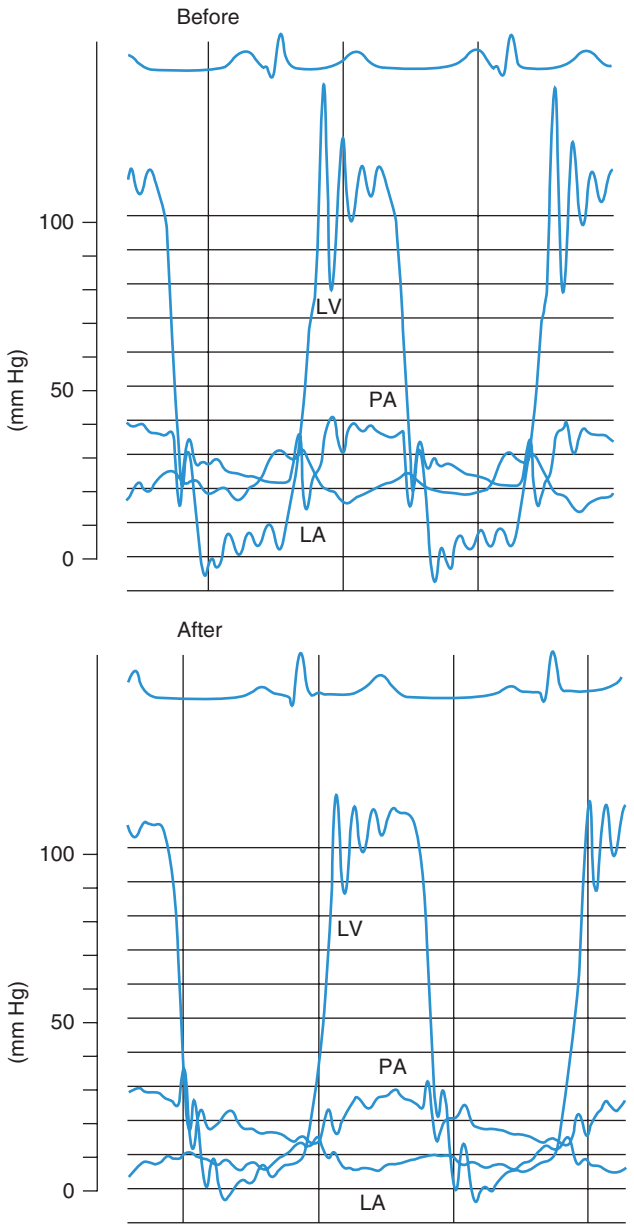


FIGURE 51-4 Hemodynamic changes after percutaneous mitral commissurotomy. *LA,* Left atrium; *LV,* left ventricle; *PA,* pulmonary artery.

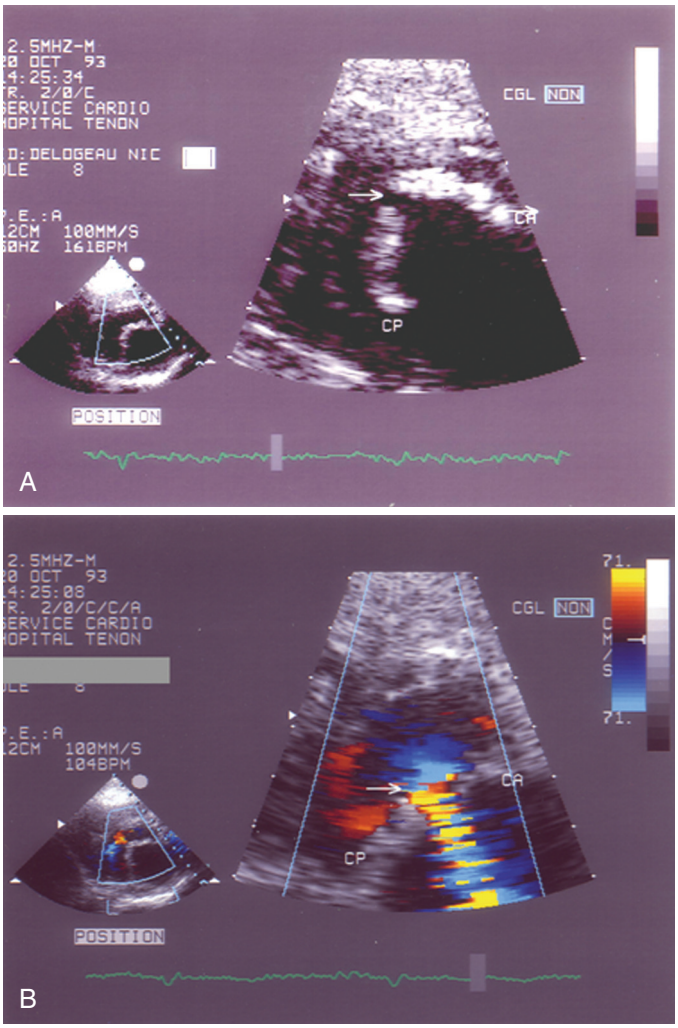


FIGURE 51-5 Severe mitral regurgitation after percutaneous mitral commissurotomy. **A,** Transthoracic echocardiography shows a tear of the anterior leaflet *(arrow)*. **B,** Doppler color flow shows severe regurgitation at the level of the leaflet tear *(arrow)*. *CA,* Anterior commissure; *CP,* posterior commissure.

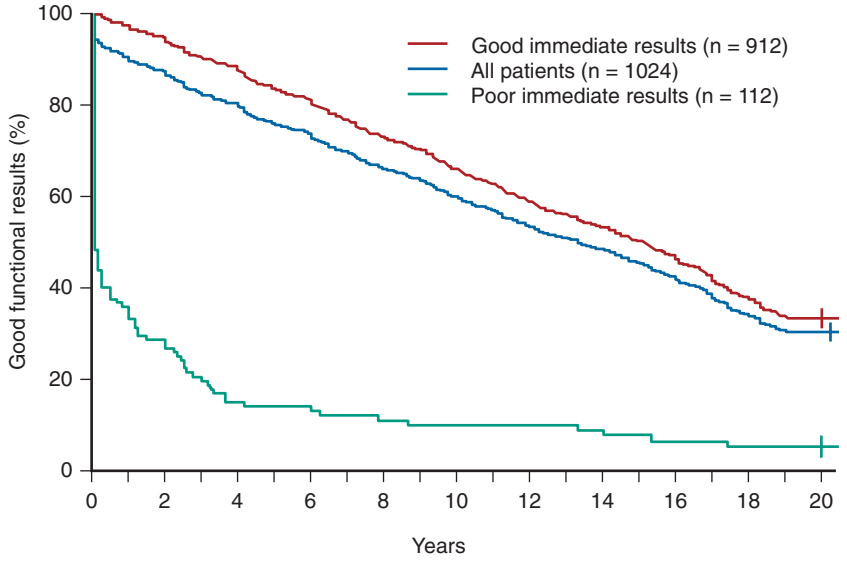
complication is virtually eliminated with the Inoue balloon technique. If hypotension occurs during PMC, hemopericardium must be suspected and echocardiography immediately performed. Pericardiocentesis in the catheter laboratory, ideally under echocardiographic guidance, usually allows stabilization of the patient's condition and secondary transfer for cardiac surgery.

Embolism is encountered in 0.5% to 5% of cases. It is seldom the cause of permanent incapacitation and even more seldom the cause of death. It can be caused by gas if it occurs immediately after balloon rupture, by fibrinothrombotic material, or occasionally, by calcium accumulation. Although the incidence of embolism is low, its potential consequences are severe, and all possible precautions must be taken to prevent it. Treatment of cerebral embolism should be provided in collaboration with a stroke unit.

In most cases, the degree of mitral regurgitation remains stable or, more often, slightly increases after PMC. In a few cases, the degree of mitral regurgitation decreases, probably because of the increased mobility of the leaflets. Severe mitral regurgitation is uncommon, with a frequency between 2% and 19%, and the occurrence of severe mitral regurgitation remains largely unpredictable for a given patient.[11,13] Surgical findings have confirmed that severe mitral regurgitation occurs almost exclusively in patients with unfavorable anatomy, extensive subvalvular disease, and valve calcification. It often is related to noncommissural tearing of the posterior or anterior leaflet (Fig. 51-5).[10] In these cases, one or both commissures are too tightly fused to be split. It may also be caused by excessive commissural splitting or rarely by rupture of a papillary muscle.

Development of severe regurgitation depends more on the distribution of morphologic changes than on their severity. Severe mitral regurgitation may be well tolerated; more often it is not, and surgery must be scheduled. In most cases, valve replacement is necessary and is more closely related to the extent of valve disease than to the tear itself.

The frequency of atrial septal defects (ASDs) after PMC varies from 10% to 90%, according to the technique used for its detection.[14] These shunts are usually small and restrictive, with high-velocity flow. Right-to-left shunts occur on rare occasions in patients with elevated right-sided heart pressures and pulmonary hypertension. Urgent surgery



No. at risk											
Good imm. results	912	839	761	673	620	507	446	375	237	111	45
All patients	1024	870	777	687	630	516	465	383	242	114	47
Poor imm. results	112	31	16	14	10	9	9	8	5	3	2

FIGURE 51-6 Good long-term functional results after percutaneous mitral commissurotomy according to immediate (imm.) results. Good functional results are defined as survival considering cardiovascular-related deaths without mitral surgery or repeat percutaneous mitral commissurotomy and in cases of New York Heart Association functional class I or II disease. Kaplan-Meier rates are presented with their standard errors. (Modified from Bouleti C, Iung B, Laouénan C, et al: Late results of percutaneous mitral commissurotomy up to 20 years: development and validation of a risk score predicting late functional results from a series of 912 patients. *Circulation* 125:2119-2127, 2012.)

(within 24 hours) is seldom needed for complications resulting from PMC. It may be required, however, for massive hemopericardium resulting from left ventricular perforation unresponsive to pericardiocentesis or, less frequently, for severe mitral regurgitation leading to hemodynamic collapse or refractory pulmonary edema.

Overall, the incidence of failures and serious complications such as tamponade is related to the surgical team's experience. When performed by experienced teams on properly selected patients, PMC is a relatively low-risk procedure.

Predictors of Immediate Results

The definition of good immediate results varies from series to series. The two definitions are frequently employed: a final valve area larger than 1.5 cm^2 and an increase of at least 25% in the valve area or a final valve area larger than 1.5 cm^2 without mitral regurgitation greater than a grade 1 of 4. Prediction of immediate results is based on morphologic factors; preoperative variables such as age, history of surgical commissurotomy, functional class, small mitral valve area, presence of mitral regurgitation before valvuloplasty, sinus rhythm, pulmonary artery pressure, and presence of severe tricuspid regurgitation; and procedural factors such as balloon size.[5,15-18]

Identification of the variables linked to outcome has enabled models to be developed with a high sensitivity of prediction.[19] Nevertheless, the specificity is low, indicating insufficient prediction of poor immediate results. This low specificity is particularly true in regard to the lack of accurate prediction of severe mitral regurgitation.

Long-Term Results

Follow-up data representing long-term results over the past 20 years have been analyzed.[9,15-19] In clinical terms, which are the most widely used, the overall long-term results of valvuloplasty are good. In our series (Fig. 51-6), which included 1024 patients, the 20-year survival rate was 73% ± 2%; the survival rate without any reintervention was 34% ± 2%.[15] When analyzing survival without surgery only, this figure increases to between 46% ± 2% and 57% ± 3% for patients younger than 50 years. Good functional results, defined as survival with no cardiovascular death or intervention, were reported for 30% ± 6% of patients with New York Heart Association (NYHA) class I or II disease.[15]

Prediction of long-term results is based on clinical variables such as age, valve anatomy as assessed by echocardiography scores, factors related to the evolutionary stage of the disease (i.e., higher NYHA class before valvuloplasty), history of previous commissurotomy, severe tricuspid regurgitation, cardiomegaly, atrial fibrillation (AF), high pulmonary vascular resistance, results of the procedure in terms of final gradient, valve area and quality of commissural opening, and existence of mitral regurgitation.[15,19,20] Quality of the late results is independent of the technique used.[18] A score combining these variables may be useful for patient selection and is relevant to follow-up (Table 51-1). Patients who have favorable immediate results but who are at high risk for further events must be carefully monitored to detect deterioration and institute timely intervention.

If PMC is initially successful, survival rates are excellent, the need for secondary surgery is uncommon, and functional improvement occurs in most cases (see Fig. 51-6). As confirmed with two-dimensional echocardiography or the Doppler technique, the improvement in valve function is stable in most cases. Determining the incidence of restenosis is compromised by the lack of a uniform definition. Restenosis after PMC has been defined as a loss of more than 50% of the initial gain, with a valve area less than 1.5 cm^2. After successful PMC, the incidence of restenosis is usually between 2% and 40% at 3 to 10 years.[15-19,21-27] Age, mitral valve area after PMC, and anatomy are predictors of restenosis.

Repeat valvuloplasty in cases of recurrent mitral stenosis can be performed with this nonsurgical procedure. Repeat valvuloplasty may be indicated if recurrent stenosis leads to symptoms, if it occurs several years after an initially successful procedure, and if the predominant mechanism of restenosis is commissural refusion. Using these criteria, repeat valvuloplasty may be performed in up to one-fourth of cases of

TABLE 51-1 Multivariable Analysis and Scoring for Predicting Long-Term Results of Percutaneous Mitral Commissurotomy

Factor	Adjusted Hazard Ratio (95% CI)	*P*	Points (Total Score of 13)*
Age and final mitral valve area			
<50 yr and MVA ≥2.00 cm^2	1		0
<50 yr and MVA 1.50-2.00 cm^2 or 50-70 yr and MVA > 1.75 cm^2	2.1 (1.6-2.9)	<.0001	2
50-70 yr and MVA 1.50-1.75 cm^2 or≥70 yr and MVA ≥1.50 cm^2	5.1 (3.5-7.5)	<.0001	5
Valve anatomy and sex			
No valve calcification	1		0
Valve calcification—Female	1.2 (0.9-1.6)	.18	0
Valve calcification—Male	2.3 (1.6-3.2)	<.0001	3
Rhythm and NYHA class			
Sinus rhythm or atrial fibrillation and NYHA class I-II	1		0
Atrial fibrillation and NYHA class III-IV	1.8 (1.4-2.3)	<.0001	2
Final mean mitral gradient			
≤3 mm Hg	1		0
3-6 mm Hg	1.1 (1.0-1.8)	.05	1
≥6 mm Hg	2.5 (1.8-3.5)	<.0001	3

Modified from Bouleti C, Iung B, Laouénan C, et al. Late results of percutaneous mitral commissurotomy up to 20 years: development and validation of a risk score predicting late functional results from a series of 912 patients. *Circulation* 125:2119-2127, 2012.
CI, Confidence interval; *MVA,* mitral valve area; *NYHA,* New York Heart Association.
*At 20 years, predicted rates of good late results were 55.1% for patients with scores of 0 to 2, 29.1% for those with scores of 3 to 5, and 10.5% for those with scores of 6 to 13. The overall C index (i.e., natural extension of the receiver-operating characteristic area to survival analysis and its 95% confidence interval) was 0.71 (95% CI, 0.58 to 0.80).

late reintervention, allowing surgery to be postponed for a substantial number of patients.

Current experience shows positive immediate and midterm outcomes for patients with favorable characteristics.[26-29] In a series comprising 85 repeat valvuloplasties, the rate of cardiovascular survival without surgery was 60% ± 6% at 10 years, whereas after 10 years, the survival rate without reintervention was 50%.[27] Although the results are less favorable for patients with worse characteristics, repeat valvuloplasty has a palliative role for patients who are at high risk for surgery.

If the immediate results are unsatisfactory, midterm functional results are usually poor. The prognosis for patients with severe mitral regurgitation after surgical commissurotomy or PMC is usually poor, with a lack of symptom alleviation and secondary objective deterioration. Surgical treatment is usually necessary in the following months.[15] In cases of an insufficient initial opening, delayed surgery is usually performed when extracardiac conditions allow it. Valve replacement is necessary in almost all cases because of the unfavorable valve anatomy that was responsible for the poor initial results.

Follow-up studies have shown that the overall degree of mitral regurgitation remains stable or slightly decreases during follow-up. ASDs are likely to close later in most cases because of a reduced interatrial pressure gradient. The persistence of shunts is related to their magnitude or to unsatisfactory relief of the valve obstruction. These defects seldom require individual treatment. The low incidence of embolism during follow-up, the progressive decrease in intensity or disappearance of spontaneous echocardiographic contrast, and the improved left atrial function after PMC suggest a beneficial effect of the procedure on left atrial blood stasis, and a lower risk of thromboembolism may be expected.[30]

There is no direct evidence that PMC reduces the incidence of AF, even though it has a favorable influence on the predictors of AF (e.g., atrial size, degree of obstruction).[31] It is recommended that electric countershock cardioversion be performed early after successful PMC if the AF is of recent onset and in the absence of severe enlargement of the left atrium.

Several studies have compared surgical commissurotomy with PMC, mostly in patients with favorable characteristics.[32] They have shown that valvuloplasty is at least comparable with surgical commissurotomy with regard to short-term and midterm follow-up up to 7 years. There is no randomized comparison of percutaneous commissurotomy and surgical commissurotomy in patients with less favorable anatomy, and the results of observational series are somewhat contradictory.[29,33,34]

SELECTION OF PATIENTS

The application of PMC depends on four major factors: the patient's clinical condition, the valve anatomy, the experience of the medical and surgical teams of the institution concerned, and the financial aspect.

Patient Evaluation

Evaluation of the patient must take into account the degree of functional disability, contraindications to transseptal catheterization, and the risks involved in surgery as a function of the underlying cardiac and noncardiac status. Because of the small but definite risk inherent in the technique, the indications for intervention are limited to truly asymptomatic patients with severe mitral stenosis (i.e., patients with normal physical working capacity on exercise testing), except in cases of urgent need for extracardiac surgery to allow continuation of pregnancy in young women or in patients with an increased risk of embolism, such as those with a previous history of embolism, heavy spontaneous contrast in the left atrium, or recurrent atrial arrhythmias.

PMC can be proposed for patients who are declared to be asymptomatic but who have pulmonary hypertension at rest (i.e., systolic pulmonary pressure >50 mm Hg) or on exercise (>60 mm Hg), the thresholds of which should be refined by the experience gained in exercise echocardiography.[35-37] The American College of Cardiology/American Heart Association (ACC/AHA) guidelines suggest that PMC is reasonable in cases with very severe mitral stenosis (valve area >1 cm^2).[36] Under these conditions, PMC should be performed only by experienced interventionalists when the anatomy is suitable to achieve a safe, effective procedure. Contraindications to transseptal catheterization include suspected left atrial thrombosis (Video 51-5) severe hemorrhagic disorder, and severe cardiothoracic deformity (Table 51-2).

Valvuloplasty is the only solution when surgery is contraindicated. It is also preferable to surgery, at least as the first attempt, in patients for whom cardiac surgery poses a high risk, as in the following situations.

In cases of *severe pulmonary hypertension,*[38] even if the valve opening is suboptimal, valvuloplasty may produce a decrease in pulmonary pressures and therefore reduce the operative risk for patients with many comorbidities. However, the procedure must be avoided when life expectancy is severely reduced due to extracardiac factors.

For *critically ill patients*, valvuloplasty may be the sole treatment available when there is an absolute contraindication to surgery, or it

TABLE 51-2 Contraindications to Mitral Valvuloplasty

Left atrial thrombosis
Mitral regurgitation greater than grade 1 of 4
Massive or bicommissural calcification
Severe aortic valve disease or severe tricuspid stenosis plus regurgitation associated with mitral stenosis
Severe concomitant coronary artery disease requiring bypass surgery

may be used as a bridge to surgery in other cases.[39] In this context, dramatic improvement has been observed in young patients, but the outcome is very dire for older patients with end-stage disease, who would probably be better treated conservatively.

For *older patients*, valvuloplasty results in a moderate but significant improvement in valve function at an acceptable risk, although subsequent functional deterioration is common.[25] When surgery is high risk or contraindicated but life expectancy is still acceptable, PMC, even if only palliative, is a useful option. In patients who still have favorable anatomy, PMC can be attempted first, and surgery resorted to if the results are unsatisfactory. In other patients, surgery is preferable as the first option.

During pregnancy, surgery carries a substantial risk of fetal mortality and morbidity, especially if extracorporeal circulation is required.[40] From a technical point of view, during the last weeks of pregnancy (which is the time of PMC in most cases), the procedure may be challenging and should be performed only by experienced operators. The procedure is effective and allows for normal delivery in most cases. PMC is safe for the fetus, provided that protection is provided against radiation exposure by a shield that completely surrounds the patient's abdomen and the procedure is performed after the 20th week. PMC also carries the potential risk of related hypotension and the ever-present risk of complications that require urgent surgery. These data suggest that PMC can be a useful technique in the treatment of pregnant patients with mitral stenosis and refractory heart failure despite medical treatment.

For *patients with a previous surgical commissurotomy,* reoperation is associated with a higher risk of morbidity and mortality and requires valve replacement in most cases. PMC is feasible in this setting, although the procedure may be technically difficult in the case of funnel-shaped stenosis. PMC significantly improves valve function. The risks appear to be low, on a par with those of initial procedures.[26,41] One series showed good long-term results, and after a good initial result, one patient in three remains free of surgery, and one in five has good functional results at 20 years.[26] Encouraging preliminary data suggest that PMC may postpone reoperation in selected patients.

The indications for PMC in this subgroup of patients are similar to those for primary PMC, but echocardiographic examination must be conducted with great care to exclude patients in whom restenosis is mainly caused by valve rigidity without significant commissural refusion. In patients who have undergone mitral ring annuloplasty for correction of mitral regurgitation, PMC can be proposed if there is commissural fusion. Otherwise, surgical or transcatheter valve implantation (i.e., valve in a ring) can be performed after discussion with the heart team.

Assessment of Valve Anatomy

The assessment of anatomy has several aims when establishing indications and prognosis. Anatomic contraindications to the technique must be excluded (see Table 51-2). One contraindication is left atrial thrombosis, which must be excluded by systematic performance of TEE a few days before the procedure. This recommendation is self-evident if the thrombus is free floating or is situated in the left atrial cavity; it also applies when the thrombus is located on the IAS. If the thrombus is located in the left atrial appendage, it has not been shown satisfactorily that the Inoue technique under TEE guidance precludes the risk of embolism.[42] If the patient is clinically stable, as in the case of most patients with mitral stenosis, anticoagulant therapy can be given for 2 to 6 months. If a new transesophageal examination then shows that the thrombus has disappeared, PMC can be attempted.[43]

TABLE 51-3 Massachusetts General Hospital Classification of Mitral Valve Anatomy

Leaflet Mobility (1 to 4)*
1. Highly mobile valve with restriction of only the leaflet tips
2. Midportion and base of leaflets have reduced mobility
3. Valve leaflets move forward during diastole, mainly at the base
4. No or minimal forward movement of the leaflets during diastole
Valvular Thickening (1 to 4)
1. Leaflets near normal (4-5 mm)
2. Midleaflet thickening, marked thickening of the margins
3. Thickening extends through the entire leaflets (5-8 mm)
4. Marked thickening of all leaflet tissue (>8-10 mm)
Subvalvular Thickening (1 to 4)
1. Minimal thickening of chordal structures just below the valve
2. Thickening of chordae extending up to one third of chordal length
3. Thickening extending to the distal third of the chordae
4. Extensive thickening and shortening of all chordae extending down to the papillary muscle
Valvular Calcification (1 to 4)
1. Single area of increased echocardiographic brightness
2. Scattered areas of brightness confined to leaflet margins
3. Brightness extending into the midportion of leaflets
4. Extensive brightness through most of the leaflet tissue

Modified from Abascal V, Wilkins GT, O'Shea JP, et al: Prediction of successful outcome in 130 patients undergoing percutaneous balloon mitral valvotomy. *Circulation* 82:448-456, 1990.
*The total score is calculated by adding each of its components. A total score of less than 8 is considered favorable anatomy for percutaneous mitral commissurotomy.

Another contraindication is moderate mitral regurgitation. PMC can, however, be carried out in selected patients with mitral regurgitation of grade 2 or more if the risks related to surgery are high, such as in pregnant patients. In cases of combined mitral stenosis and severe aortic disease, surgery is indicated in the absence of contraindications. However, the coexistence of moderate aortic valve disease and severe mitral stenosis is another situation for which PMC is preferable so that the inevitable later surgical treatment of both valves can be postponed.

Combined severe tricuspid stenosis and tricuspid regurgitation with clinical signs of heart failure is an indication for surgery on both valves. Conversely, the existence of tricuspid regurgitation alone is not a contraindication to the procedure, even though it is a negative prognostic factor, especially when it is associated with severe enlargement of the right atrium and AF.[44]

The definition of a threshold of valve area above which PMC should not be performed is somewhat arbitrary. Besides measuring the valve area and the mean gradient, the stature of the patient, his or her functional disability, and pulmonary pressures at rest and on exercise should also be taken into account. Overall, for most patients with a mitral valve area greater than 1.5 cm^2, the risks probably outweigh the benefits, indicating medical treatment only. However, PMC may be considered in selected patients with symptoms and no other cause, even more so if exercise testing is positive.[36]

Echocardiographic assessment allows the classification of patients into anatomic groups with a view to predicting the results. Most investigators use the Wilkins score[5] (Table 51-3). Others use a general assessment of valve anatomy (Table 51-4) based on the potential surgical alternatives.[15] A score has been developed that takes into account novel parameters such as the maximal excursion of the leaflets from the annulus in diastole and the ratio between the commissural areas, which is an approach used to evaluate the commissural area.[19]

TABLE 51-4 Grading of Mitral Valve Anatomy by the Bichat Hospital, Paris, Classification

Echocardiographic Grade	Mitral Valve Anatomy	Implications
1	Pliable, noncalcified anterior mitral leaflet and mild subvalvular disease (i.e., thin chordae ≥10 mm long)	Ideal anatomy for percutaneous mitral commissurotomy
2	Pliable, noncalcified anterior mitral leaflet and severe subvalvular disease (i.e., thickened chordae <10 mm long)	Intermediate anatomy that may be treated by commissurotomy or valve replacement
3	Calcification of mitral valve of any extent as assessed by fluoroscopy, whatever the state of subvalvular apparatus	Unfavorable anatomy for which the only option is valve replacement

Adapted from Iung B, Cormier B, Ducimetiere P, et al: Immediate results of percutaneous mitral commissurotomy. *Circulation* 94:2124-2130, 1996.

EXPERIENCE OF THE MEDICAL AND SURGICAL TEAMS

The incidence of technical failures and complications and the quality of results are related to the operator's experience.[3] PMC should be restricted to teams that have extensive experience with transseptal catheterization and are able to perform an adequate number of procedures. The interventionalists who perform PMC must also be able to perform emergency pericardiocentesis.

Because of the low prevalence of mitral stenosis in developed countries, ongoing experience is difficult to obtain.[45] It seems appropriate to concentrate the performance of the procedure in experienced centers so that the management of the interventional procedure is made more effective by improving the selection of patients through clinical evaluation and echocardiographic assessment and by decreasing risks.

INDICATIONS FOR PERCUTANEOUS MITRAL COMMISSUROTOMY

Selection of a candidate for PMC must be based on clinical and anatomic variables. Anatomy is a simple, practical way to select patients for PMC, even though it should not be the sole criterion (Figs. 51-7 and 51-8).

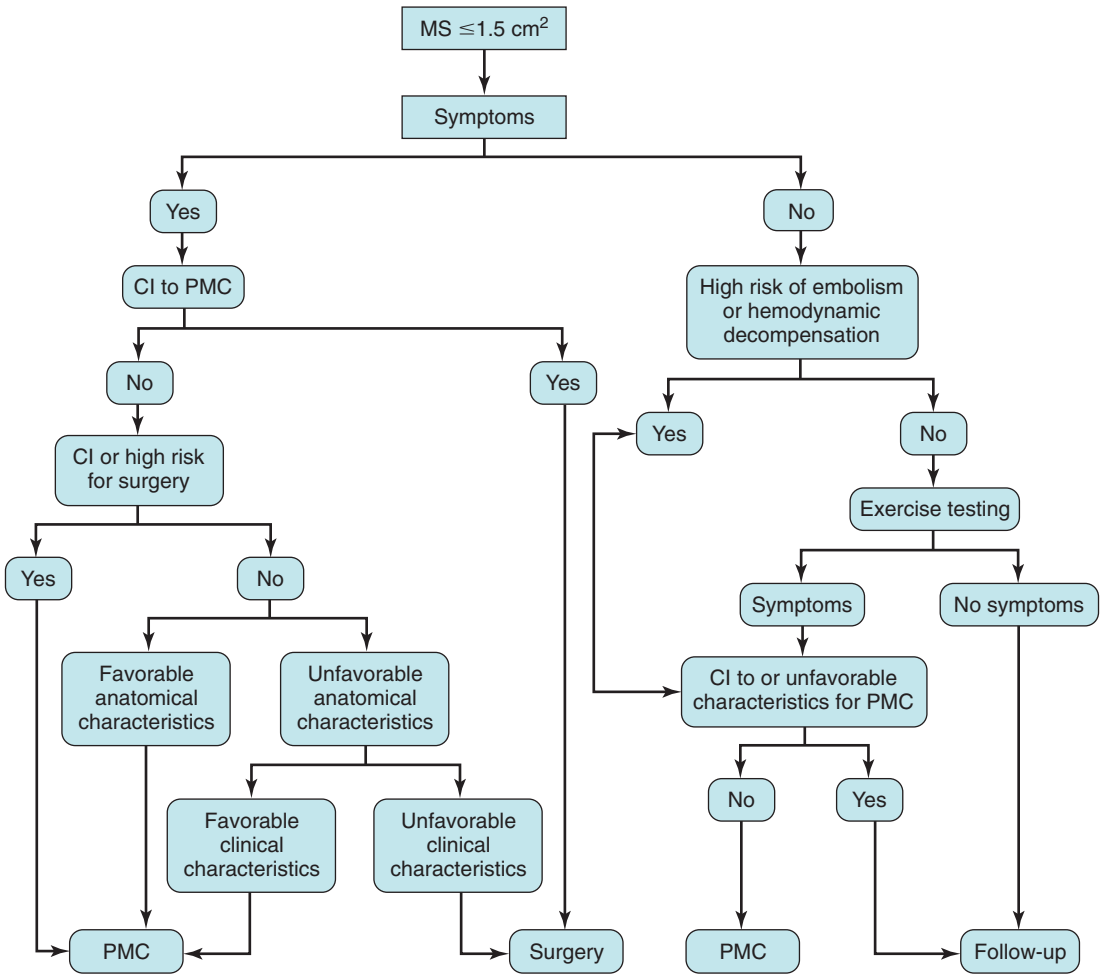


FIGURE 51-7 Management of severe mitral stenosis. Surgical commissurotomy may be considered by experienced surgical teams for patients with contraindications to percutaneous mitral commissurotomy. *CI,* Contraindication; *MS,* mitral stenosis; *PMC,* percutaneous mitral commissurotomy. (Modified from Vahanian A, Alfieri O, Andreotti F, et al: Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 33:2451-2496, 2012.)

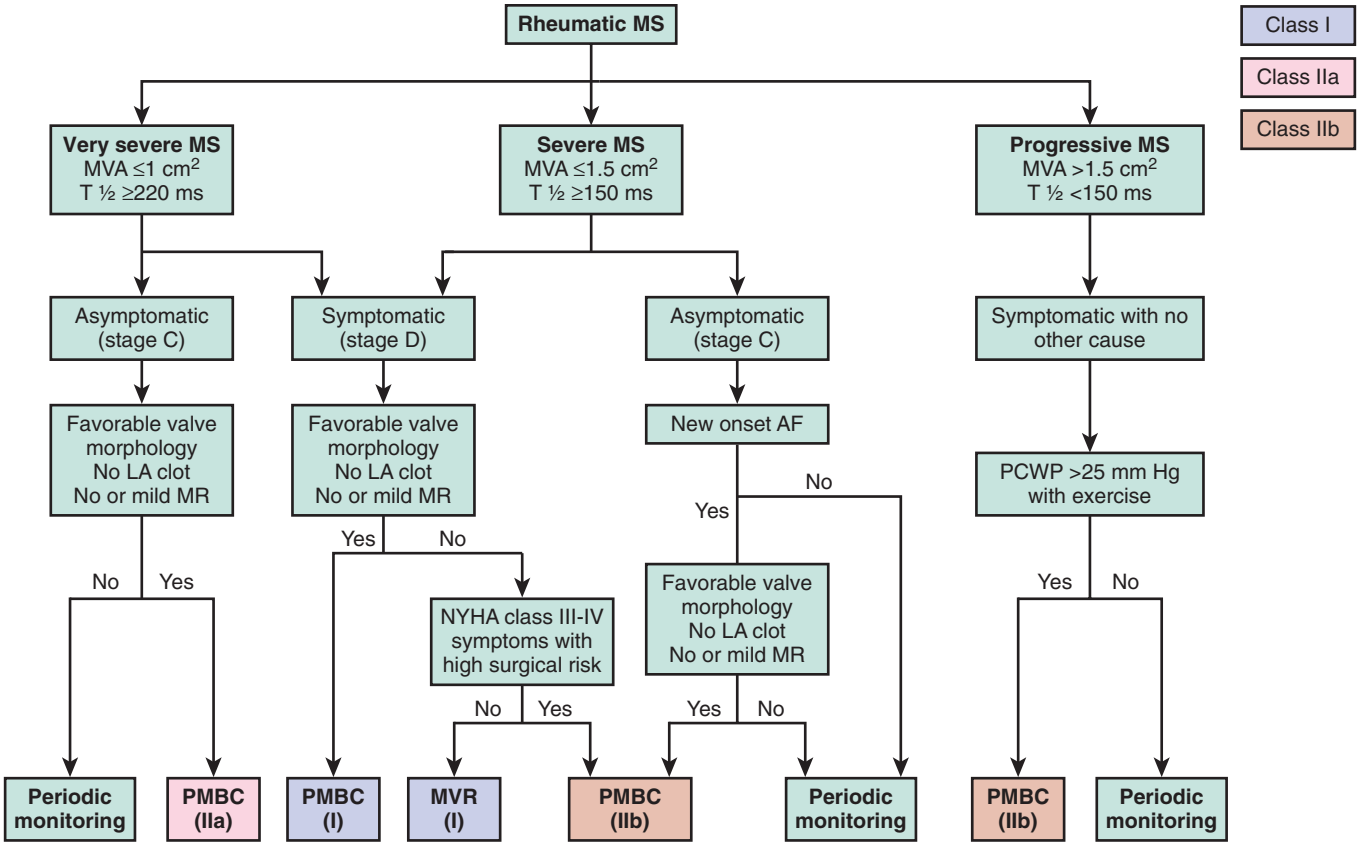


FIGURE 51-8 Indications for intervention for rheumatic mitral stenosis according to the ACC/AHA guidelines for the management of valvular heart disease. *AF,* Atrial fibrillation; *LA,* left atrial; *MR,* mitral regurgitation; *MS,* mitral stenosis; *MVA,* mitral valve area; *MVR,* mitral valve surgery (repair or replacement); *NYHA,* New York Heart Association; *PCWP,* pulmonary capillary wedge pressure; *PMBC,* percutaneous mitral balloon commissurotomy; *T ½,* pressure half-time.

The indication for PMC is clear when surgery is contraindicated and in ideal candidates such as young adults with good anatomy (e.g., pliable valves) and only moderate subvalvular disease (echocardiography score <8) (see Table 51-3).[46] In Europe, PMC has virtually replaced surgical commissurotomy.[47] PMC is the procedure of choice for patients with favorable anatomy, provided that it is affordable. If restenosis occurs, patients treated with valvuloplasty can undergo repeat balloon catheterization or surgery without the difficulties and inherent risks resulting from pericardial adhesions and chest wall scarring.

Much remains to be done to refine the indications for other patients, especially those with unfavorable anatomy, who are more common in Western countries. For this group, some advocate immediate surgery because of the less satisfying results of valvuloplasty, whereas others prefer valvuloplasty as an initial treatment for selected candidates, reserving surgery for cases of failure or late deterioration.[48] Unfortunately, data on these patients from randomized studies are not available, and a comparison of the results of balloon commissurotomy with those of surgical series is difficult because of differences in the patients involved and because the surgical alternative is valve replacement in most cases (because open commissurotomy is seldom performed).

Valve replacement has its drawbacks, including operative mortality, particularly for older adults; and prosthesis-related complications, which have a cumulative incidence that compromises the late outcome, particularly for young patients who are most susceptible to the risk of long-term deterioration. The indications in this subgroup must take into account its heterogeneity with respect to anatomy, especially the extent and location of calcification. Clinical status is vital because this group includes patients in good clinical condition and others who are not surgical candidates because of comorbidities. In this group of patients, we favor an individualistic approach that allows for the multifactorial nature of prediction. It is not possible to exclude the possibility of positive results for patients with unfavorable anatomy; consequently, we propose wider indications for valvuloplasty as the initial treatment of selected patients.

Current opinion is that surgery can be considered the treatment of choice for patients with bicommissural or heavy calcification. Conversely, data suggest that balloon valvuloplasty can be attempted as a first approach in patients with somewhat unfavorable anatomy, the more so because their clinical status argues in favor of it. The following cases fall into this category:

- Extensive lesions of the subvalvular apparatus
- Mild or moderate calcification, for which the 15-year event-free survival rates are 35% ± 4% and 24% ± 6%, respectively[49]
- Unicommissural calcification, for which successful PMC can be achieved in 73% of patients[48]

In these cases, surgery should be considered reasonably early if the results are unsatisfactory or there is secondary deterioration.

FUTURE PROSPECTS

The positive results that have been obtained with PMC during the past 20 years support the important place of this technique in the treatment of mitral stenosis. It has virtually replaced surgical commissurotomy. PMC is a proof of concept in the field of percutaneous structural intervention. The success was anticipated because it reproduces an

effective surgical procedure, and it is less invasive and carries a lower risk than surgery when performed in experienced centers.

Large-scale use of the technique could be beneficial in developing countries, where mitral stenosis occurs frequently in patients with anatomy favorable for PMC. However, application depends on the solution of logistic and economic problems. In developed countries, the problems are different because most candidates are older and have somewhat less favorable anatomy. Careful evaluation of results in this population is still needed to clearly define the indications for PMC and valve replacement.

Evaluation and treatment can be improved through better imaging, especially three-dimensional echocardiography. Further improvement may be achieved by combining PMC with other interventional procedures such as closure of the left atrial appendage, ablation of the pulmonary veins, and in the distant future, percutaneous mitral valve implantation in cases of contraindication and failure or deterioration after PMC. When treating mitral stenosis, we think that PMC and valve replacement must be considered complementary, not opposing, techniques. Each is applicable at the appropriate stage of the disease.

REFERENCES

1. Inoue K, Owaki T, Nakamura T, et al: Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg* 87:394–402, 1984.
2. Marijon E, Iung B, Mocumbi AO, et al: What are the differences in presentation of candidates for percutaneous mitral commissurotomy across the world and do they influence the results of the procedure? *Arch Cardiovasc Dis* 10:611–617, 2008.
3. Iung B, Nicoud-Houel A, Fondard O, et al: Temporal trends in percutaneous mitral commissurotomy over a 15-year period. *Eur Heart J* 25:701–707, 2004.
4. Silvestry FE, Kerber RE, Brook MM, et al: Echocardiography-guided interventions. *J Am Soc Echocardiogr* 22:213–231, 2009.
5. Palacios IF, Sanchez PL, Harrell LC, et al: Which patients benefit from percutaneous mitral balloon valvuloplasty? Prevalvuloplasty and postvalvuloplasty variables that predict long-term outcome. *Circulation* 105:1465–1471, 2002.
6. Messika-Zeitoun D, Brochet E, Holmin C, et al: Three-dimensional evaluation of the mitral valve area and commissural opening before and after percutaneous mitral commissurotomy in patients with mitral stenosis. *Eur Heart J* 28:72–79, 2007.
7. Arora R, Kalra GS, Sing S, et al: Percutaneous transvenous mitral commissurotomy: immediate and long-term follow-up results. *Catheter Cardiovasc Interv* 55:450–456, 2002.
8. Chen CR, Cheng TO: Percutaneous balloon mitral valvuloplasty by the Inoue technique: a multicenter study of 4832 patients in China. *Am Heart J* 129:1197–1202, 1995.
9. Ben Farhat M, Betbout F, Gamra H, et al: Predictors of long-term event-free survival and of freedom from restenosis after percutaneous balloon mitral commissurotomy. *Am Heart J* 142:1072–1079, 2001.
10. Varma PK, Theodore S, Neema PK, et al: Emergency surgery after percutaneous transmitral commissurotomy: operative versus echocardiographic findings, mechanisms of complications, and outcomes. *J Thorac Cardiovasc Surg* 130:772–776, 2005.
11. Zimet AD, Almeida AA, Harper RW, et al: Predictors of surgery after percutaneous mitral valvuloplasty. *Ann Thorac Surg* 82:828–833, 2006.
12. Jneid H, Cruz-Gonzalez I, Sanchez-Ledesma M, et al: Impact of pre- and postprocedural mitral regurgitation on outcomes after percutaneous mitral valvuloplasty for mitral stenosis. *Am J Cardiol* 104:1122–1127, 2009.
13. Kim M-J, Song J-K, Song J-M, et al: Long-term outcomes of significant mitral regurgitation after percutaneous mitral valvuloplasty. *Circulation* 114:2815–2822, 2006.
14. Cequier A, Bonan R, Dyrda I, et al: Atrial shunting after percutaneous mitral valvuloplasty. *Circulation* 81:1190–1197, 1990.
15. Bouleti C, Iung B, Laouénan C, et al: Late results of percutaneous mitral commissurotomy up to 20 years: development and validation of a risk score predicting late functional results from a series of 912 patients. *Circulation* 125:2119–2127, 2012.
16. Cruz-Gonzalez I, Sanchez-Ledesma M, Martin-Moreiras J, et al: Predicting success and long-term outcomes of percutaneous mitral valvuloplasty: a multifactorial score. *Am J Med* 122:581.e9–581.e11, 2009.
17. Ramondo A, Napodano M, Fraccaro C, et al: Relation of patient age to outcome of percutaneous mitral valvuloplasty. *Am J Cardiol* 98:1493–1500, 2006.
18. Kang DH, Park SW, Song JK, et al: Long-term clinical and echocardiographic outcome of percutaneous mitral valvuloplasty: randomized comparison of Inoue and double-balloon techniques. *J Am Coll Cardiol* 35:169–175, 2000.
19. Nunes MCP, Tan TC, Elmariah S, et al: The echo score revisited: impact of incorporating commissural morphology and leaflet displacement to the prediction of outcome for patients undergoing percutaneous mitral valvuloplasty. *Circulation* 129:886–895, 2014.
20. Messika-Zeitoun D, Blanc J, Iung B, et al: Impact of degree of commissural opening after percutaneous mitral commissurotomy on long-term outcome. *JACC Cardiovasc Imaging* 2:1–7, 2009.
21. Song JK, Song JM, Kang DH, et al: Restenosis and adverse clinical events after successful percutaneous mitral valvuloplasty: immediate post-procedural mitral valve area as an important prognosticator. *Eur Heart J* 30:1254–1262, 2009.
22. Wang A, Krasuski RA, Warner JJ, et al: Serial echocardiographic evaluation of restenosis after successful percutaneous mitral commissurotomy. *J Am Coll Cardiol* 39:328–334, 2002.
23. Hernandez R, Bañuelos C, Alfonso F, et al: Long-term clinical and echocardiographic follow-up after percutaneous mitral valvuloplasty with the Inoue balloon. *Circulation* 99:1580–1586, 1999.
24. Fawzy ME, Shoukri M, Al Buraiki J, et al: Seventeen years clinical and echocardiographic follow up of mitral balloon valvuloplasty in 520 patients, and predictors of long-term outcome. *J Heart Valve Dis* 16:454–460, 2007.
25. Hildick-Smith DJR, Taylor GJ, Shapiro LN: Inoue balloon mitral valvuloplasty: long-term clinical and echocardiographic follow-up of a predominantly unfavorable population. *Eur Heart J* 21:1691–1698, 2000.
26. Bouleti C, Iung B, Himbert D, et al: Long-term efficacy of percutaneous mitral commissurotomy for restenosis after previous mitral commissurotomy. *Heart* 99:1336–1341, 2013.
27. Bouleti C, Iung B, Himbert D, et al: Reinterventions after percutaneous mitral commissurotomy during long-term follow-up, up to 20 years: the role of repeat percutaneous mitral commissurotomy. *Eur Heart J* 34:1923–1929, 2013.
28. Turgeman Y, Atar S, Suleiman K, et al: Feasibility, safety, and morphologic predictors of outcome of repeat percutaneous balloon mitral commissurotomy. *Am J Cardiol* 95:989–991, 2005.
29. Kim JB, Ha JW, Kim JS, et al: Comparison of long-term outcome after mitral valve replacement or repeated balloon mitral valvotomy in patients with restenosis after previous balloon valvotomy. Does atrial fibrillation persist? *Europace* 5:47–53, 2003.
30. Chiang C-W, Lo S-K, Ko Y-S, et al: Predictors of systemic embolism in patients with mitral stenosis: a prospective study. *Ann Intern Med* 128:885–889, 1998.
31. Krasuski RA, Assar MD, Wang A, et al: Usefulness of percutaneous balloon mitral commissurotomy in preventing the development of atrial fibrillation in patients with mitral stenosis. *Am J Cardiol* 93:936–939, 2004.
32. Ben Fahrat M, Ayari M, Maatouk F: Percutaneous balloon versus surgical closed and open mitral commissurotomy: seven-year follow-up results of a randomized trial. *Circulation* 97:245–250, 1998.
33. Cardoso LF, Grinberg M, Pomerantzeff PM, et al: Comparison of open commissurotomy and balloon valvuloplasty in mitral stenosis: a five-year follow-up. *Arq Bras Cardiol* 83:248–252, 2004.
34. Song JK, Kim MJ, Yun SC, et al: Long-term outcomes of percutaneous mitral balloon valvuloplasty versus open cardiac surgery. *J Thorac Cardiovasc Surg* 139:103–110, 2010.
35. Vahanian A, Alfieri O, Andreotti F, et al: Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 33:2451–2496, 2012.
36. Nishimura RA, Otto CM, Bonow RO, et al: 2014 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 63:e57–e185, 2014.
37. Kang DH, Lee CH, Kim DH, et al: Early percutaneous mitral commissurotomy vs. conventional management in asymptomatic moderate mitral stenosis. *Eur Heart J* 33:1511–1517, 2012.
38. Maoqin S, Guoxiang H, Zhiyuan S, et al: The clinical and hemodynamic results of mitral balloon valvuloplasty for patients with mitral stenosis complicated by severe pulmonary hypertension. *Eur J Intern Med* 16:413–418, 2005.
39. Vahanian A, Ducrocq G: Emergencies in valve disease. *Curr Opin Crit Care* 14:555–560, 2008.
40. Esteves C, Munoz J, Braga S, et al: Immediate and long-term follow-up of percutaneous balloon mitral valvuloplasty in pregnant patients with rheumatic mitral stenosis. *Am J Cardiol* 98:812–816, 2006.
41. Fawzy ME, Hassan W, Shoukri M, et al: Immediate and long-term results of mitral balloon valvotomy for restenosis following previous surgical or balloon mitral commissurotomy. *Am J Cardiol* 96:971–975, 2005.
42. Shaw TRD, Northridge DB, Sutaria N: Mitral balloon valvotomy and left atrial thrombus. *Heart* 91:1088–1089, 2005.
43. Silaruks S, Thinkhamrop B, Kiatchoosakun S, et al: Resolution of left atrial thrombus after 6 months of anticoagulation in candidates for percutaneous transvenous mitral commissurotomy. *Ann Intern Med* 140:101–105, 2004.
44. Song H, Kang DH, Kim JH, et al: Percutaneous mitral valvuloplasty versus surgical treatment in mitral stenosis with severe tricuspid regurgitation. *Circulation* 116(Suppl):I246–I250, 2007.
45. Iung B, Vahanian A: Epidemiology of valvular heart disease in the adult. *Nat Rev Cardiol* 8:162–172, 2011.
46. Gamra H, Betbout F, Ben Hamda K, et al: Balloon mitral commissurotomy in juvenile rheumatic mitral stenosis: a ten-year clinical and echocardiographic actuarial results. *Eur Heart J* 24:1349–1356, 2003.
47. Iung B, Baron G, Butchart EG, et al: A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. *Eur Heart J* 13:1231–1243, 2003.
48. Dreyfus J, Cimadevilla C, Nguyen V, et al: Feasibility of percutaneous mitral commissurotomy in patients with commissural mitral valve calcification. *Eur Heart J* 35:1617–1623, 2014.
49. Bouleti C, Iung B, Himbert D, et al: Relationship between valve calcification and long-term results of percutaneous mitral commissurotomy for rheumatic mitral stenosis. *Circ Cardiovasc Interv* 7:381–389, 2014.

52 Percutaneous Mitral Valve Repair

AMAR KRISHNASWAMY | SAMIR R. KAPADIA

KEY POINTS

- Mitral regurgitation (MR) is a significant problem, and the number of patients with MR is growing together with an increase in the number of patients with congestive heart failure.
- Various percutaneous approaches to mitral valve repair are under preclinical and clinical investigation and show promise. These approaches are predominantly based on established surgical strategies and include edge-to-edge repair, direct and indirect annuloplasty methods, and chamber remodeling strategies.
- Different percutaneous techniques provide specific advantages, depending on the anatomic and functional characteristics of MR. Selection of the appropriate technique or techniques for each patient will ultimately determine the success of these emerging technologies.
- Integration of established imaging modalities both in and out of the catheterization laboratory is critical for the safety and efficacy of percutaneous repair technologies. The development of emerging imaging modalities will likely play a role in the future of percutaneous technologies.
- Evaluation of new percutaneous devices poses a significant challenge because these devices have to be compared with surgical or medical options depending on the surgical indication. It is likely that percutaneous techniques will play a complementary role to surgery or medical therapy.

Chronic mitral regurgitation (MR) poses a significant public health burden, with more than 3 million people in the United States alone suffering from moderate or severe MR.[1] Left untreated, chronic MR results in heart failure symptoms, left ventricular (LV) cavity dilatation and systolic dysfunction, enlargement of the left atrium (LA), atrial fibrillation, and pulmonary hypertension. Medical therapy may provide some relief from symptoms and is necessary to treat ischemic heart disease and heart failure in patients with MR and these underlying disease states. However, there has been no proven benefit of these treatments with regard to MR itself.[2] Therefore surgical correction with mitral valve repair (MVRe) or replacement remains the mainstay of therapy for chronic MR. However, because of the invasive nature of open heart surgery and the frequent presence of comorbidities in this group, up to 50% of patients with severe MR may not be offered surgery.[3] This is especially true for older patients and those with impaired LV function.[4] Further, the role of surgery in patients with functional MR (FMR) remains unproven.

As a result, percutaneous technology is poised to significantly alter the treatment paradigm for chronic MR. Percutaneous MVRe offers the potential benefits of decreased morbidity, improved recovery time, and shorter hospital stay compared with open heart surgery. Current percutaneous options are loosely based on surgical repair techniques, with four primary methods to accomplish a reduction in MR: (1) edge-to-edge (E2E) leaflet repair, (2) indirect coronary sinus annuloplasty, (3) direct annuloplasty, and (4) septal-lateral annular cinching. Percutaneous MV replacement is also being developed, although it is in its infancy. Overall, the field is very exciting, with promising initial studies highlighting the need for a better understanding of patient selection for appropriate management of MR.

MITRAL VALVE DISEASE

Mitral Valve Anatomy

The mitral valve (MV) complex is composed of the mitral annulus, anterior and posterior leaflets, chordae tendineae, and papillary muscles.[5] The mitral annulus is the elliptical area of attachment of the MV to the base of the LA (Fig. 52-1). The posterior leaflet has three lobes or "scallops": the lateral (P1), central (P2), and medial scallops (P3). The anterior leaflet scallops are named A1, A2, and A3, respectively, corresponding to the posterior scallops. The anatomic position of the valve is such that the two leaflets meet at the anterolateral and posteromedial commissures. Chordae connect the leaflets to both the anterolateral and the posteromedial papillary muscles. The primary chordae connect to the free edge of the leaflet; the secondary chordae ("strut" chords) are thicker and connect to the rough zone of the leaflet; and the tertiary chordae are short and connect the basal zone of the leaflet to the ventricular free wall.

Etiology and Mechanism of Mitral Regurgitation

Anatomic or functional abnormalities of any of the structures in the MV apparatus may lead to MR.[6,7] The disease process leading to MR may be primary MV disease, secondary regurgitation resulting from another cardiac disease, or MV involvement in a systemic inflammatory disease (Table 52-1). Various terminologies are used to characterize the mechanisms of MR. The morphologic description, proposed by Carpentier, classifies the mechanism of regurgitation according to leaflet pathophysiology (Fig. 52-2).[8] Type I regurgitation occurs in the presence of normal leaflet motion and is usually caused by annular dilatation or leaflet perforation. Type II is caused by leaflet prolapse, which is commonly the result of degenerative (myxomatous) disease, chordal elongation or rupture, or papillary muscle elongation or rupture. Type III is caused by restricted leaflet motion, which may arise from posterior wall motion abnormality or papillary muscle dysfunction due to ischemic cardiac disease. The restricted leaflet motion may also be caused by commissural fusion, leaflet or chordal thickening from rheumatic heart disease, or both.

This simplification has usefulness in terms of both the surgical approach and the percutaneous approach, because the goal of therapy is to restore normal leaflet function but not necessarily normal valve anatomy. Another common method of categorizing MR is based on the etiology and mechanism of the MR. This classification is commonly used in the literature to study the clinical outcomes of patients (Table 52-2). In this classification scheme, MR is loosely categorized on the basis of an abnormal or normal MV as degenerative or rheumatic disease (*primary MR*) and functional or ischemic disease (*secondary MR*), respectively. However, the terms *functional MR*, *ischemic MR*, and *secondary MR* are often used interchangeably and may represent many different mechanisms and morphologic variants.

Degenerative disease includes Barlow disease (myxomatous degeneration) and fibroelastic deficiency, both of which can result in MV leaflet prolapse and degenerative MR (DMR). Fibroelastic deficiency is the most common etiology (approximately 70%) among patients undergoing surgical MVRe in the United States. MR in rheumatic disease is a result of leaflet deformity caused by severe calcification and

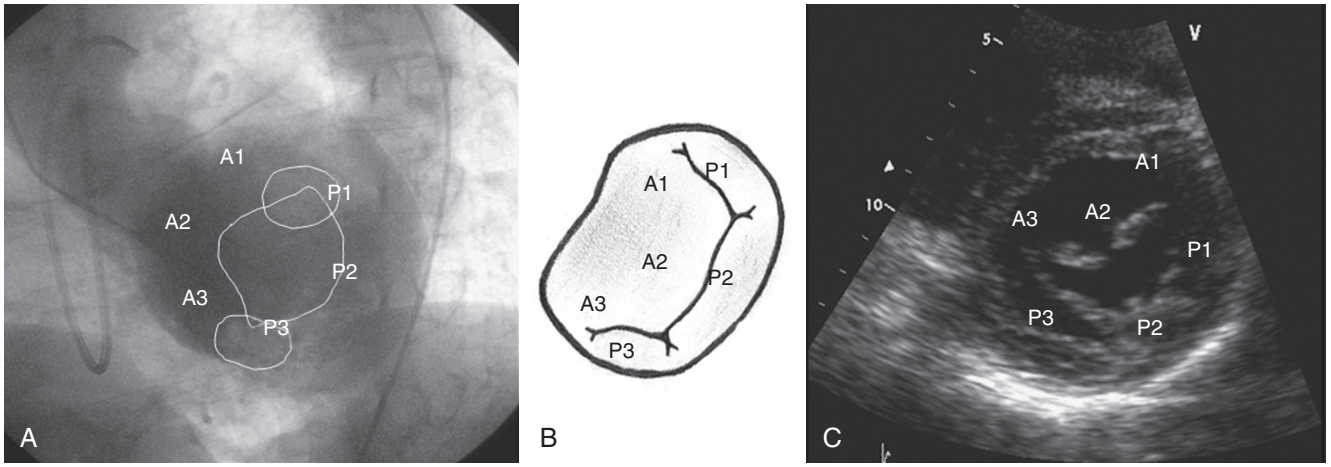


FIGURE 52-1 Mitral valve anatomy. **A,** Left ventriculogram in the left anterior oblique projection shows the mitral valve in short axis, with labeled leaflet segments. **B,** A schematic diagram of the mitral valve in short axis. **C,** A transthoracic echocardiographic image of the mitral valve in the parasternal short-axis projection. *A1, A2,* and *A3,* Lateral, central, and medial scallops of the anterior leaflet; *P1, P2,* and *P3,* lateral central, and medial scallops of the posterior leaflet.

TABLE 52-1 Causes of Chronic Mitral Regurgitation

Primary mitral valve disorder
Degenerative valve disease
Myxomatous degeneration
Fibroelastic deficiency
Rheumatic valve disease
Infective endocarditis
Chordal rupture
Idiopathic causes
Traumatic causes
Congenital lesions
Cleft anterior mitral leaflet or fenestration
Parachute mitral valve abnormality
Prosthetic valve disorder
Paravalvular regurgitation
Prosthetic valve degeneration
Prosthetic valve endocarditis
Secondary mitral valve disorder (cardiac cause)
Ischemic mitral regurgitation (coronary artery disease)
Papillary muscle dysfunction or rupture
Mitral valve annular dilatation
Global or regional ventricular dysfunction
Left ventricular dilatation
Dilatated (nonischemic) cardiomyopathy
Hypertrophic cardiomyopathy
Systemic or inflammatory disease
Systemic lupus erythematosus
Amyloidosis
Connective tissue disorder
Rheumatoid arthritis

apical leaflet doming. Although this is a common cause of MR worldwide, it is less frequently encountered in the United States.

FMR occurs in the setting of LV dysfunction and is seen in patients with coronary artery disease (ischemic MR) or with dilatated cardiomyopathy from other causes. Ischemic MR results from decreased closing force and increased tethering force on the leaflets.[9] Various factors can lessen the closing force, including diminished left ventricular ejection fraction (LVEF), LV dyssynchrony, and decreased annular contraction; similarly, many factors can increase the tethering force, including papillary muscle displacement, LV remodeling, and annular dilatation.[10-13] It is becoming increasingly clear that significant interaction among ventricular, valvular, and annular factors is involved in the generation, perpetuation, and progression of so-called functional MR (Fig. 52-3).

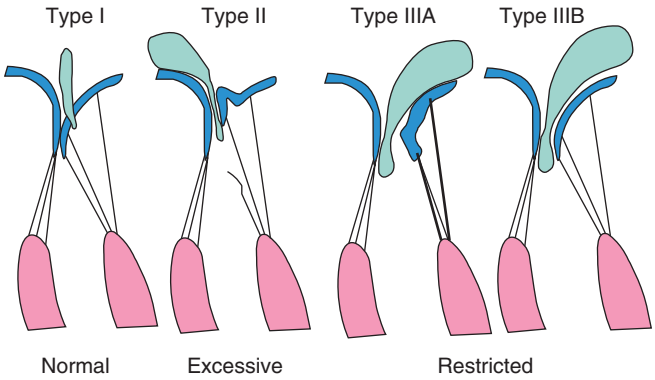


FIGURE 52-2 Carpentier classification of mitral regurgitation according to function leaflet mobility. Type I exhibits normal leaflet mobility, as with endocarditis. Type II exhibits excessive leaflet mobility, as in degenerative disease or mitral valve prolapse. Type IIIA exhibits restricted leaflet motion caused by chordal and leaflet thickening due to rheumatic heart disease. Type IIIB exhibits restricted leaflet motion caused by ventricular wall motion abnormality resulting from dilatated or ischemic cardiomyopathy.

TABLE 52-2 Carpentier's Morphologic Classification With Mechanisms of Mitral Regurgitation (MR)

Type I: Normal Leaflet Motion
Annular dilatation
Dilatated cardiomyopathy—"functional MR"*
Leaflet perforation
Annular calcification
Type II: Leaflet Prolapsed
Chordal rupture or flail leaflet
Chordal elongation—"degenerative MR"
Papillary muscle elongation
Papillary muscle rupture
Type III: Restricted Leaflet Motion
IIIA: Fibrosis of the subvalvular apparatus—"rheumatic MR"
IIIB: Regional left ventricular remodeling or wall motion abnormality—"ischemic MR"

*The term "functional MR" is sometimes used to describe both ischemic and nonischemic MR because they share the characteristics of left ventricular geometric remodeling and annular dilatation with normal leaflet morphology.

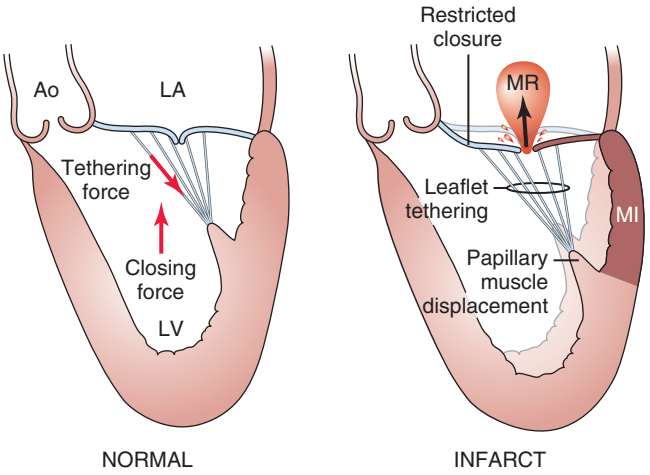
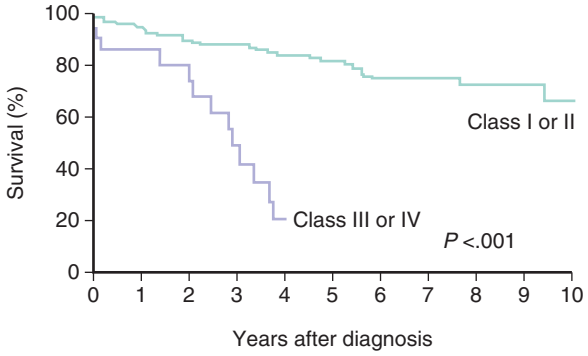


FIGURE 52-3 *Left panel,* Balance of forces acting on mitral leaflets in systole. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle. *Right panel,* Infarction causes LV cavity dilatation and papillary muscle displacement, which together result in annular dilatation, leaflet tethering, and restricted leaflet motion. Both factors contribute to functional mitral regurgitation (MR). Dark shading indicates inferobasal myocardial infarction (MI); light shading indicates normal baseline. (Modified from Liel-Cohen N, Guerrero JL, Otsuji Y, et al: Design of a new surgical approach for ventricular remodeling to relieve ischemic mitral regurgitation: insights from three-dimensional echocardiography. *Circulation* 101:2756-2763, 2000.)



No. at risk

Class I or II	162	117	102	95	80	69	50	33	20	12	7
Class III or IV	66	15	12	7	3						

FIGURE 52-4 Long-term survival of patients with flail leaflet according to New York Heart Association functional class. Survival is significantly less in patients with class III or IV heart failure. (From Ling LH, Enriquez-Sarano M, Seward JB, et al: Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl Med* 335:1417-1423, 1996.)

Natural History

The natural history of chronic MR depends on the degree of regurgitation, the cause of the underlying disorder, and the degree of LV dysfunction.[14-16] Available data on the natural history of the disease are limited by small sample size, selection bias, inconsistent measures of MR severity, and the inclusion of disparate etiologies of regurgitation. However, it appears that many patients with chronic MR remain asymptomatic for many years.[17] Among patients with mild MR, there is an inconsistent rate of progression to severe MR that appears to be independent of medical treatment.[18] When chronic severe MR is present, approximately 5% to 10% of patients per year develop significant symptoms, clinical indication for surgery, death, or all of these.[17,19]

Whether there is a small risk of sudden cardiac death in patients with severe asymptomatic MR remains controversial, and the data are not compelling enough to subject patients to intervention for this reason alone in the absence of other indications for MVRe.[19] The importance of symptoms in regard to long-term prognosis is demonstrated by the high mortality rate reported for patients with New York Heart Association (NYHA) class III or IV symptoms, even in degenerative MV disease (Fig. 52-4). LVEF is also an important independent predictor of outcome in patients with FMR.[16]

Patients with degenerative MV disease have a favorable long-term prognosis whether they are treated conservatively or, when indicated, surgically. However, patients with degenerative MV disease and coronary disease are fundamentally different from those with degenerative disease alone; the former have a worse prognosis that is dominated by the contribution of coronary disease.[15] Conversely, in the absence of degenerative disease, the presence and degree of MR after myocardial infarction is an independent predictor of mortality, emphasizing the need for accurate quantification; further studies are needed to investigate whether treatment of MR in these patients modifies outcomes.[20,21]

Imaging: Echocardiography

Echocardiography is the dominant modality for imaging the MV and for the assessment of MR severity. Two-dimensional transthoracic echocardiography (TTE) is useful to evaluate the valvular anatomy, to determine the structure and function of the LV, and to assess the origin and degree of regurgitation. Therefore TTE provides an understanding of MR severity as well as an insight into the primary or secondary nature of the disease. Furthermore, the anatomic assessment of the MV and the LV also allows determination of whether surgical or percutaneous MVRe may be feasible or whether valve replacement will be necessary. Longitudinal data collected by serial echocardiography may be used to determine the timing of intervention and to follow up the results. If transthoracic images are not adequate, transesophageal echocardiography (TEE) provides an excellent assessment of MV anatomy and severity of regurgitation. This can be particularly useful to determine whether valve repair is feasible.

Evaluation of the severity of valvular regurgitation with echocardiography relies heavily on Doppler methods, including color, pulsed-wave, and continuous-wave Doppler. The American Society of Echocardiography has determined the qualitative and quantitative echocardiographic parameters that are useful in grading MR (Table 52-3).[22] The assessment of severity should rely on the integration of both quantitative and qualitative measures obtained by Doppler techniques.[23] In addition, structural findings such as a flail leaflet or an enlarged LA can add useful information with regard to regurgitation severity.

Color Doppler provides a number of qualitative and quantitative means to determine MR severity. A proximal flow convergence on color Doppler is present in severe regurgitation. The proximal isovelocity surface area (PISA) of this flow convergence can be used to accurately quantitate the effective regurgitant orifice area (EROA).[24] The width of the regurgitant jet at or just downstream from the regurgitant orifice is known as the *vena contracta* and is slightly smaller than the anatomic regurgitant orifice.[25] This distinction is particularly relevant in some patients with FMR, in which the regurgitant orifice has a slit-like rather than an oval shape. The area of the MR jet occupying the LA can provide a rapid semiquantitative assessment of regurgitation severity. However, this is influenced by instrument factors (e.g., gain) and by jet orientation (e.g., a central jet may appear more severe than an equally large jet that adheres to the atrial wall). In addition, the color jet area is influenced by the driving pressure across the valve and can

TABLE 52-3 Qualitative and Quantitative Parameters Useful in Grading Mitral Regurgitation Severity

	Mild	Moderate	Severe
Structural Parameters			
LA size	Normal	Normal or dilatated	Usually dilatated
LV size	Normal	Normal or dilatated	Usually dilatated
Mitral leaflets or support apparatus	Normal or abnormal	Normal or abnormal	Abnormal/flail leaflet/ruptured papillary muscle
Doppler Parameters			
Color flow jet area	Small, central jet (usually <4 cm^2 or <20% of LA area	Variable	Large central jet (usually >10 cm^2 or >40% of LA area) or variable size wall-impinging jet swirling in LA
Mitral inflow—PW	A wave dominant	Variable	E wave dominant
Jet density—CW	Incomplete or faint	Dense	Dense
Jet contour—CW	Parabolic	Usually parabolic	Early peaking—triangular
Pulmonary vein flow	Systolic dominance	Systolic blunting	Systolic flow reversal
Quantitative Parameters			
Vena contracta width (cm)	<0.3	0.3-0.69	≥0.7
Regurgitant volume (mL/beat)	<30	30-59	≥60
Regurgitant fraction (%)	<30	30-49	≥50
EROA (cm^2)	<0.20	0.20-0.39	≥0.40

CW, Continuous wave; *EROA,* effective regurgitant orifice area; *LA,* left atrium; *LV,* left ventricle; *PW,* pulse wave.
Data from Zoghbi WA, Enriquez-Sarano M, Foster E, et al: Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 16(7):777, 2003.

be enhanced by elevated blood pressure. Color Doppler imaging is also important in the parasternal short-axis view to determine the origin of the MR jet because percutaneous approaches (especially the MitraClip) are more effective in centrally originating jets than in medial or lateral ones.

Regurgitant volume can be assessed with the use of continuous-wave Doppler data. Regurgitant volume is calculated by applying the continuity equation (conservation of mass), in which left-sided regurgitation volume is calculated as the difference between Doppler-derived flows across the aortic and mitral valves.[26] The stroke volume equals the cross-sectional area of the valve annulus, multiplied by the velocity-time integral of flow across the annulus. The regurgitant volume at the MV is calculated as the difference between stroke volumes across the MV and the aortic valve. This can also be expressed as a regurgitant fraction.

Pulsed-wave Doppler is useful to assess the effect of regurgitation on the pulmonary venous flow. A pulmonary venous flow that is blunted or reversed in systole can indicate severe regurgitation.[27,28] The contour and density of the regurgitant envelope on continuous-wave Doppler is also useful: A dense, early-peaking, or triangular envelope is most consistent with severe regurgitation. In addition, the mitral inflow pattern is typically E-wave dominant (>1.2 m/sec) in severe regurgitation, reflecting increased flow across the valve.

Alternative Imaging Modalities

Although historically, echocardiography has been the dominant imaging modality in the assessment of MR, cardiac computed tomography (CT), cardiac magnetic resonance imaging (MRI), and three-dimensional (3-D) echocardiography are beginning to play more important roles.[23,29-31] Coronary sinus devices that indirectly alter annular geometry are under development, so the relationship of the coronary sinus to the mitral annulus is becoming increasingly important (Fig. 52-5). In addition, the coronary sinus and left circumflex arteries are close to each other and overlap in more than 90% of patients, creating the potential for cinching devices to hinder coronary blood flow.[32] Cardiac CT has the potential to provide significant anatomic details in the screening of patients and procedural planning.

With cardiac MRI, it is possible to obtain significant structural information regarding the geometry of the LV, mitral annulus, and leaflets, as well as quantitative regurgitant volumes.[31] It is likely that regurgitant volumes calculated with the use of cardiac MRI are more accurate and more operator or reader independent compared with those derived from TTE. However, limited experience with this modality currently limits its usefulness for research purposes.

3-D Echocardiography is a developing imaging modality that provides a more in-depth understanding of the anatomy of the MV apparatus and the changes of MR. Because the position of the MV apparatus in the LV can be disrupted in all directions, 3-D echocardiography is more likely to define the exact mechanism of MR in ischemic disease and to detect multiple jets of MR that may affect the treatment approach.[33] Furthermore, with recent advances, the ability to acquire real-time 3-D images allows use of the procedure to gauge safety and efficacy during both percutaneous and traditional surgical repairs.

SURGICAL MITRAL VALVE REPAIR

The American College of Cardiology and American Heart Association (ACC/AHA) guidelines provide a framework for patient selection and timing of MV surgery.[34] Any patient with acute severe MR should undergo valve surgery. Valve surgery is also recommended for patients with chronic severe MR in the presence of symptoms and for patients without symptoms in the presence of LV systolic dysfunction or LV cavity dilatation (end-systolic dimension >40 mm). Valve surgery results in the preservation of LV function and improved survival.[35,36]

The onset of atrial fibrillation or the development of significant pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg at rest or >60 mm Hg with exercise) in an asymptomatic patient with normal LV size and systolic function is a reasonable indication for surgery. Management of asymptomatic patients with severe MR and normal LV size and function remains controversial, but surgery is considered reasonable at centers where repair is likely (>95% chance) and has a low operative risk (<1%); this is provided a class IIa recommendation in the most recent ACC/AHA Guidelines.[34,37,38]

MVRe is the preferred method for surgical management of MR to restore normal leaflet function and annular size.[34] When compared with MV replacement, the major advantages of MVRe are improved survival, preservation of LV function, freedom from anticoagulation, and fewer complications.[39,40] Despite the advantages of MVRe, this technique appears to be underutilized: fewer than 50% of the patients undergoing MV surgery currently receive a repair procedure, even though about 90% are suitable.[41,42]

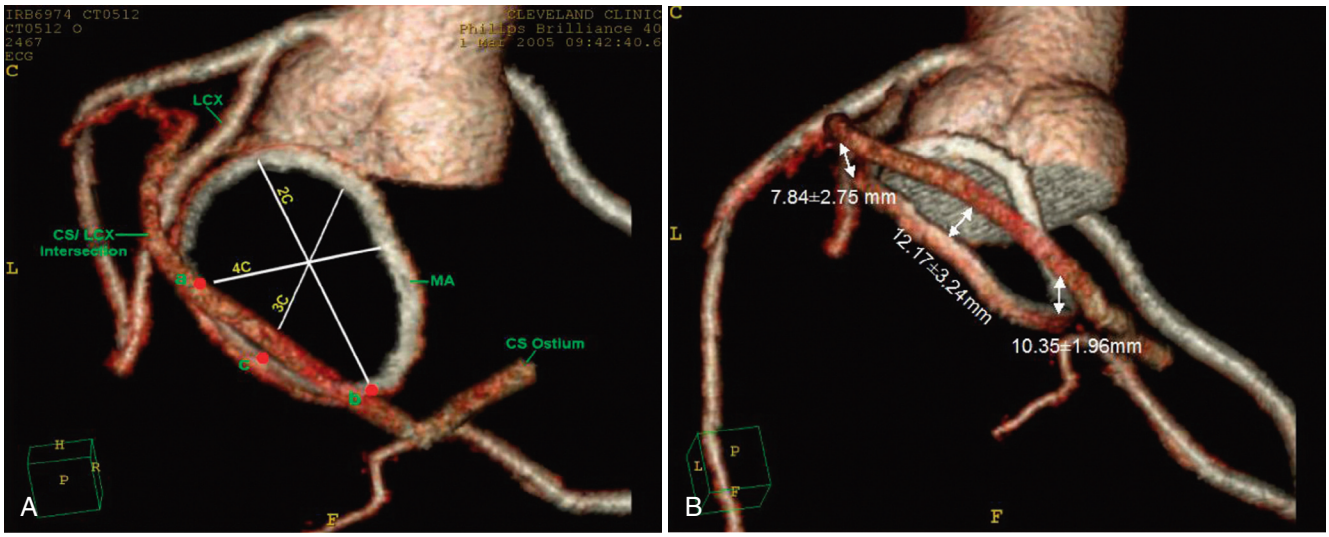


FIGURE 52-5 Computed tomographic images of the relationships among the mitral annulus (MA), the coronary sinus (CS), and the left circumflex (LCX) coronary artery. **A,** The CS travels along the posterior MA and crosses over the LCX artery. **B,** The distance between the MA and the CS varies depending on the location along the annulus.

Surgical Approach

MV surgery can be performed via median sternotomy, a minimally invasive approach that uses partial upper sternotomy or small right thoracotomy, or it can be performed robotically through multiple "ports." Median sternotomy is required if concomitant coronary artery bypass is undertaken. Cardioplegic arrest and cardiopulmonary bypass are necessary regardless of the type of chest wall incision, although typically less than 1 hour is required for a valve repair.[8] Techniques of repair address the annulus (annuloplasty with or without a rigid or flexible ring, decalcification, débridement), the leaflets (triangular or quadrangular resection, sliding annuloplasty, patch enlargement, decalcification, E2E repair), the chordae (resection or elongation of chords), the myocardium itself (e.g., remodeling through the Dor procedure, plication of scar, pericardial cushions, transventricular slings), the papillary muscles (realignment), or some combination of all these.

Isolated Annuloplasty

Isolated mitral annuloplasty is usually reserved for patients with FMR. Available annuloplasty techniques include suture alone, suture with buttressing material, and prosthetic annuloplasty devices. The choice of annuloplasty technique is surgeon and patient specific. A prosthetic annuloplasty band or ring is placed to correct annular dilatation, increase leaflet coaptation by reducing the anteroposterior dimension of the annulus, and prevent future annular dilatation.

Annuloplasty for FMR results in significant improvement in NYHA class, decreased hospital admissions for heart failure, and modest survival rates of 71% to 82% at 2 years and 58% at 5 years. Although favorable changes in LV size, shape, and function have been demonstrated after successful MVRe, a propensity analysis failed to demonstrate any mortality benefit compared with matched patients not undergoing valve surgery.[38,43] The recurrence rate of FMR after isolated annuloplasty is disappointing (28% at 1 year) and, along with the usually comorbid conditions of this patient population, remains a limitation to widespread use of the procedure.[44]

Annuloplasty With Leaflet Repair

The combination of annuloplasty and leaflet repair, referred to as *Carpentier's techniques*, is most frequently performed for degenerative MV disease. Among the surgical methods of mitral leaflet repair, correction of posterior leaflet or bileaflet prolapse is the most common. Posterior leaflet prolapse occurs in most cases of degenerative MV disease and is the primary cause of regurgitation in approximately 50% of patients. Prolapse results from chordal elongation or rupture and affects the central P2 segment most frequently. This type of problem is most often corrected by posterior leaflet quadrangular resection and plication of the valve annulus,[8] usually accompanied by the placement of a prosthetic annuloplasty ring except in cases of severe calcification of the annulus.

Anterior leaflet prolapse, although less common than posterior leaflet prolapse, is a more challenging problem and has been commonly treated with initial valve replacement. However, several methods have been developed to treat anterior leaflet prolapse with leaflet repair. The most common are chordal transfer, artificial chordae creation, and the Alfieri E2E repair. Chordal transfer is performed by resection of a segment of the posterior leaflet, which is then transferred and sewn to the prolapsing segment of the anterior leaflet. A quadrangular repair of the anterior leaflet completes this procedure. Another method of anterior leaflet repair involves the creation of artificial chordae from Gore-Tex sutures. These artificial chordae are attached to the prolapsing leaflet and the papillary muscle by pledgeted sutures.

The long-term results for mortality, recurrent MR, and reoperation with MVRe in experienced centers are outstanding and are far superior than those for MV replacement, and the mortality rate is similar to that of the general population (86% to 93% survival at 5 years).[45-48] The Cleveland Clinic has achieved excellent results, including a 0.3% operative mortality rate, and a 10-year freedom-from-reoperation rate of 93% in a reported series of 1000 consecutive patients (Fig. 52-6).[47]

Isolated Leaflet Repair With Edge-to-Edge Technique

Dr. Ottavio Alfieri (Milan, Italy) pioneered a creative repair known as the double-orifice, or E2E, technique. This procedure was initially developed for anterior leaflet prolapse: the free edges of the anterior and the posterior leaflets are sewn together in an attempt to increase leaflet contact and coaptation and reduce regurgitation.[49] This technique also works for repair of posterior leaflet and bileaflet prolapse.[50] The resulting double-orifice MV usually does not cause stenosis, even when combined with an annuloplasty ring.

The first report of this technique was published in 1998.[49] A larger series, published in 2001, consisted of 260 patients who underwent E2E repair, 81% of whom had DMR, and 80% of whom also had an

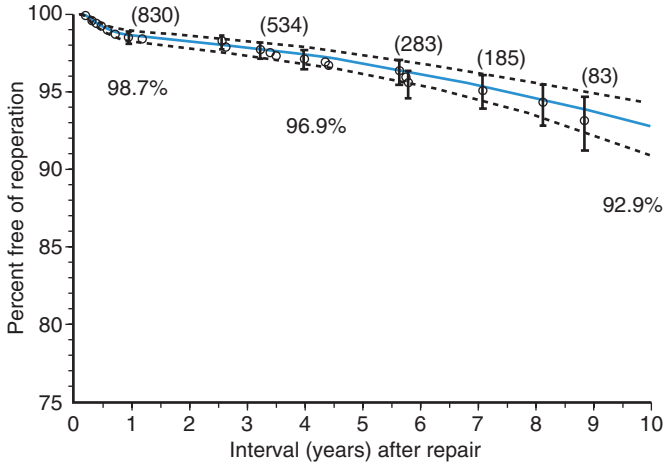


FIGURE 52-6 Freedom from reoperation after standard Carpentier repair for degenerative disease. (From Gillinov AM, Cosgrove DM, Blackstone EH, et al: Durability of mitral valve repair for degenerative disease. *J Thorac Cardiovasc Surg* 116:734, 1998.)

annuloplasty ring placed.[51] There was a low rate of in-hospital mortality (0.7%), and overall survival was good (94% at 5 years), with 95% freedom from reoperation (see Fig. 52-8). Most patients (>80%) were NYHA class I or II. A subsequent report comparing patients who did with patients who did not receive concomitant annuloplasty demonstrated worse freedom from significant MR and a higher rate of reoperation in those with isolated E2E repair.[52]

Following Dr. Alfieri's lead, the technique was adopted into practice at many prominent institutions performing MVRe, although usually as a specialized technique and not as a primary method. The introduction of percutaneous E2E repair has fueled interest in the surgical outcomes of this procedure, leading to the publication of a number of single-center case series.[50,51,53-56] The procedure has been applied to both DMR and ischemic MR with favorable results. Although the surgical double-orifice MVRe has been shown to be effective as a treatment for structural or functional MV disease, the surgical literature is limited by a lack of data on isolated E2E repair.[57]

A series of patients with up to 18 years (mean 9.2 years) of follow-up after surgical E2E repair was recently published by Dr. Alfieri's group.[58] Of the 61 patients, 36 did not have concomitant annuloplasty due to heavy annular calcification or limited annular dilatation. The average age was 64 years, the average LVEF was 60%, and the indications for surgery were bileaflet prolapse/flail (46%), anterior prolapse/flail (18%), and posterior prolapse/flail (36%). Survival at 12 years was 51%, and freedom from reoperation was 58%. Of these 36 patients, 55% had 3+ or greater MR, and residual MR greater than 1+ at hospital discharge was a significant predictor of severe MR at follow-up (hazard ratio, 3.8; 95% confidence interval, 1.7 to 8.2; $P = .001$). Although this was a small series, these results question the long-term benefit of isolated E2E repair in a group of relatively young patients with DMR and may be relevant to the discussion of percutaneous E2E repair in young and otherwise healthy patients.

Percutaneous Mitral Valve Repair

The aim of percutaneous strategies for MVRe is to provide relief from severe MR in patients who would otherwise not be candidates for surgical correction or in those who prefer a less invasive approach without the need for cardiopulmonary bypass. The latter is a more difficult proposition, especially in patients with primary (degenerative) MR, given the historical success and safety of surgical MVRe in treating this problem. These new technologies have shown promise in their various stages of evolution from preclinical to randomized trials.

TABLE 52-4 Percutaneous or Minimally Invasive Mitral Valve Repair Devices Under Development

Device Design	Developmental Phase
Edge-to-Edge Leaflet Repair	
MitraClip (Evalve, Menlo Park, CA)	FDA approval for DMR Phase III trial for FMR CE Mark approval
Indirect Annuloplasty via Coronary Sinus	
CARILLON Mitral Contour System (Cardiac Dimensions, Kirkland, WA)	Phase II trial enrolling CE Mark approval
Cardiac Chamber Remodeling	
iCoapsys (Myocor, Maple Grove, MN)	First-in-human implants Development halted
Basal Annuloplasty of the Cardia Externally (BACE) (Mardil, Plymouth, MN)	First-in-human implants Development halted
PS3 System (Ample Medical, Foster City, CA)	First-in-human implants Development halted
Direct Annuloplasty	
Mitralign Direct Annuloplasty System (Mitralign, Salem, NH)	First-in-human implants Phase II clinical trial
GDS Accucinch Annuloplasty system (Guided Delivery Systems, Santa Clara, CA)	First-in-human implants
Valtech Cardioband Annuloplasty System (Valtech Cardio, Or-Yehuda, Israel)	Phase II clinical trial
Other Annuloplasty Devices	
QuantumCor RF Annuloplasty (Quantumcor, Lake Forest, CA)	Animal studies
Artificial Chordae Insertion	
NeoChord DS1000 system (NeoChord, Minneapolis, MN)	First-in-human implants
Transcatheter Mitral Valve Replacement	
Tiara valve (Neovasc, Inc,, Richmond, Ontario, Canada)	First-in-human implants
Medtronic Transcatheter Mitral Valve (Medtronic, Minneapolis, MN)	Animal studies
Edwards FORTIS Transcatheter Mitral Valve (Edwards Lifesciences, Irvine, CA)	First-in-human implants

DMR, Degenerative mitral regurgitation; *FDA,* U.S. Food and Drug Administration; *FMR,* functional mitral regurgitation; *RF,* radiofrequency.

There are currently five major approaches to percutaneous repair. The best-studied approach is the E2E repair, based loosely on the surgical repair championed by Dr. Alfieri. The second approach uses the proximity of the coronary sinus to the mitral annulus to accomplish favorable changes in annular geometry, bringing the posterior leaflet toward the anterior leaflet and thereby improving coaptation. In the third approach, LV reshaping, which accomplishes a reduction in septal-to-lateral diameter and improves leaflet coaptation, can reduce MR. In the fourth approach, called the transventricular (direct) approach, mitral annuloplasty is performed by various methods. Another novel approach involves the implantation of artificial chordae. Finally, recent preclinical and clinical work in transcatheter MV replacement has produced interesting results (Table 52-4).

Edge-to-Edge (Double-Orifice) Leaflet Repair With the MitraClip System

The MitraClip system (Evalve, Menlo Park, CA) is the best-studied of the options for percutaneous MVRe, and results of a randomized trial of its use were reported in 2010.[59] The device uses a 24-Fr steerable delivery guide catheter and a transseptal approach to place a V-shaped clip (MitraClip) on the mitral leaflets, effectively achieving a double-orifice repair similar to the Alfieri stitch (Fig. 52-7).[60] The clip is

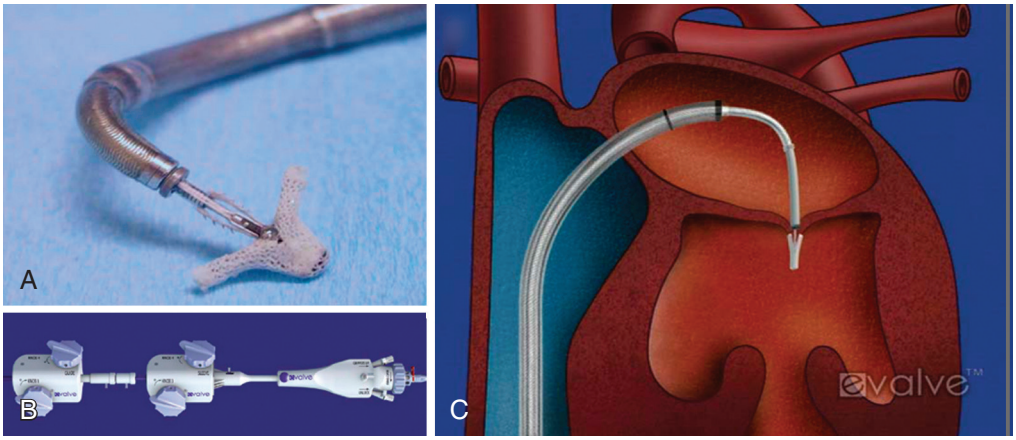


FIGURE 52-7 The MitraClip device and delivery system. **A,** The device with gripper arms open, attached to the delivery catheter. **B,** The device delivery manipulation system. **C,** A schematic diagram of placement of the delivery catheter and device across the septum and on the mitral valve before device release.

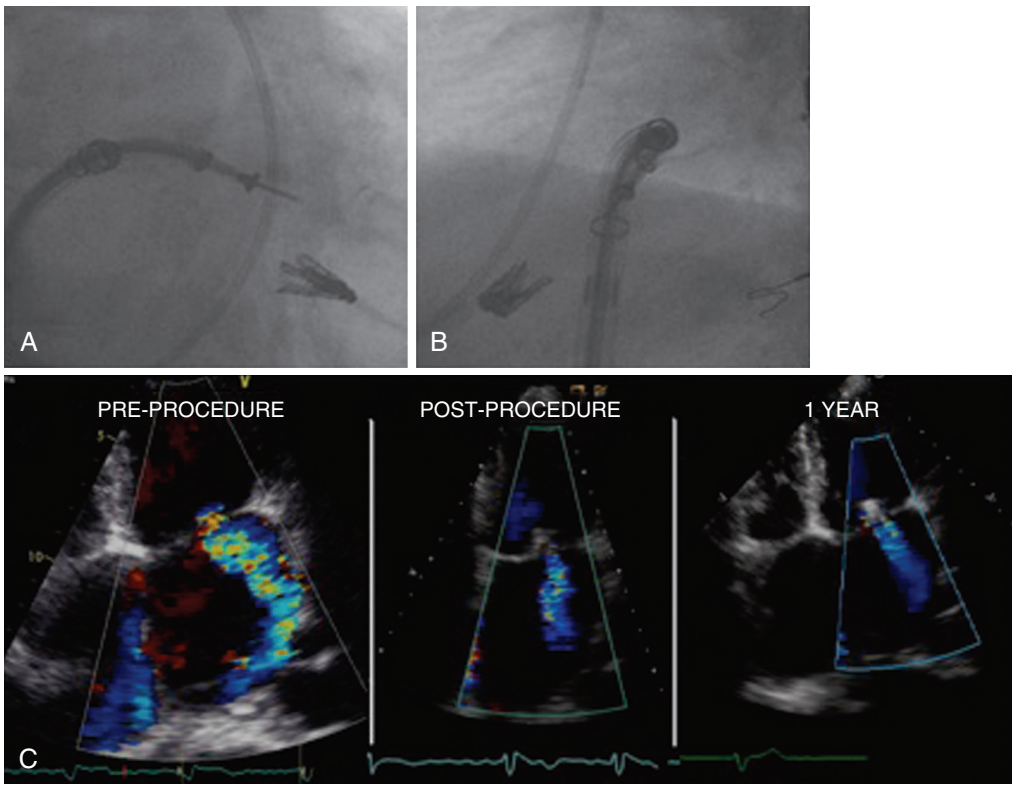


FIGURE 52-8 MitraClip implantation. **A,** Right anterior oblique projection shows the two clips and a single delivery catheter after the second clip has been released. **B,** Left anterior oblique projection. **C,** Transthoracic echocardiography images of a patient before, immediately after, and 1 year after percutaneous mitral valve repair with the Evalve MitraClip.

introduced via the guiding catheter into the LA, where the arms of the clip are opened when the clip is aligned with the long axis of the heart. The arms of the clip are rotated until they are perpendicular to the line of coaptation of the valve leaflets. The open clip is advanced into the LV and retracted during systole to grasp the middle scallops of the anterior and posterior valve leaflets in the gripper arms. Positioning is confirmed with TEE, and the clip is locked into position. If needed, the clip can be reopened, detached from the leaflets, and withdrawn into the LA, and the process can be repeated until a satisfactory functional double orifice is created. When the positioning is considered adequate, the clip is released and remains attached to the MV leaflets. Eventually, fibrosis and scarring occur in the bridging segment, similar to that seen with surgical E2E repair (Fig. 52-8).[61]

MitraClip for Degenerative Mitral Regurgitation

Initial results from 27 patients in the phase I prospective, multicenter safety and feasibility trial called EVEREST I (Endovascular Valve Edge-to-Edge Repair Study I) were published in 2005.[62] All patients had moderate to severe MR (3+ or 4+), and most had primary MR (93%). Patients with rheumatic disease, severe mitral annular calcification,

severe LV systolic dysfunction, or severe LV cavity dilatation were excluded. The clip was successfully deployed initially in 24 patients (89%), and 3 patients went on to successful surgical repair[6] or replacement.[5] Of the 27 original patients, 13 (48%) received a clip successfully and remained with MR severity 2+ or less at 6-month follow-up. The 2-year results of the first human implantation have also been reported and showed only mild regurgitation and positive ventricular remodeling.[63] The primary end point of EVEREST I was acute safety at 30 days, defined as freedom from death, myocardial infarction, cardiac tamponade, cardiac surgery for failed clip, clip detachment, stroke, or septicemia. Ultimately, only 15% of patients experienced a major adverse cardiac event (three clip detachments and one permanent stroke), less than the 34.4% required based on comparison with surgical event rates, thus demonstrating noninferiority for the clip.

The pivotal EVEREST II trial randomized 279 patients in a 2:1 fashion, assigning 184 to the MitraClip group and 95 to surgery.[64] Of these subjects, 73% had DMR. One primary end point was a safety end point (major adverse events such as death, stroke, myocardial infarction, reoperation, and transfusion), which was designed to show superiority of the endovascular strategy. At 30 days, the primary safety end point was experienced by 9.6% of the percutaneous group and 57% of the surgical (control) group, although much of this difference was accounted for by the need for transfusion of more than 2 units of blood in the surgical group (53.2%, compared with 8.8% in the percutaneous group). Also notable, however, was the lack of death, major stroke, urgent/emergent surgery, or MV reoperation in any of the 136 MitraClip patients who achieved acute procedural success.

The second primary end point was for efficacy and was designed to show noninferiority to cardiac surgery with respect to a composite end point of freedom from surgery for valve dysfunction, death, or MR 2+ or worse. Analysis of clinical effectiveness showed the MitraClip to be noninferior to surgery (72.4% versus 87.8%, with a prespecified margin for noninferiority of 31%). At 4 years' follow-up, Mauri and colleagues demonstrated similar survival (mortality rate, 17.4% versus 17.8%) and functional improvement, although patients receiving the clip had a much higher need for MV surgery (24.8% versus 5.5%).[65] The presence of MR of 3+ or 4+ (18.8% versus 3.0%) was greater with MitraClip at 1 year, although there was no significant difference in worsening MR or need for MV intervention between years 1 and 4. Subgroup analysis demonstrated that patients with FMR may derive greater benefit from the MitraClip (see later discussion).

Given the excellent results of MVRe in patients with DMR who had acceptable surgical risk, interest turned to the use of the MitraClip for those patients at prohibitive surgical risk. The published experience consists of 127 patients in EVEREST II and the high-risk Real-World Expanded Multi-Center Study of the MitraClip System (REALISM) continued access registry.[66] The mean age of the group was 82 years; 48% had prior cardiac surgery; and 86% had NYHA III or IV symptoms. Despite a predicted 30-day mortality rate of 13.2% based on mean Society of Thoracic Surgeons (STS) score, the observed mortality rate was only 6.3%. Mortality at 1 year was 23.6% and was correlated to the degree of residual MR at the time of index hospital discharge. Of the surviving patients, at 87% were in NYHA Class II or II at 1 year, and 85% had 2+ or less MR.

The safety and efficacy of the MitraClip thus far has been encouraging, especially for patients who are at high risk for complications from surgical MV surgery. Given the published data, the U.S. Food and Drug Administration (FDA), in 2013, approved the device for use in patients with DMR who are considered to be at prohibitive risk for surgery.

MitraClip for Functional Mitral Regurgitation

As mentioned previously, surgery in patients with FMR is generally high risk, has poor durability, and is associated with worse overall survival than in patients with DMR.[67,68] As a result, the major professional societies, including the ACC/AHA, the European Society of Cardiology (ESC), and the International Society for Heart and Lung Transplantation (ISHLT) provide a class IIb indication for MV surgery in patients with FMR. A percutaneous strategy to improve MR and quality of life in these patients would be an important advance, and use of the MitraClip for this indication has produced encouraging results.

Among 149 patients with FMR included in the high-risk surgical cohort of EVEREST II and the continued access registry, 63% had prior cardiac surgery and 87% had NYHA class III or IV symptoms.[69] Despite their high-risk profile, these patients demonstrated a low (4.7%) mortality rate at 30 days. At 1 year, 82% had 2+ or less MR, and patients demonstrated significant reduction in LV volumes. The ACCESS-EU trial (A Two-Phase Observational Study of the MitraClip System in Europe) involved 567 high-risk patients, including 393 patients (69%) with FMR; the average Logistic EuroSCORE (predicted mortality according to a logistic regression equation) was 23.[70] Of the patients with FMR, 66% had an LVEF of less than 40%. Despite the high-risk profile, the mortality rate was only 2.8% at 30 days and 17% at 1 year. At 1 year, 78.6% of the FMR patients had 2+ or less MR, and 71% of the entire group had NYHA class I or II symptoms.

The understanding that FMR patients fare relatively better with MitraClip than with surgical repair (as opposed to patients with DMR who are able to undergo surgery) is reflected in the clinical enrollment of the major trials. Whereas FMR patients constituted only 26% of the EVEREST I trial, they made up 71% of the EVEREST II/REALISM high-risk cohort and 77% of the ACCESS-EU registry. Furthermore, 67% of the European commercial MitraClip experience has been in patients with FMR. This indication is not approved by the U.S. FDA, and patients with FMR who have prohibitive risks for surgery must be randomized to medical therapy versus MitraClip as part of the upcoming Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial.

ANNULOPLASTY-BASED MITRAL VALVE REPAIR

Annuloplasty is an integral part of MVRe in most surgical approaches to improving MV leaflet coaptation and reducing MR, and it usually achieves a reduction in mitral annulus diameter of 25% or more. The coronary sinus covers about 50% of the mitral annulus perimeter and 80% of the posterior intertrigonal distance.[71] Indirect annuloplasty uses the anatomic proximity of the coronary sinus to the mitral annulus to modulate annular size and shape. However, there are several challenges to exploiting this relationship. The proximity and location of the coronary sinus to the annulus is variable (see Fig. 52-5).[72] Furthermore, the left circumflex artery crosses between the myocardium and the coronary sinus in almost 50% of patients, increasing the risk of arterial compromise.[71,72] Because pf marginal results and financial difficulties, most of the indirect annuloplasty devices are no longer available except the CARILLON Mitral Contour System developed by Cardiac Dimensions (Kirkland, WA). Other approaches include direct annuloplasty, radiofrequency or ultrasound energy delivery to shrink the annulus, and "cinching" devices to remodel the annulus. These are all in various phases of development and clinic use. Proper definition of the anatomic relationships with various imaging techniques, including cardiac CT, angiography, and echocardiography, may be helpful in matching the appropriate approach to the anatomy.

Indirect Annuloplasty

CARILLON Mitral Contour System

The CARILLON Mitral Contour System is a fixed-length, double-anchor device (Fig. 52-9) that is advanced through a catheter and positioned in the coronary sinus. After the device is deployed and locked into position, tension is applied to the anchors of the device, resulting in tissue plication that reduces the MV annular diameter and MR. The procedure is performed percutaneously with internal jugular vein access followed by distal coronary sinus cannulation with a 9-Fr catheter. A measuring catheter is used to determine the optimal positioning of the distal anchor in the coronary sinus. The nitinol annuloplasty device is advanced down the catheter to the target position in

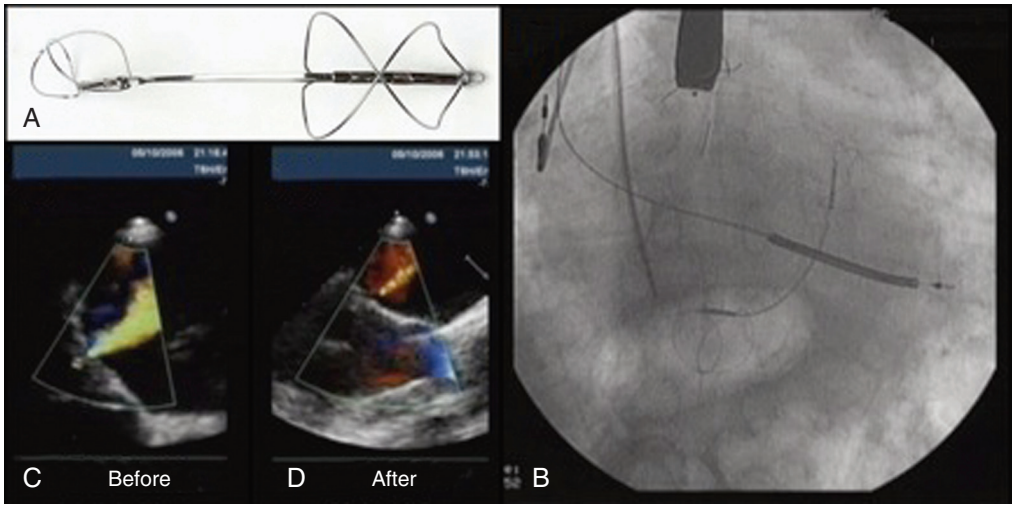


FIGURE 52-9 The CARILLON Mitral Contour System. **A,** Photograph of the device with proximal and distal anchors and tension element. **B,** A fluoroscopic image of the device in place in the coronary sinus. **C,** An echocardiographic image of mitral regurgitation before device placement. **D,** The same view after device placement shows a significant reduction in the color jet of mitral regurgitation. (Courtesy Cardiac Dimensions, Kirkland, WA.)

the coronary sinus. The distal anchor of the device is deployed by passive expansion and is locked into the fully expanded position by use of the delivery catheter. Tension is placed on the delivery system, bringing the proximal anchor toward the coronary sinus ostium. The amount of tension can be manipulated as needed to optimize reduction in annular dimension (approximately 25%) and reduction in MR, which is verified by real-time echocardiography. If the device position is considered to be optimal, the proximal anchor is deployed and locked into position in a similar fashion. If there is a concern about safety or efficacy, the device can be recaptured by advancing the delivery catheter over the device to collapse the anchors, and the apparatus can be adjusted or removed as necessary.

Clinical feasibility was evaluated in the prospective CARILLON Mitral Annuloplasty Device European Union Study (AMADEUS) trial using the next-generation CARILLON XE device in 48 patients with FMR and LV systolic dysfunction.[73] The device was successfully implanted in 30 patients. At the 6-month follow-up, there was a durable and significant decrease in mitral annulus diameter (from 4.2 to 3.78 cm [10%]), MR (average reduction, 23%), and NYHA class (from 2.9 to 1.8), as well as improvement in the quality-of-life score and 6-minute walk testing (from 307 to 403 meters). Of the remaining 18 patients, 5 did not receive implantation because of coronary sinus–related complications ($n = 3$) or fluoroscopic equipment failure ($n = 2$), and 13 patients had retrieval of the device after implantation because of inadequate MR reduction or coronary compromise. With respect to safety, six patients (13%) experienced a total of seven complications within 30 days of the procedure: one patient died of multiorgan failure, three experienced myocardial infarction (none requiring percutaneous coronary intervention), and three experienced coronary sinus dissection or perforation. The complications were clustered early in the experience and resulted in changes to the implantation procedure; improvement in safety was observed later in the study. On the basis of this early work, the CARILLON system was granted the CE mark of approval for use in Europe.

Improvements to the device were evaluated in the follow-up Tighten the Annulus Now (TITAN) study, which enrolled 53 patients at eight centers across Europe. The 36 patients in whom implantation was successful were compared with the 17 patients in whom the device was retrieved. Patients were relatively young (mean age, 62 years) with a mean LVEF of 28% and NYHA class III symptoms. Mortality was 1.9% at 30 days and 22.6% at 12 months, without a substantial difference between those who did and did not receive an implant. There was an average 50% reduction in regurgitant volume in the implanted patients, compared with a relatively stable volume in nonimplanted patients. LV systolic and diastolic volumes were significantly decreased in the implanted patients, whereas those nonimplanted demonstrated increase in volumes. Reduction in NYHA class from III to II was sustained in the implanted group out to 2 years.[74]

Direct Annuloplasty

Mitralign Direct Annuloplasty System

Based on the concept of direct suture annuloplasty, the Mitralign Direct Annuloplasty System (Mitralign, Tewksbury, MA) uses a device composed of three metal anchors connected by standard suture material. The anchors are placed in the mitral annulus, and the suture is cinched to perform the annuloplasty. The device is placed via retrograde ventricular access with the use of a unique translation catheter with a two-pronged "bi-dent" design for device delivery. The initial design used a magnetic guiding catheter placed in the coronary sinus, but in the most recent iteration, the anchors are placed from the ventricular side using standard imaging techniques. The two anchors are positioned below the valve at the level of each posterior leaflet scallop and then deployed directly through the mitral annulus; they remain connected by suture material. The suture is then cinched, directly plicating the annulus and emulating the results of a surgical, suture-based annuloplasty.

Successful implantation in one patient in South America and two patients in Europe was reported in 2008 as part of the pilot clinical study. Recently, the results of implantation in 15 high-risk patients with FMR was reported[75]: two patients required surgery, and at 30 days 80% of the patients had 2+ or less MR accompanied by significant quality-of-life improvement. The 61-patient CE mark trial has completed enrollment, though data have not yet been presented.

GDS AccuCinch Annuloplasty System

Another device currently under development is the GDS Accucinch Annuloplasty System (Guided Delivery Systems, Santa Clara, CA). Like the Mitralign, it provides a catheter-based, retrograde transventricular approach to place anchors in the myocardium directly beneath the mitral annulus, yielding a plication annuloplasty. No results of device implantation have been formally published, although some reports have been made. Among 18 patients who underwent implantation, 5 were converted to surgery, and no patients died within 30 days.

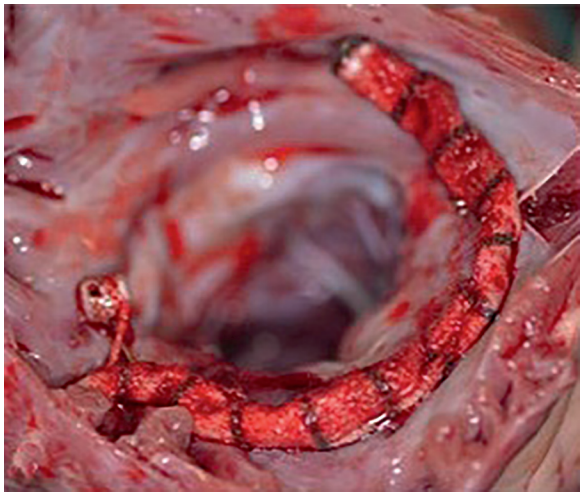


FIGURE 52-10 Valtech Cardioband direct annuloplasty system (Valtech Cardio, Or-Yehuda, Israel) in place in the posterior mitral annulus. (Modified from Taramasso M, Maisano F: Transcatheter mitral valve repair: transcatheter mitral valve annuloplasty. *EuroIntervention* 10: U129-U135, 2014.)

Valtech Cardioband Annuloplasty System

The Valtech Cardioband Annuloplasty System (Valtech Cardio, Or-Yehuda, Israel) is implanted via a transseptal route. The device consists of a Dacron band that is implanted from trigone to trigone using multiple anchors (Fig. 52-10). The length of the band is then shortened under echocardiography guidance to provide optimal leaflet coaptation. Recently presented results of the procedure in 24 patients with FMR are encouraging.[76] There was an average 20% reduction in annular dimension, and 85% of patients had 1+ or less MR at hospital discharge. At 6 months, 88% had NYHA I or II symptoms, and 88% had MR 2+ or less.

Cardiac Chamber Remodeling Devices

FMR caused by dilatated cardiomyopathy and ischemic MR caused by geometric alterations affect not only the mitral annulus but also the LA and the LV and their relationships to the annulus. One potential limitation of the typical ring annuloplasty is that it does not address these alterations in paravalvular geometry. Devices have therefore been engineered with this consideration in mind. However, financial hardship has led to abandonment of the Coapsys device, and the PS3 and BACE devices have been demonstrated only in limited use. They are included here for historical reference.

Coapsys and iCoapsys

The Coapsys (Myocor, Maple Grove, MN) annuloplasty system involves the surgical placement of pericardial implants off pump. These implants are placed on the epicardial surface of the heart, with a tethering subvalvular cord that crosses the ventricle internally. This cord is then cinched to decrease the mitral annulus diameter and eliminate MR. Advantages of the Coapsys system include the ability to treat FMR off pump, which allows the combination of off-pump bypass and MVRe. Conceptually, the device provides a more comprehensive mechanism of action by preserving normal valve dynamics and addressing the mitral annulus as well as the subvalvular space and abnormal LV geometry.

In the initial clinical feasibility trial, the device was successfully implanted in 34 patients with FMR at the time of bypass surgery. Data on the first 11 patients completing 1-year follow-up confirmed the durability of MR decrease (grade, from 2.9 to 1.1; jet area, from 7.4 cm^2 to 3.0 cm^2) and NYHA class improvement (from 2.5 to 1.2) at 12 months.[70] A U.S. randomized trial (Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve [RESTORE-MV]) enrolled patients with coronary artery disease and ischemic MR, comparing traditional open-heart coronary artery bypass grafting (CABG) with MVRe to CABG with Coapsys device placement. Intraoperative results from this trial were reported for the first 19 patients receiving the implant and showed a reduction in MR grade, from 2.7 ± 0.8 to 0.4 ± 0.7, after implantation ($P < .0001$).[71] Because of funding issues, the trial was prematurely terminated after randomization of 165 patients (77 treated with MVRe and 87 with Coapsys); the results of this trial have not yet been published.

A percutaneous version of the system, the iCoapsys, is implanted through a pericardial access sheath. The ingeniously designed device was tried in two patients, but the Valvular and Ventricular Improvement Via iCoapsys Delivery (VIVID) trial of clinical feasibility was prematurely discontinued because of financial constraints.[72]

Percutaneous Septal Sinus Shortening System

The Percutaneous Septal Sinus Shortening (PS3) system (Ample Medical, Foster City, CA) differs from the Coapsys system in that it creates a transatrial bridge rather than a transventricular bridge. This device uses the coronary sinus and a septal closure device to place a cord across the atrium, create tension on the annulus, and remodel the mitral annulus and the LA. Septal-lateral annular cinching occurs because of traction applied between the interatrial septum and the coronary sinus at the level of the P2 mitral segment.

Palacios and colleagues published the first human use of the PS3 in two patients with FMR. Both patients received implants before planned open heart surgery (at which time the device was removed). The results were encouraging, with a reduction in MR grade from 2 to 1 in one patient and from 3 to 1 in the other. There was a substantial reduction in mitral annulus diameter (31% in one patient and 29% in the other), comparable to that achieved with surgical annuloplasty and greater than that achieved by other percutaneous coronary sinus–based indirect annuloplasty devices. No further testing is being done because of financial constraints.

Basal Annuloplasty of the Cardia Externally

The Basal Annuloplasty of the Cardia Externally (BACE) device (Mardil, Plymouth, MN) is a silicone band that is slipped around the base of the heart and positioned at the atrioventricular groove to "cinch" the annular and subvalvular LV and provide improved MV coaptation.[77] The device is sutured to the myocardium, and chambers in the band are filled with saline to provide the appropriate level of LV support. Among nine sheep with FMR induced by continuous pacing, five sheep survived to 6-month follow-up. The MR was reduced from grade 4 to 0, a benefit that was sustained at 6 months. A follow-up study of five patients with depressed LVEF undergoing CABG who were implanted with the BACE device demonstrated a reduction in MR from an average of grade 3.3 to grade 0.8 (<1 in all patients). There were no device-specific complications.

Other Annuloplasty Devices

The application of subablative radiofrequency (RF) energy to remodel the mitral annulus is being investigated by QuantumCor (Lake Forest, CA).[74] The concept, termed *transventricular annulus remodeling*, relies on scarring and shrinkage of the mitral annulus after application of RF energy directly to the annulus. The device is intended for both surgical and transcatheter (transseptal) uses; it has a malleable tip with seven electrodes to deliver RF energy. The catheter is connected to a pulse generator that is modulated by temperature sensors in the electrodes to regulate the amount and duration of energy delivery. The catheter can be manipulated to deliver energy to specific locations on the annulus, allowing for adjustment of the procedure to individual anatomy. Human data are not available.

Artificial Chord Implantation

The NeoChord DS1000 system (NeoChord, Minneapolis, MN) allows transapical implantation of chordae on a beating heart without the need for cardiopulmonary bypass. Results of the Transapical Artificial Chordae Tendinae (TACT) trial, a prospective study in 30 patients at seven centers, were recently published.[78] Patients on average were 64 years of age with an LVEF of 59%, and all had severe MR due to isolated posterior leaflet prolapse. Six patients underwent conversion to standard MVRe, four suffered early chord dehiscence, and two did not demonstrate acute procedure success and required standard MVRe. Acute procedural success was defined as reduction of MR to 2+ or less and was achieved in 26 patients (86.7%); four patients did not have NeoChords placed and underwent standard MVRe. One patient died as a result of sepsis. At 30-day follow-up, 17 (58.6%) of 29 patients continued with 2+ or less MR. Although these results are not as good as those of traditional MVRe, the less invasive nature of this procedure demonstrates an interesting option for these patients. Further study is expected.

TRANSCATHETER MITRAL VALVE REPLACEMENT

Whereas transcatheter aortic valve implantation has made significant progress, and thousands of successful implantations have been performed, transcatheter mitral valve implantation has been applied in only a handful of patients. In large part, this is because radial force, which is used to secure aortic prostheses in a calcified aortic root, cannot be applied as easily in the mitral position. Furthermore, the saddle-shaped and dynamic mitral annulus that moves with each cardiac cycle makes it difficult to securely place a transcatheter prosthesis. A few valves are in preclinical or early clinical use (Fig. 52-11).

Transcatheter Mitral Valve Devices

The Tiara valve (Neovasc, Richmond, Ontario, Canada) is a transapically implanted, self-expanding valve constructed of a metal alloy frame and bovine pericardial leaflets. It is implanted via a transapical approach. Initial animal studies demonstrated successful implantation in 29 of 36 swine without any migration or embolization.[79] Subsequent implantation was performed in seven cows that were monitored for 150 days. Six of these animals had mild or moderate paravalvular leak over the follow-up period, perhaps due to size mismatch in the setting of only one available prosthesis size. Two patients underwent implantation in early 2014; both were not candidates for surgery because of their severe FMR with an LVEF of 20% to 30%. The procedures were performed without complication. One patient had trivial paravalvular leak and a well-functioning valve but died 69 days later due to progressive cardiac and renal failure. The other patient had no paravalvular leak at follow-up and was alive at 5 months with NYHA class II symptoms.

Medtronic's transcatheter mitral valve (Medtronic, Minneapolis, MN) consists of a self-expanding nitinol frame that is deployed via a surgical transatrial approach[80] A transseptal device is currently under development. Animal studies have been performed, reportedly with good success and minimal paravalvular leak. First-in-man implantation is expected soon.

The Edwards FORTIS transcatheter mitral valve (Edwards Lifesciences, Irvine, CA) is a cloth-covered, self-expanding nitinol stent with three bovine pericardial leaflets that is implanted via a transapical approach.[81] Results of implantation in five patients considered inoperable for traditional open heart surgery were recently reported. Two patients had successful implantation with good device function and trivial MR and were doing well at follow-up. One patient had a good result of the valve replacement, with echocardiography 30 days later demonstrating good prosthesis function, but died at day 76 due to

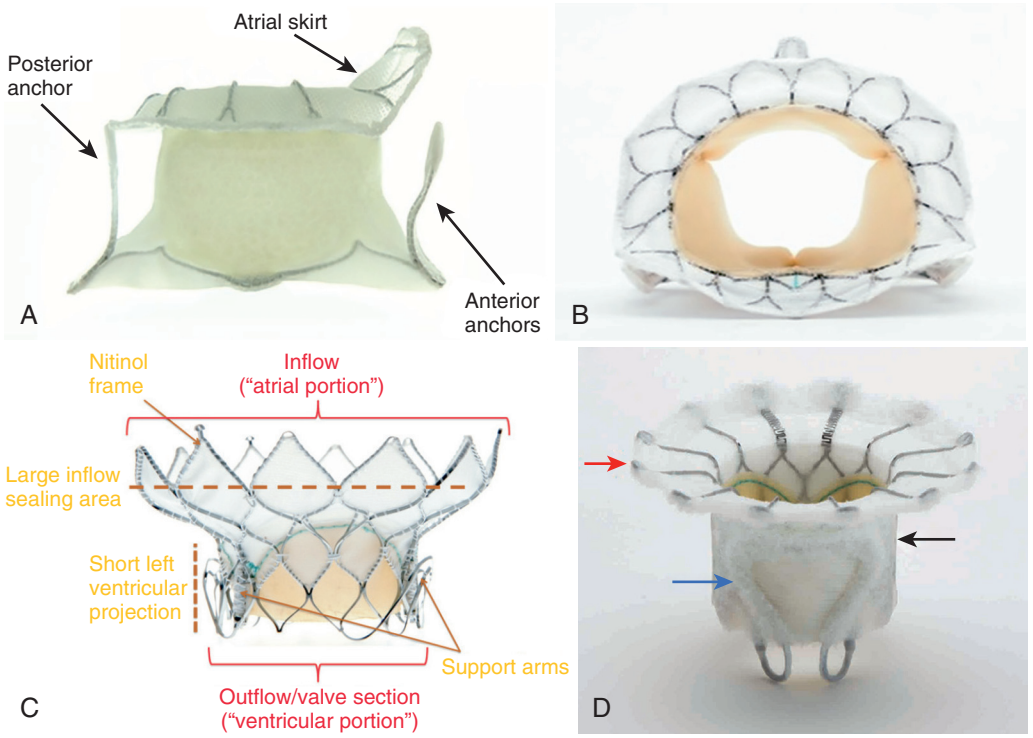


FIGURE 52-11 Transcatheter mitral valve replacement technologies. **A** and **B,** Tiara mitral valve. **C,** Medtronic mitral valve. **D,** Edwards FORTIS Valve. (**A** and **B,** From Cheung A, Stub D, Moss R, et al: Transcatheter mitral valve implantation with Tiara bioprosthesis. *EuroIntervention* 10:U115-U119, 2014; **C,** from Piazza N, Bolling S, Moat N, Treede H: Medtronic transcatheter mitral valve replacement, *EuroIntervention* 10:U112-U114, 2014; **D,** from Bapat V, Buellesfeld L, Peterson MD, et al: Transcatheter mitral valve implantation (TMVI) using the Edwards FORTIS device. *EuroIntervention* 10:U120-U128, 2014.)

progressive heart failure. In another patient, placement was difficult because of an LV apical aneurysm that necessitated a suboptimal transapical cannulation site. Despite initial successful placement, the valve was found to be displaced 2 days later, and the patient ultimately died. In a fifth patient, initial placement appeared successful but repeat echocardiography 15 days later in the setting of sepsis demonstrated reduced leaflet motion and prosthetic mitral stenosis; the patient died later that day.

Patient Selection

Indications for percutaneous intervention for MR remain similar to those for surgical intervention.[33] Although there has been some interest in lowering the threshold for the severity of MR for percutaneous therapies, with the contention that these treatments are less invasive and safer, there are no data to implement such liberalization. The major excitement in the field is derived from the ability to provide options for patients with higher surgical risk who are symptomatic with severe MR and who do not have any other options. The surgical risk assessment should take into consideration not just the estimated mortality but also the morbidity and the risk of compromising quality of life. With this in mind, the most common target for these therapies, at least initially, will be older patients (irrespective of the etiology of MR) with poor LV function and patients with severe FMR, as identified in the Euro Survey, who are not undergoing surgical intervention. It is difficult to justify the use of these techniques in young patients with degenerative MV disease who are otherwise appropriate candidates for surgical MVRe. However, the fact that some of these therapies usually do not impair future surgical options is encouraging.

In many ways, percutaneous MV therapies fit the mold of "personalized medicine," which has been cast in the world of pharmacotherapy. Identifying the mechanisms of MR and then defining the anatomy to predict whether a certain device will work is critical to the clinical application of these procedures. A clear understanding of the specific pathology causing MR is necessary to determine whether a percutaneous E2E repair is required or whether annular dilatation needs to be addressed with a direct or indirect annuloplasty device. A comprehensive understanding of imaging technologies and parameters is key to success. Currently, in the United States, only the MitraClip is available as a commercial device, and only for patients with DMR. With the availability of some of these devices in Europe under the CE mark of approval, clinical data are accumulating to shed more light on the proper selection of patients.

FUTURE DIRECTIONS

Percutaneous MVRe is an exciting new field with many devices at early stages of preclinical and clinical evaluation. Most strategies are based on principles learned from surgical MVRe techniques. The most advanced technique is the E2E repair, although interesting data are accumulating for a variety of the direct and indirect annuloplasty techniques. Percutaneous MVRe has the potential to be a "preventive" technology, because it may be applied early in the disease course to alter the natural history of MR by disrupting the pathologic feedback loop of MR and LV dysfunction.

It is unclear whether percutaneous devices need to eliminate all of the MR to be effective. If a percutaneous repair can achieve a significant and durable reduction of MR, albeit not complete elimination, it may still remain a worthy procedure if it prevents clinical events. However, it is important that percutaneous devices preserve future surgical options. If the procedure is safe, is relatively free of complications, and preserves surgical options, then the "nothing to lose" standard may be applied to these devices.

The need to determine which patients should be targeted in clinical trials is still present. Trials may have to address specific populations and progressively expand the role of these therapies to lower-risk surgical populations. Surgical techniques are beginning to be tailored to the specific valve anatomy, but the percutaneous techniques, in their investigational stages, continue to be limited to one type of device per patient. It seems likely that the future of percutaneous repair will be a combination of techniques to address the complexity of MR in most patients. However, this poses significant limitations to the device development process with current regulations, and the use of multiple devices in the same patient is unlikely at the present time in the United States.

Percutaneous devices are becoming more specifically tailored to the etiology of MR and the anatomy of the individual patient; thus the proper imaging and patient selection criteria for each device will have to be learned by interventionalists. Improvements both in imaging techniques and in the interpretation of these techniques with regard to percutaneous repair will be necessary in preprocedural planning, in assessing intraprocedural efficacy and complications, and in postprocedural follow-up. Finally, it will be critical to develop collegial interaction among the specialties of cardiac imaging, interventional cardiology, and cardiothoracic surgery to achieve proper patient selection and clinical advancement in this burgeoning field.

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, et al: Burden of valvular heart diseases: a population-based study. *Lancet* 368(9540):1005–1011, 2006.
2. Carabello BA: The current therapy for mitral regurgitation. *J Am Coll Cardiol* 52(5):319–326, 2008.
3. Mirabel M, Iung B, Baron G, et al: What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? *Eur Heart J* 28(11):1358–1365, 2007.
4. Goel SS, Bajaj N, Aggarwal B, et al: Prevalence and outcomes of unoperated patients with severe symptomatic mitral regurgitation and heart failure: comprehensive analysis to determine the potential role of MitraClip for this unmet need. *J Am Coll Cardiol* 63:185–186, 2014.
5. Ho SY: Anatomy of the mitral valve. *Heart* 88(Suppl 4):iv5–iv10, 2002.
6. Roberts WC, Perloff JK: Mitral valvular disease: a clinicopathologic survey of the conditions causing the mitral valve to function abnormally. *Ann Intern Med* 77:939–975, 1972.
7. Braunwald E: Valvular heart disease. In Zipes DP, Braunwald E, editors: *Braunwald's heart disease: a textbook of cardiovascular medicine*, ed 7, Philadelphia, 2005, Saunders.
8. Carpentier A: Cardiac valve surgery: the "French correction,". *J Thorac Cardiovasc Surg* 86:323–337, 1983.
9. Levine RA, Schwammenthal E: Ischemic mitral regurgitation on the threshold of a solution: from paradoxes to unifying concepts. *Circulation* 112(5):745–758, 2005.
10. Filsoufi F, Salzberg SP, Adams DH: Current management of ischemic mitral regurgitation. *Mt Sinai J Med* 72(2):105–115, 2005.
11. Paparella D, Malvindi PG, Romito R, et al: Ischemic mitral regurgitation: pathophysiology, diagnosis and surgical treatment. *Expert Rev Cardiovasc Ther* 4(6):827–838, 2006.
12. Timek TA, Lai DT, Tibayan F, et al: Annular versus subvalvular approaches to acute ischemic mitral regurgitation. *Circulation* 106(12 Suppl 1):127–132, 2002.
13. Dent JM, Spotnitz WD, Nolan SP, et al: Mechanism of mitral leaflet excursion. *Am J Physiol* 269:H2100–H2108, 1995.
14. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, et al: Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med* 352:875–883, 2005.
15. Gillinov AM, Blackstone EH, Rajeswaran J, et al: Ischemic versus degenerative mitral regurgitation: does etiology affect survival? *Ann Thorac Surg* 80:811–819, discussion 809, 2005.
16. Ling LH, Enriquez-Sarano M, Seward JB, et al: Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl J Med* 335:1417–1423, 1996.
17. Rosenhek R, Rader F, Klaar U, et al: Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation* 113:2238–2244, 2006.
18. Enriquez-Sarano M, Basmadjian AJ, Rossi A, et al: Progression of mitral regurgitation: a prospective Doppler echocardiographic study. *J Am Coll Cardiol* 34:1137–1144, 1999.
19. Rosen SE, Borer JS, Hochreiter C, et al: Natural history of the asymptomatic/minimally symptomatic patient with severe mitral regurgitation secondary to mitral valve prolapse and normal right and left ventricular performance. *Am J Cardiol* 74:374–380, 1994.
20. Grigioni F, Enriquez-Sarano M, Zehr KJ, et al: Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation* 103:1759–1764, 2001.
21. Mihaljevic T, Lam BK, Rajeswaran J, et al: Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. *J Am Coll Cardiol* 49(22):2191–2201, 2007.
22. Zoghbi WA, Enriquez-Sarano M, Foster E, et al: Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 16:777–802, 2003.
23. Khanna D, Miller AP, Nanda NC, et al: Transthoracic and transesophageal echocardiographic assessment of mitral regurgitation severity: usefulness of qualitative and semiquantitative techniques. *Echocardiography* 22:748–769, 2005.
24. Enriquez-Sarano M, Miller FA, Jr, Hayes SN, et al: Effective mitral regurgitant orifice area: clinical use and pitfalls of the proximal isovelocity surface area method. *J Am Coll Cardiol* 25:703–709, 1995.
25. Fehske W, Omran H, Manz M, et al: Color-coded Doppler imaging of the vena contracta as a basis for quantification of pure mitral regurgitation. *Am J Cardiol* 73:268–274, 1994.
26. Enriquez-Sarano M, Seward JB, Bailey KR, Tajik AJ: Effective regurgitant orifice area: a noninvasive Doppler development of an old hemodynamic concept. *J Am Coll Cardiol* 23:443–451, 1994.
27. Klein AL, Stewart WJ, Bartlett J, et al: Effects of mitral regurgitation on pulmonary venous flow and left atrial pressure: an intraoperative transesophageal echocardiographic study. *J Am Coll Cardiol* 20:1345–1352, 1992.

28. Pu M, Griffin BP, Vandervoort PM, et al: The value of assessing pulmonary venous flow velocity for predicting severity of mitral regurgitation: a quantitative assessment integrating left ventricular function. *J Am Soc Echocardiogr* 12:736–743, 1999.
29. Alkadhi H, Bettex D, Wildermuth S, et al: Dynamic cine imaging of the mitral valve with 16-MDCT: a feasibility study. *AJR Am J Roentgenol* 185:636–646, 2005.
30. Delgado V, Tops LF, Schuijf JD, et al: Assessment of mitral valve anatomy and geometry with multislice computed tomography. *JACC Cardiovasc Imaging* 2(5):556–565, 2009.
31. Fujita N, Chazouilleres AF, Hartiala JJ, et al: Quantification of mitral regurgitation by velocity-encoded cine nuclear magnetic resonance imaging. *J Am Coll Cardiol* 23:951–958, 1994.
32. Gopal A, Shah A, Shareghi S, et al: The role of cardiovascular computed tomographic angiography for coronary sinus mitral annuloplasty. *J Invasive Cardiol* 22:67–73, 2010.
33. Daimon M, Saracino G, Gillinov AM, et al: Local dysfunction and asymmetrical deformation of mitral annular geometry in ischemic mitral regurgitation: a novel computerized 3D echocardiographic analysis. *Echocardiography* 25(4):414–423, 2008.
34. Nishimura RA, Otto CM, Bonow RO, et al: 2014 AHA/ACC guideline for the management of patients with valvular heart disease–executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 63:2438–2488, 2014.
35. Dare AJ, Veinot JP, Edwards WD, et al: New observations on the etiology of aortic valve disease: a surgical pathologic study of 236 cases from 1990. *Hum Pathol* 24:1330–1338, 1993.
36. Rozich JD, Carabello BA, Usher BW, et al: Mitral valve replacement with and without chordal preservation in patients with chronic mitral regurgitation: mechanisms for differences in postoperative ejection performance. *Circulation* 86:1718–1726, 1992.
37. Griffin BP: Timing of surgical intervention in chronic mitral regurgitation: is vigilance enough? *Circulation* 113:2169–2172, 2006.
38. Bishay ES, McCarthy PM, Cosgrove DM, et al: Mitral valve surgery in patients with severe left ventricular dysfunction. *Eur J Cardiothorac Surg* 17:213–221, 2000.
39. Enriquez-Sarano M, Schaff HV, Orszulak TA, et al: Valve repair improves the outcome of surgery for mitral regurgitation: a multivariate analysis. *Circulation* 91:1022–1028, 1995.
40. Grossi EA, Goldberg JD, LaPietra A, et al: Ischemic mitral valve reconstruction and replacement: comparison of long-term survival and complications. *J Thorac Cardiovasc Surg* 122:1107–1124, 2001.
41. Savage EB, Ferguson TB, Jr: DiSesa VJ: Use of mitral valve repair: analysis of contemporary United States experience reported to the Society of Thoracic Surgeons National Cardiac Database. *Ann Thorac Surg* 75:820–825, 2003.
42. Oliveira JM, Antunes MJ: Mitral valve repair: better than replacement. *Heart* 92:275–281, 2006.
43. Wu AH, Aaronson KD, Bolling SF, et al: Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. *J Am Coll Cardiol* 45:381–387, 2005.
44. McGee EC, Gillinov AM, Blackstone EH, et al: Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. *J Thorac Cardiovasc Surg* 128:916–924, 2004.
45. Braunberger E, Deloche A, Berrebi A, et al: Very long-term results (more than 20 years) of valve repair with Carpentier's techniques in nonrheumatic mitral valve insufficiency. *Circulation* 104(12 Suppl 1):I8–I11, 2001.
46. Mohty D, Orszulak TA, Schaff HV, et al: Very long-term survival and durability of mitral valve repair for mitral valve prolapse. *Circulation* 104(12 Suppl 1):I1–I7, 2001.
47. Gillinov AM, Cosgrove DM, Blackstone EH, et al: Durability of mitral valve repair for degenerative disease. *J Thorac Cardiovasc Surg* 116:734–743, 1998.
48. Flameng W, Herijgers P, Bogaerts K: Recurrence of mitral valve regurgitation after mitral valve repair in degenerative valve disease. *Circulation* 107:1609–1613, 2003.
49. Maisano F, Torracca L, Oppizzi M, et al: The edge-to-edge technique: A simplified method to correct mitral insufficiency. *Eur J Cardiothorac Surg* 13:240–245, discussion 245–246, 1998.
50. Bhudia SK, McCarthy PM, Smedira NG, et al: Edge-to-edge (Alfieri) mitral repair: results in diverse clinical settings. *Ann Thorac Surg* 77:1598–1606, 2004.
51. Alfieri O, Maisano F, De Bonis M, et al: The double-orifice technique in mitral valve repair: a simple solution for complex problems. *J Thorac Cardiovasc Surg* 122(4):674–681, 2001.
52. Maisano F, Caldarola A, Blasio A, et al: Midterm results of edge-to-edge mitral valve repair without annuloplasty. *J Thorac Cardiovasc Surg* 126(6):1987–1997, 2003.
53. Lorusso R, Borghetti V, Totaro P, et al: The double-orifice technique for mitral valve reconstruction: predictors of postoperative outcome. *Eur J Cardiothorac Surg* 20:583–589, 2001.
54. Kherani AR, Cheema FH, Casher J, et al: Edge-to-edge mitral valve repair: the Columbia Presbyterian experience. *Ann Thorac Surg* 78:73–76, 2004.
55. De Bonis M, Lapenna E, La Canna G, et al: Mitral valve repair for functional mitral regurgitation in end-stage dilated cardiomyopathy: role of the "edge-to-edge" technique. *Circulation* 112(9 Suppl):I402–I408, 2005.
56. Kuduvalli M, Ghotkar SV, Grayson AD, Fabri BM: Edge-to-edge technique for mitral valve repair: medium-term results with echocardiographic follow-up. *Ann Thorac Surg* 82:1356–1361, 2006.
57. Maisano F, Vigano G, Blasio A, et al: Surgical isolated edge-to-edge mitral valve repair without annuloplasty: clinical proof of the principle for an endovascular approach. *EuroIntervention* 2:181–186, 2006.
58. DeBonis M, Lapenna E, Maisano F, et al: Long-term results (≤18 years) of the edge-to-edge mitral valve repair without annuloplasty in degenerative mitral regurgitation: implications for the percutaneous approach. *Circulation* 130:S19–S24, 2014.
59. Feldman T, on behalf of the EVEREST II investigators: Endovascular valve edge-to-edge repair study (EVEREST II) randomized clinical trial: primary safety and efficacy endpoints. Presented at the Late Breaking Clinical Trials session of the annual meeting of the American College of Cardiology/i2, Atlanta, GA, March 14, 2010.
60. St Goar FG, Fann JI, Komtebedde J, et al: Endovascular edge-to-edge mitral valve repair: short-term results in a porcine model. *Circulation* 108:1990–1993, 2003.
61. Fann JI, St Goar FG, Komtebedde J, et al: Beating heart catheter-based edge-to-edge mitral valve procedure in a porcine model: efficacy and healing response. *Circulation* 110:988–993, 2004.
62. Feldman T, Wasserman HS, Herrmann HC, et al: Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. *J Am Coll Cardiol* 46:2134–2140, 2005.
63. Condado JA, Acquatella H, Rodriguez L, et al: Percutaneous edge-to-edge mitral valve repair: 2-year follow-up in the first human case. *Catheter Cardiovasc Interv* 67:323–325, 2006.
64. Feldman T, Foster E, Glower DD, et al: Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 364(15):1395–1406, 2011.
65. Mauri L, Foster E, Glower DD, et al: Four-year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. *J Am Coll Cardiol* 62(4):317–328, 2013.
66. Lim DS, Reynolds MR, Feldman T, et al: Improved functional status and quality of life in prohibitive surgical risk patients with degenerative mitral regurgitation after transcatheter mitral valve repair. *J Am Coll Cardiol* 64:182–192, 2014.
67. DiBardino DJ, ElBardissi AW, McClure RS, et al: Four decades of experience with mitral valve repair: analysis of differential indications, technical evolution, and long-term outcome. *J Thorac Cardiovasc Surg* 139:76–83, 2010.
68. McGee EC, Gillinov AM, Blackstone EH, et al: Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. *J Thorac Cardiovasc Surg* 128:916–924, 2004.
69. Kar S: Presented at the Transcatheter Cardiovascular Therapeutics meeting, November 2013, San Francisco, CA.
70. Maisano F, Franzen O, Baldus S, et al: Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. *J Am Coll Cardiol* 62(12):1052–1061, 2013.
71. Lansac E, Di Centa I, Al Attar N, et al: Percutaneous mitral annuloplasty through the coronary sinus: an anatomic point of view. *J Thorac Cardiovasc Surg* 135:376–381, 2008.
72. Choure AJ, Garcia MJ, Hesse B, et al: In vivo analysis of the anatomical relationship of coronary sinus to mitral annulus and left circumflex coronary artery using cardiac multidetector computed tomography: implications for percutaneous coronary sinus annuloplasty. *J Am Coll Cardiol* 48:1938–1945, 2006.
73. Schofer J, Siminiak T, Haude M, et al: Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. *Circulation* 120(4):326–333, 2009.
74. Siminiak T, Wu JC, Haude M, et al: Treatment of functional mitral regurgitation by percutaneous annuloplasty: results of the TITAN trial. *Eur J Heart Fail* 14(8):931–938, 2012.
75. Taramasso M, Maisano F: Transcatheter mitral valve repair: transcatheter mitral valve annuloplasty. *EuroIntervention* 10:U129–U135, 2014.
76. Maisano F: *Percutaneous mitral valve direct annuloplasty with a "surgical-like" device: multicentre feasibility trial.* Presented at the EuroPCR Conference, Paris, 2014.
77. Raman J, Jagannathan R, Chandrashekar P, Sugeng L: Can we repair the mitral valve from outside the heart? A novel extracardiac approach to functional mitral regurgitation. *Heart Lung Circ* 20:157–162, 2011.
78. Seeburger J, Rinaldi M, Nielsen SL, et al: Off-pump transapical implantation of artificial neo-chordae to correct mitral regurgitation: the TACT Trial (Transapical Artificial Chordae Tendinae) proof of concept. *J Am Coll Cardiol* 63:914–919, 2014.
79. Cheung A, Stub D, Moss R, et al: Transcatheter mitral valve implantation with Tiara bioprosthesis. *EuroIntervention* 10: U115–U119, 2014.
80. Piazza N, Bolling S, Moat N, Treede H: Medtronic transcatheter mitral valve replacement. *EuroIntervention* 10:U112–U114, 2014.
81. Bapat V, Buellesfeld L, Peterson MD, et al: Transcatheter mitral valve implantation (TMVI) using the Edwards FORTIS device. *EuroIntervention* 10:U120–U128, 2014.

Transcatheter Aortic Valve Interventions: From Balloon Aortic Valvuloplasty to Transcatheter Aortic Valve Implantation

53

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KEY POINTS

- Balloon aortic valvuloplasty is used to palliate the symptoms of severe aortic stenosis and as a bridge to more definitive therapy when benefit is uncertain.
- Transcatheter aortic valve replacement (TAVR) provides a survival and symptomatic advantage for patients with severe aortic stenosis who are at high or extreme risk for surgical complications, and it is the treatment of choice for this patient population.
- Appropriate patient selection by a multidisciplinary team, advances in catheter delivery systems, and the availability of alternative access routes have improved the rates of vascular complications and paravalvular aortic insufficiency.
- Results of ongoing clinical trials evaluating patients with moderate operative risk, placement of valve prostheses in degenerated bioprostheses, and the use of fully repositionable and retrievable catheter valves are expected to further expand the indications for TAVR.

Aortic stenosis (AS) remains the most common form of adult acquired valvular heart disease in developed countries, and the prevalence increases with age.[1] Ross and Braunwald[2] described the natural history of symptomatic AS and confirmed that it carries a poor prognosis. Medically treated patients with symptomatic AS have 1- and 5-year survival rates of 60% and 32%, respectively.[3]

Surgical aortic valve replacement (SAVR) has been for decades the only effective treatment for severe, symptomatic AS that alleviates symptoms and improves survival. For ideal candidates, SAVR has an estimated operative mortality rate of 4%.[4] However, the operative mortality rate and incidence of postoperative complications increase with age, becoming significantly higher when surgery is done urgently and increasing in the setting of extant comorbidities such as coronary artery disease, poor left ventricular function, renal insufficiency, pulmonary disease, and diabetes.[6] Because of these factors, one third of patients with valve disease are not referred for surgery.[7]

Before the introduction of balloon aortic valvuloplasty (BAV) by our group in 1986,[8] SAVR was the only recommended therapy for patients with severe, symptomatic AS, but it was not offered to older adult or high-risk patients.[9] Old age as a contraindication has continued to be redefined as devices and techniques have evolved, often making study comparisons difficult. Age is no longer considered an absolute contraindication to surgery, and octogenarians and nonagenarians are offered the option if they do not have significant physical or psychological comorbidities.[10-12] The percentage of patients 90 years of age or older undergoing heart surgery doubled from 1994 to 2001.[11] Patients with poor left ventricular function also were more aggressively managed surgically.[13-15] However, in Europe and the United States, many patients with severe AS were still not offered valve replacement.[16,17]

In the 1990s, the early enthusiasm for BAV in adult patients as a possible alternative to SAVR disappeared after recognition of the problem of restenosis. BAV appeared to provide only temporary benefit in terms of symptoms and a modest survival benefit with a relatively high complication rate.[18,19] The role of BAV in adults remained controversial, as reflected in the updated American College of Cardiology (ACC) guidelines.[20] Despite patients being designated as too sick for surgery, BAV was not offered to them in most centers because of its perceived limitations.[16]

Interest in learning the technique resurged with the development of transcatheter aortic valve replacement (TAVR) because balloon predilation of the aortic valve is integrated into the procedure. BAV continues to be indicated as a palliative procedure for patients with contraindications to TAVR and SAVR, and it can be used as a bridge to those procedures for some subsets of patients.

Developing TAVR has been for our group a fascinating 20-year-long odyssey with a happy ending. TAVR emerged in 2002 to profoundly alter the landscape of cardiovascular medicine.[21] This "disruptive" technology has provided an important medical breakthrough. It evoked skepticism and criticism in the beginning, but thanks to many clinical trials and evidence-based investigations, it is widely accepted by the medical community. In the past decade, TAVR has been performed in more than 100,000 patients around the world, and its use is growing by 40% annually.

The field of TAVR is rapidly evolving through major refinements in technology, procedural techniques, patient selection, and biomedical engineering. With the development of better devices, new approaches, and new implantation strategies, TAVR has become much simpler and safer. Although the indications were initially limited to older adult AS patients with multiple comorbidities, they are appropriately expanding to include a broader population of patients with lower surgical risks, degenerated surgical bioprostheses, and other valvular diseases such as pure aortic or mitral insufficiency.

Most of our knowledge is founded on the extensive experience acquired with two devices, the balloon-expandable Edwards prosthesis and the self-expanding Medtronic CoreValve prosthesis, which have been implanted in equal numbers outside of the United States. U.S. Food and Drug Administration (FDA) approval for nonsurgical patients and high-risk patients was obtained for the Edwards device based on the results of the pivotal U.S. Placement of Aortic Transcatheter Valve (PARTNER) trial,[22,23] and approval for the CoreValve device was obtained after the results of the U.S. CoreValve pivotal trials.[24,25]

Indications for TAVR were specified in the European and U.S. guidelines in 2012 and 2014, respectively.[20,26] TAVR can be performed in patients with severe AS without a surgical option and as an alternative to surgery in high-risk patients for whom TAVR is favored by the heart team based on the individual risk profile and anatomic suitability. Based on these guidelines, TAVR is currently indicated for about 20% of all AS patients, with two thirds of the patient population sent to surgery and the remaining patients left with medical treatment.

In this chapter, we review BAV, highlight modifications in its technique and materials, analyze its results, and discuss its role in the era of TAVR. We describe the development of TAVR for calcific AS in adults, explain the implantation technique, review its short- and medium-term follow-up results, and consider future advances and clinical applications.

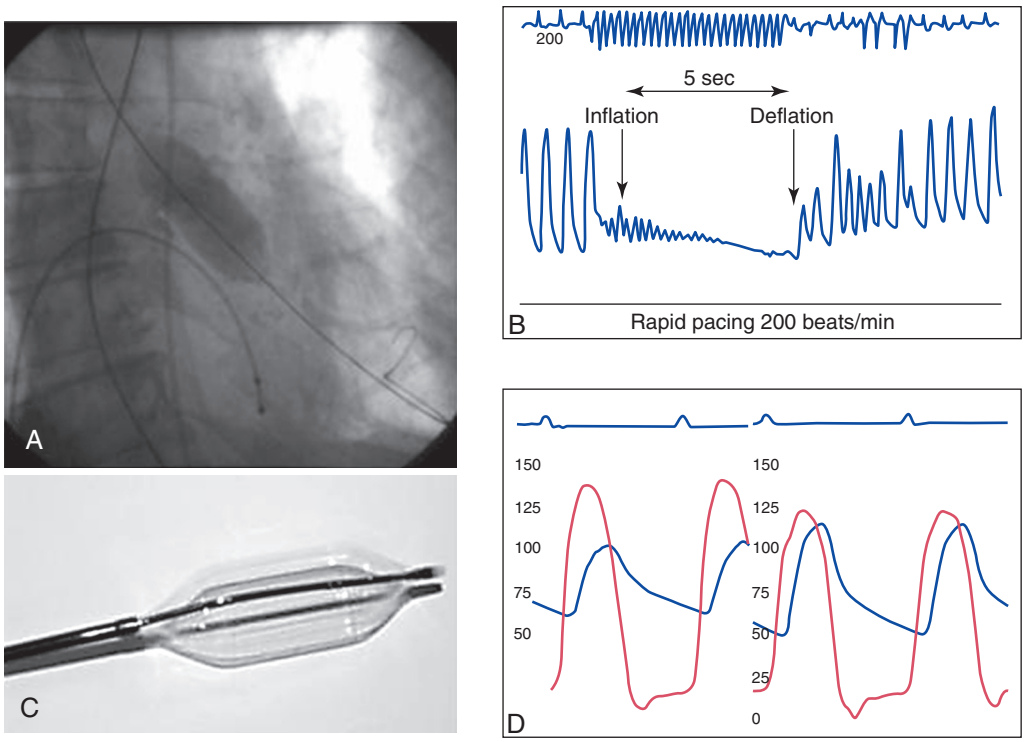


FIGURE 53-1 Balloon aortic valvuloplasty for transcatheter aortic valve implantation is performed under rapid ventricular pacing (**A**), which decreases the effective cardiac output by inducing ventricular tachycardia (**B**). The balloon catheter (**C**) must be sized to the aortic annulus to avoid severe aortic insufficiency. Doubling of the valve area or a decrease in the transvalvular gradient by more than 50% (**D**) is considered a successful result.

BALLOON AORTIC VALVULOPLASTY

Since our first reported cases,[8] we have published our experience with more than 1500 cases.[27-34] Like others,[18,19] we obtained immediate improvement in symptoms, hemodynamics, and left ventricular function but had disappointing medium- and long-term results. In our hands, BAV remains a valuable palliative procedure for frail, older adult patients who often have compromised clinical status due to concomitant coronary artery disease and other extracardiac comorbidities. Most of our patients have been turned down by surgeons, and BAV is attempted as a bridge to TAVR or surgical valve replacement in about 50% of cases. The technique can obtain improved hemodynamic results and reduce complications for these high-risk patients.[34]

The goal of the procedure is to achieve a 100% increase in aortic valve area, which is a determinant of prognosis.[18] In some reported series, the increase in aortic valve area after the procedure was very modest.[35-37] The results of BAV are limited by the cardiac pathology. Degenerative AS is the most common reason for intervention,[38-40] and it appears to be associated with a chronic inflammatory process.[41] Unlike rheumatic mitral stenosis, commissural fusion is not the predominant feature in most older adult patients with calcific AS,[42] and the primary mechanism of the balloon action is fracture of the nodular calcium deposits, which improves leaflet mobility during left ventricular contraction.[43]

Early restenosis occurring within hours or days results from early recoil and may be related to the pathology of the valve components or inappropriate balloon diameter (due to size or insufficient inflation).[30,44] When restenosis occurs after several months, the process may be multifactorial, including the original degenerative process and an altered healing process with fibrosis and ossification.[45,46] When patients develop recurrent symptoms, BAV can be repeated, usually after an interval of 12 to 24 months, and the dilations can be done serially.[32-34,47,48] In many cases, the patient may undergo BAV as a bridge to SAVR or TAVR.[20] Despite its limitations, BAV can provide marked symptomatic relief for selected older adult patients who have no other option.[18-20,35]

In most cases, BAV is done using the retrograde approach, but in a limited number of cases with poor femoral access, it can be performed through an antegrade approach. For both approaches, we typically perform the baseline hemodynamic study to confirm severe AS at the same time as the planned BAV intervention.

Retrograde Approach

Using our technique for the retrograde approach, the procedure is usually performed in less than 1 hour and has few complications (Fig. 53-1). We have learned methods that make the procedure faster and safer for critically ill, fragile, and older adult patients. For patient preparation, we use mild sedation with intravenous midazolam and local anesthesia. Unfractionated heparin (3000 to 5000 IU) is given intravenously at the start of the procedure.

Cardiac Catheterization and Rapid Ventricular Pacing

Femoral arterial and venous access is obtained with 8-Fr sheaths. Coronary angiography is obtained, and if indicated, coronary intervention is performed in the same setting, but it usually is done after the BAV is completed. Right heart catheterization is performed using a Swan-Ganz thermodilution catheter. If the patient is being considered for TAVR, ascending aortic angiography is followed by abdominal aortic, iliac, and femoral angiography.

When using the appropriate technique, the stenotic aortic valve can be crossed within a few minutes in most cases. An Amplatz left coronary catheter 2 (AL-2) is commonly used for this task. A straight-tip, fixed-core, 0.035-inch guidewire is positioned at the tip of the catheter. In the 40-degree left anterior oblique projection, the catheter tip is positioned at the rim of the valve. The catheter is slowly pulled back while maintaining firm clockwise rotation to direct the catheter tip toward the center of the valve plane. The guidewire is carefully moved

in and out of the catheter tip over a short distance, sequentially mapping the valve surface and exploring for the valve orifice.

After the wire crosses the valve, the catheter is advanced over the wire in the right anterior oblique view and positioned in the middle of the left ventricle. The transvalvular gradient is obtained using the side arm of the femoral sheath or through a dual-lumen catheter to record aortic pressure. Cardiac output can then be measured and the aortic valve area calculated using the Gorlin formula.[49] An extra-stiff Amplatz 0.035-inch, 270-cm-long guidewire (Cook, Bjaeverskov, Denmark) is used to perform all catheter exchanges and to assist in stabilizing the valvuloplasty balloon during inflation, deflation, and withdrawal.

Before inserting the wire, a large pigtail-shaped curve is formed at the distal end of the wire using a dull instrument to prevent ventricular perforation and decrease ectopy. A temporary 6-Fr bipolar pacing lead is positioned in the right ventricular posterior wall and connected to a pulse generator capable of pacing at up to 220 beats/min. Pacing and sensing parameters are determined, and the blood pressure response to pacing at 200 to 220 beats/min is evaluated. Rapid ventricular pacing (RVP) causes a precipitous fall in blood pressure to at least 50 mm Hg, which is required to be effective. If this is not achieved at a rate of 200 beats/min, the response is checked again at 220 beats/min. If a 2:1 conduction block is seen, the rate needs to be reduced to 180 beats/min or the lead position modified. The pacer is set on demand mode at 80 beats/min, serving as a backup in the event that a vagal episode or interruption of atrioventricular (AV) conduction occurs, resulting in bradycardia or asystole in response to balloon inflations.

Balloon Preparation and Balloon Aortic Valvuloplasty

The diagnostic catheter is removed from the left ventricle over the extra-stiff wire while carefully maintaining the looped flexible segment of wire in the left ventricular (LV) cavity. The 8-Fr sheath is replaced by a 10-Fr sheath over the extra-stiff wire. In our center, all procedures are performed using a 10-Fr sheath (Cook, Bjaeverskov, Denmark). The evolution of the technique has seen a reduction in the profile of the devices, decreasing local complications at the femoral artery puncture site; which was previously the most common complication reported.[50] At the end of the procedure, hemostasis is obtained by using an 8-Fr Angioseal vascular closure device (St. Jude Medical, Brussels, Belgium).

Most of our experience was obtained with specifically designed balloon catheters for BAV, the double-sized Cribier-Letac catheters. When their production was discontinued, we chose the Z-Med II balloon catheter (NuMed, Hopkinton NY), which is compatible with a 12- or 14-Fr sheath. We currently use the lower-profile Cristal balloons (Balt Extrusion, Montmorency, France), which are compatible with a 10-Fr sheath. The 20- and 23-mm-diameter balloons are 45 mm long, and the 25-mm-diameter balloon is 50 mm long. We usually start with a 23-mm balloon. A 20-mm balloon is used if the valve is densely calcified or the aortic annulus is small (<19 mm as determined by echocardiography). In up to 25% of cases, the 25-mm balloon can be used if the aortic annulus diameter is larger than 24 mm. Other catheters, such as the True balloon (Bard, Murray Hill, NJ) or the V8 (InterValve, Minneapolis, MN), minimize balloon migration and facilitate valve expansion.

Short extension tubing with a three-way stopcock attached is connected to a hand-held 30-mL Luer-Lok syringe filled with diluted contrast. The contrast is diluted (15% contrast and 85% saline) to reduce viscosity to facilitate the inflation and deflation cycles. After flushing the distal lumen, the balloon is partially inflated and then completely deflated one or more times to completely purge it of air bubbles.

The balloon catheter is advanced across the aortic valve, centering the valve between the two markers. Before using RVP, it was challenging to maintain the balloon in an optimal position during inflation. There must be clear communication between the operators manipulating the balloon catheter and the pacing device. RVP is turned on, and balloon inflation is started quickly and with enough pressure to rapidly inflate the balloon as soon as the blood pressure falls. RVP is continued for a few seconds after the balloon reaches maximal inflation.

The balloon is rapidly deflated, the pacer is turned off, and the balloon is withdrawn from the valve. This step requires coordination of the two operators to quickly allow restoration of antegrade flow while maintaining a safe wire position in the left ventricle. Rapid balloon deflation and restoration of blood flow is important to minimize the time of hypotension and hypoperfusion. Time must be allowed for the heart rate and blood pressure to return to preinflation values before deciding to inflate the balloon again. Because the pressure gradient cannot be measured through balloon catheters, it is important to assess the effects of balloon dilation and the hemodynamic consequences by observing the waveform of the aortic pressure tracing and the heart rate response, rhythm, and blood pressure recovery. A sudden change in waveform with loss of the dicrotic notch or falling diastolic blood pressure may indicate severe aortic regurgitation. Improvement in the pressure slope suggests a successful procedure.

If the balloon does not appear to be fully expanded or there is no hemodynamic improvement, repeat inflations are usually carried out before remeasuring the transaortic pressure gradient. The residual gradient is obtained by simultaneous measurement of the pressure in the left ventricle and aorta. If there is a significant gradient, the next larger size of balloon may be chosen, and the sequence is repeated. A pullback gradient is also obtained after the final balloon inflation.

For the final results, the pacemaker is removed, the cardiac output measured, and the final aortic valve area calculated. An optimal result is considered to be a doubling of the valve area or decrease of the gradient by 50% compared with the baseline value. Supravalvular angiography is used to determine aortic regurgitation and its severity. If contrast cannot be used, assessment of aortic insufficiency and its severity may be performed by transthoracic echocardiography (TTE).

Immediate Management After Balloon Aortic Valvuloplasty

Manual compression is used for hemostasis at the venous entry site. Arterial hemostasis is achieved with the closure device as specified earlier. If a technical failure occurs, a pneumatic pressure device is used (FemoStop II Plus, Radi Medical Systems, Uppsala, Sweden).

When the case is uncomplicated, the patient is usually discharged within 2 days. However, when BAV is performed in patients with severely impaired LV function or when rescuing a patient from cardiogenic shock, hemodynamic monitoring with inotropic support is usually required in the intensive care unit (ICU). Vagal reactions are the most common cause of hypotension associated with BAV. There must be a low threshold for ruling out pericardial tamponade or retroperitoneal bleeding when evaluating the hypotensive patient after BAV.

Antegrade Transseptal Approach

Patient preparation is similar to that described for the retrograde approach. Transseptal catheterization is performed through the right femoral vein using the left lateral view. The puncture is made in the middle third of a virtual line connecting the aortic calcification and the posterior border of the heart. When entry into the left atrium is confirmed, 5000 IU of heparin is administered intravenously. A Mullins sheath is then used to direct a 7-Fr Swan-Ganz catheter, which has an inner lumen compatible with a 0.035-inch guidewire (Edwards LifeSciences, Irvine, CA), across the mitral valve into the left ventricle under fluoroscopic guidance in the 40-degree anterior oblique projection. The transaortic gradient is determined with the Swan-Ganz catheter in the left ventricle and the pigtail catheter in the aorta. The aortic valve area is calculated using the Gorlin formula.

For crossing the aortic valve, the Mullins sheath is advanced approximately 2 cm beyond the mitral valve. The balloon of the Swan-Ganz catheter is inflated and directed into the LV outflow while approaching the native aortic valve. A 0.035-inch, straight wire may facilitate crossing the aortic valve with the balloon deflated as the catheter is pushed over the wire into the ascending aorta. The wire is removed, and the balloon is reinflated. The catheter is advanced into the descending aorta and positioned at the level of the distal aortic bifurcation with an Amplatz 0.035-inch, 360-cm-long extra-stiff

guidewire (Cook, Bjaeverskov, Denmark). The balloon is deflated, and the Swan-Ganz catheter is removed. The 8-Fr venous sheath is replaced with a 10-Fr sheath for subsequent balloon dilations using the Cristal balloon catheter (12 or 14 Fr for NuMed balloons). The atrial septum is then dilated with an 8-mm-diameter balloon septostomy catheter through the 10-Fr sheath. The same balloon catheters are used as for the retrograde approach.

Dilation of the aortic valve is done preferentially with the 23-mm-diameter balloon, which is advanced through the 10-Fr sheath and positioned across the aortic valve while the loop in the left ventricle is carefully maintained. BAV is then performed as described earlier using RVP. TTE can assess the residual pressure gradient.

When two or three inflations using the largest selected balloon size are completed, the balloon catheter is removed. A 6-Fr pigtail catheter is advanced over the extra-stiff wire and positioned over the arch so that the wire can be removed shielded by the catheter, avoiding injury to the aorta or mitral valve. The final pressure gradient is obtained with the pigtail catheter in the left ventricle and another catheter in the aorta. Supraaortic angiograms may be obtained.

Hemostasis is obtained with manual compression of the femoral artery and vein after sheath removal. Bed rest is recommended for 24 hours. ICU observation with inotropic support and prolonged hemodynamic monitoring is required only for hemodynamically unstable patients, typically those presenting in cardiogenic shock.

Results of Balloon Aortic Valvuloplasty

Over the past 20 years, the results of BAV have been reported from many series and multicenter registries.[51-55] Results have varied greatly, reflecting the different parameters and techniques used.

Our series included 323 consecutive patients with severe AS who underwent BAV (with the exception of patients undergoing percutaneous heart valve implantation) between January 2005 and December 2008.[33,34] In this group of patients, the average age was 80.5 ± 10 years, 42% were women, and the mean logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) was 28.7 ± 12.5. New York Heart Association (NYHA) functional class III or IV disease was observed in 82% of patients, and the procedure was done emergently for the 15% of patients in cardiogenic shock.

BAV was done using the retrograde approach in 100% of cases. Success was achieved in 80.8% of the procedures. The in-hospital mortality rate was 2.5%. Patients were discharged from the hospital after 5.6 ± 3 days.

Over a mean follow-up of 20.7 ± 20.0 months, 26.3% of patients were bridged to SAVR or TAVR, and 8.7% had repeat BAV. The other patients received medical treatment alone. Patients bridged to SAVR had the most favorable outcomes. Patients bridged to TAVR had better outcomes than those treated by a single BAV. Our study confirmed that survival was poor for patients treated by a single BAV (56% mortality rate at 1 year). In our series, the frequency of clinically apparent neurologic events was less than 2%. This compares favorably with the reported incidence of cerebrovascular events in a series of retrograde catheterizations of the aortic valve without intervention.[55]

Minimizing the duration of RVP and proper balloon inflation are important technical issues, and maintaining optimal heart rate and blood pressure during the procedure are crucial. Improvements in the procedure such as the use of RVP and vascular closure devices and continued experience with the procedure have resulted in decreased complication rates despite an increasingly older and sicker population of patients (Table 53-1).

TABLE 53-1 Comparisons of Complication Rates in the Rouen Series and Mansfield Registry

Complications	Mansfield Scientific Aortic Valvuloplasty Registry 1986-1988 (*N* = 492)	Rouen Series 2002-2005 (*N* = 141)
Procedural death	2 (4.9%)	3 (2.1%)
Postprocedural death (<7 days)	12 (2.6%)	3 (2.1%)
Cerebral embolic events	11 (2.2%)	2 (1.4%)
Transient ischemic attacks	5 (1.1%)	0 (0%)
Ventricular perforation with tamponade	11 (2.2%)	0 (0%)
Severe aortic insufficiency	5 (1.1%)	2 (1.4%)
Vascular complications (surgical repair)	27 (5.5%)	0 (0%)
Nonfatal arrhythmias	5 (1.1%)	5 (3.5%)
Other: myocardial infarction, sepsis, renal failure	8 (1.6%)	1 (1%)

Data from Agatiello C, Eltchanino H, Tron C, et al: Balloon aortic valvuloplasty in the adult. Immediate results and in-hospital complications in the latest series of 141 consecutive patients at the University Hospital of Rouen (2002-2005). *Arch Mal Coeur Vaiss* 99:195-200, 2006.

Applications of Balloon Aortic Valvuloplasty

The updated American College of Cardiology and American Heart Association (ACC/AHA) guidelines for the management of patients with valvular heart disease continue to regard the role of BAV as controversial.[20] There are no class I or IIa recommendations for BAV. The class IIb indications for adult patients with severe AS are for those at high risk for SAVR because they are hemodynamically unstable and those who are candidates for BAV as a bridge to surgery or as a palliative procedure because they have serious comorbid conditions that preclude SAVR. BAV may be indicated for other reasons:

- It may be used for patients who have symptomatic AS in need of emergent noncardiac surgery. The hemodynamic improvement of BAV is immediate, and it may decrease the risk of general anesthesia. In these situations, the BAV should be reserved for patients with severe AS who have the potential for hemodynamic compromise.
- It may be used to determine the contributing role of AS to dyspnea in patients with concomitant severe lung disease and to gauge potential improvement and risks of undergoing SAVR or TAVR.
- It may be used to assess the myocardial contractile reserve in patients with a low pressure gradient or low ejection fraction in whom associated cardiomyopathy is questionable. Patients with no demonstrated contractile reserve can have a perioperative mortality rate as high as 62%.[56] The indication for SAVR or TAVR can be clarified 2 to 3 weeks after BAV if the left ventricular ejection markedly improves.

BAV continues to have a role in the management of AS, particularly as a palliative modality for the increasing older adult population for whom the risk of valvular intervention is too high or inappropriate.[32,33,48,57,58] Interventional cardiologists and surgeons should become familiar with BAV, particularly if they are interested in TAVR, because it plays a crucial role in patient selection and valve implantation.

TRANSCATHETER AORTIC VALVE IMPLANTATION

Background

Treatment of patients who have valvular disease with percutaneous catheter–based systems has been an exciting area of research since the mid-1960s. The initial animal investigations were performed by Davies in 1965,[59] followed by groups led by Moulopoulos in 1971,[60] Phillips in 1976,[61] and Matsubara in 1992.[62] These investigators reported various catheter-based systems used for the temporary relief of AS, but no further human application was possible due to unsolved major limitations.

A new era of investigations started with the development of endovascular stents, advancing the concept of balloon-expandable valvular prosthesis. In 1992, Andersen and colleagues[63] reported their work in a porcine model in which they evaluated a transluminal stented heart

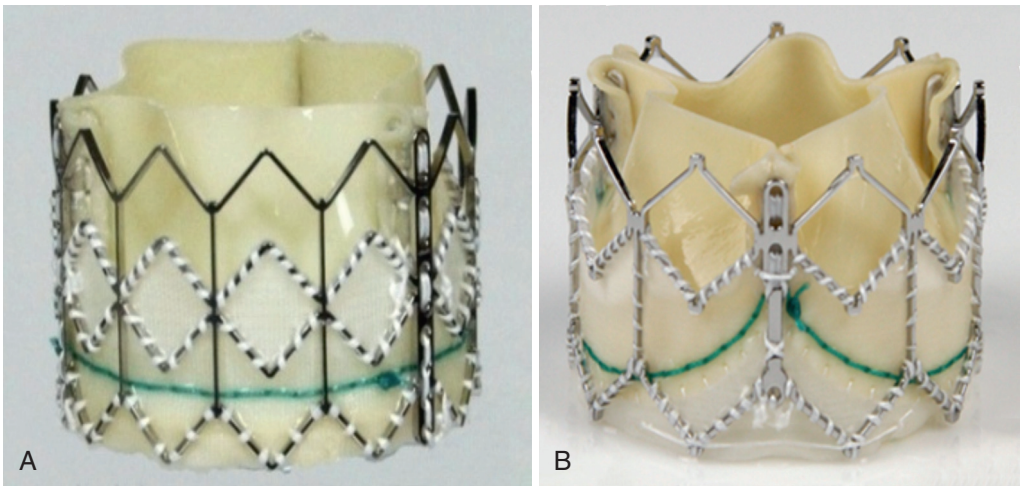


FIGURE 53-2 **A,** The Sapien valve is a trileaflet bovine pericardial valve mounted on a balloon-expandable stainless steel stent. **B,** The second-generation Sapien XT valve has a new bovine pericardial leaflet design, and it is mounted on a cobalt-chromium stent, reducing its profile.

valve. Despite encouraging experimental results, there was no development of a human application. In 2000, Bonhoeffer and coworkers, using a valve from a bovine jugular vein mounted within an expandable stent, reported the feasibility of delivering the device inside the native pulmonary valve of lambs[64] and thereafter were able to perform the first successful human percutaneous replacement of a pulmonary valve in a right ventricle–to–pulmonary artery prosthetic conduit with valve dysfunction.[65]

Our team in Rouen, France, has been working since the early 1990s on the development of a catheter-based treatment for nonsurgical patients with severe calcific AS that could overcome the high restenosis rate seen after BAV. Early cadaver work in 1994 provided information about the ability to deploy a Palmaz stent in the aortic position and contributed to designing appropriate stent dimensions. In 1999, under the auspices of Percutaneous Valve Technologies (Fort Lee, NJ), an original catheter valve was developed and tested in a sheep model.[66] In vitro testing confirmed the valve's hemodynamic profile and durability. An original animal model of chronic aortic regurgitation that allows the long-term evaluation of the catheter valve in the systemic circulation was developed for in vivo testing.[67]

The first TAVR in a human was performed by our group in April 2002,[21] followed by an initial series of human implantations for compassionate use that were serially reported.[68-72] After the acquisition of Percutaneous Valve Technologies by Edwards LifeSciences in 2003, further modifications of the Cribier-Edwards device were achieved with the development of the Edwards Sapien heart valve, which preceded multicenter clinical trials and the pivotal randomized PARTNER study in the United States.[22,23]

The first series of patients with severe AS treated with the self-expanding CoreValve Revalving System (Medtronic, Minneapolis, MN) was later reported by Grube and colleagues.[73] Since the first implantation of this device in 2004, several technologic improvements were obtained, and efficacy of the CoreValve was demonstrated in multiple registries and in the U.S. CoreValve pivotal trials.[24,25]

Edwards and Medtronic have developed new models of transcatheter valves and delivery systems, producing a clear-cut improvement in results and a decreased rate of complications. Other models of transcatheter valves have been launched by several companies, and some have already been approved in Europe.

In the following sections, we describe patient selection, procedural techniques and results, and future strategies for the balloon-expandable Edwards valves (Fig. 53-2) and the self-expanding Medtronic CoreValve. Other valve prostheses in different stages of development are reviewed.

Risk Stratification

According to the guidelines,[20,26] TAVR is being offered to patients who are at high risk for surgical complications due to their age or comorbidities. Patients are considered to have a high operative risk when their scores are in the upper decile for mortality or have a 30-day mortality risk greater than 15%. Surgical risk is most commonly estimated by the Society of Thoracic Surgery Predicted Risk of Mortality (STS-PROM) and the EuroSCORE. The EuroSCORE II has been validated for patients undergoing valvular surgery.[74] Previous versions of the EuroSCORE had overestimated the surgical mortality risk for high-risk patients, and as a result, the logistic EuroSCORE II was developed.[74-76]

The STS-PROM was derived from the STS database, a voluntary registry of practice outcomes. It estimates the risk of mortality, morbidity, renal failure, and length of hospital stay after valvular and nonvalvular cardiac surgery.[77,78] This score underestimates the true mortality rate after cardiac surgery, but it more closely reflects the operative and 30-day mortality rates for the highest-risk patients having aortic valve replacement.[79]

The STS-PROM and the EuroSCORE provide an objective way to quantify risk. Although thorough, these risk scores do not include certain characteristics that can complicate surgery and increase the operative mortality rate, such as previous mediastinal irradiation, chest wall deformity, severe calcification in the thoracic aorta (i.e., porcelain aorta), history of mediastinitis, liver cirrhosis, previous bypass grafting preventing safe reentry to the chest, or the patient's frailty. The algorithms for scoring were calculated from patients who underwent surgery, limiting their applicability to patients who are not considered surgical candidates. Clinical judgment and the patient's level of independent function are subjective parameters that influence outcomes after cardiac surgery but are difficult to measure. More accurate risk calculators that can more precisely estimate the risk of patients selected for TAVR are being investigated.

Patient Selection

Over the past decade, heart valve teams have become more proficient in performing TAVR while minimizing complications and obtaining perfect outcomes. Not every high-risk patient with severe, symptomatic AS needs to be treated with TAVR; the procedure should be performed in patients who can consistently benefit. Certain patient characteristics have been associated with a poor prognosis after TAVR. Among surgically inoperable patients, those who were inoperable for

technical reasons had a better prognosis that those who were considered inoperable for medical reasons.[80]

Preprocedural risk assessment is performed using the EuroSCORE or the STS-PROM as described earlier. Patients are usually classified as at high risk for surgery when the logistic EuroSCORE and the STS-PROM are greater than 20% and 10%, respectively. However, in Europe, there is a trend to include lower-risk patients (EuroSCORE >15%), and the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) and PARTNER II trials are evaluating lower-risk patients.

Patient frailty, which has a significant impact on clinical outcome after SAVR and TAVR,[81-83] has become another inclusion criteria. Severe lung disease, oxygen dependence, low body mass index, worsening renal function, and low transvalvular pressure gradients are factors associated with a poor prognosis.[84] Until a dedicated TAVR risk score is created, patient selection should be based on objective evidence associated with an elevated risk of surgical mortality and use a multidisciplinary approach. The indication for TAVR and the benefit-risk profile must be discussed in detail by a multidisciplinary team (i.e., heart valve team) of primary cardiologists, interventional cardiologists, cardiac surgeons, echocardiographers, radiologists, anesthesiologists, and geriatricians. Inclusion requires patients to have severe, symptomatic AS; be considered at high risk for surgical complications; have a greater than 1-year survival of their comorbidities; and benefit from valve replacement (Table 53-2).

Preprocedure Planning

Meticulous preprocedure planning with multimodality imaging assessment must be done for each patient to determine the feasibility and safety of TAVR and select the best approach. Prostheses can be placed by a transfemoral, transapical, transaortic, or subclavian approach.[22,23,85,86]

TABLE 53-2 Patient Characteristics Associated With Poor Prognosis After Transcatheter Aortic Valve Replacement

Chronic kidney disease (>stage 3)
Severe lung disease
Oxygen dependence
Slow 5-meter walk
Frailty
Low body mass index
Low mean aortic gradient
Abnormal Mini-Mental State Examination result
Limited 6-minute walk test distance
Nontechnical reasons for inoperability
Moderate or severe tricuspid regurgitation

Cardiac Catheterization and Angiography

Right and left catheterization can identify pulmonary hypertension and concomitant coronary artery disease, which may need to be treated before valve implantation. Aortic angiography establishes the correct angulation of the image intensifier during valve positioning and determines potential complicating factors in the aortic arch that may interfere with the procedure. Iliofemoral angiography is regularly performed as the first evaluation of vessels diameters, calcification, and tortuosity.

Echocardiography

TTE or transesophageal echocardiography (TEE), or both, can assess the anatomy of the aortic valve (i.e., trileaflet or bicuspid valve), the severity of AS, the degree and distribution of valvular calcification, the annulus diameter (which was for many years the only way to select the appropriate prosthesis size), the left ventricular function, the pulmonary pressures, and concomitant valvular diseases. Cross-sectional, three-dimensional TEE can be usefully added to the baseline evaluation.[87]

Computed Tomography

Computed tomography (CT) with three-dimensional reconstruction is invaluable for assessing the valvular (e.g., calcium distribution, leaflet length) and aortic root anatomy (e.g., diameters, angulation, calcification, sinus of Valsalva), distance between the coronary ostia and annulus (i.e., assessing the risk of coronary occlusion during TAVR), and the aortobifemoral anatomy. CT is considered the best tool for accurately evaluating the dimensions of the ovoid aortic annulus (e.g., diameter, circumference, area) and selecting the appropriate size of prosthesis size to prevent valve embolization and paravalvular regurgitation (by an undersized device) or annulus rupture (by an oversized device). This information is applied to the model of prosthesis chosen (Fig. 53-3).

CT has a key role in evaluating the peripheral arteries and preventing complications of the transfemoral approach caused by using large introducers and delivery systems. The prosthesis may be delivered by various approaches. he transfemoral approach is considered the default approach by most teams because it is less invasive than alternative routes. Decreased sheath size allows the transfemoral approach to be used in more than 80% of the cases, whereas it was limited to 50% of cases by the first-generation devices. Selection depends on the tortuosity, calcification, and internal diameter of the femoral, external iliac, and common iliac arteries. Abdominal aortic aneurysms or a history of their repair favors the use of alternative approaches.

Vascular complications have been associated with significant mortality and may be prevented with appropriate screening.[88,89] Safety should not be sacrificed if an approach other than transfemoral is available and patients are considered to be good candidates. If chronic renal insufficiency precludes a study with full contrast, intraarterial administration of a small contrast bolus[90] or CT without contrast may provide appropriate images for the necessary measurements.

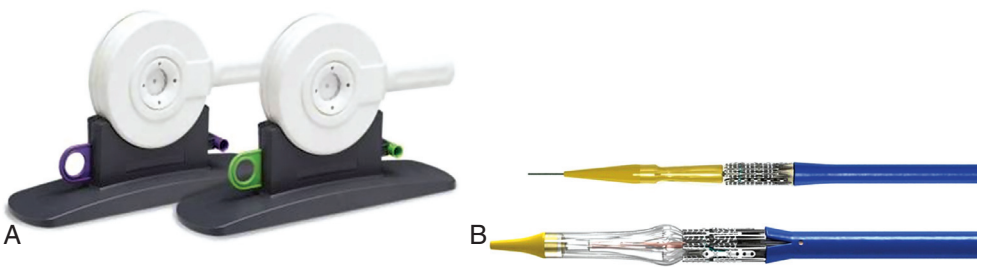


FIGURE 53-3 **A,** The original crimping device in two sizes adapted to the 23- and 26-mm Sapien valves. **B,** The RetroFlex 3 delivery system for the Sapien valve *(top)* and the NovaFlex delivery system for the Sapien XT valve *(bottom)*.

Transcatheter Aortic Valves

Sapien Heart Valve

The Sapien prosthesis is the first generation of balloon-expandable valve. It was developed by Edwards LifeSciences in 2005, after the acquisition of Percutaneous Valve Technology. The device is a modified version of the percutaneous valve used in the first-in-human implantations and subsequent feasibility studies performed between 2002 and 2005 by our group[21,68-70] and then by other investigators.[71,72] This valve has been used in all feasibility studies in Europe and Canada and was later used in the U.S. PARTNER trial and in many registries outside the United States, including the Sapien Aortic Bioprosthesis European Outcome (SOURCE) registry. This balloon-expandable model was the first one approved in the United States. The device consists of a bioprosthetic valve, a balloon catheter on which it is mounted, and a crimping tool.

The Sapien prosthesis is a trileaflet bioprosthesis made of bovine pericardium that is mounted in a balloon-expandable stainless steel stent (see Fig. 53-2, *A*). It has been pretreated to decrease calcification and functional deterioration. The stent has a fabric cuff placed on the ventricular side that covers one half of the frame, limiting stent expansion and decreasing perivalvular insufficiency. Because the device has no sewing ring, the valve is oversized for the aortic annulus to ensure stability after deployment. It is available in two sizes: a 23-mm valve (for an aortic annulus of 18 to 22 mm) with a stent height of 14.5 mm and a 26-mm valve (for an aortic annulus of 21 to 25 mm) with a stent height of 16 mm. Bench-top testing showed its durability to be greater than 10 years. The Sapien valve provides a larger effective orifice area and lower hemodynamic profile than corresponding surgically implanted valves, but it is associated with a higher incidence of perivalvular insufficiency.[91]

The valve is mounted on a custom balloon that is 30 mm long with a diameter that corresponds to the prosthesis size. At its distal end, it contains a nose cone that facilitates crossing the native valve (Fig. 53-4). The crimping tool is used to manually and symmetrically compress the overall diameter of the prosthesis from its expanded size to its minimal delivery profile. A cylindrical gauge is used to confirm the collapsed profile of the delivery system to ensure that it can move smoothly through the introducer sheath. A measuring ring is used to calibrate the balloon inflation to its desired size and to determine the amount of saline and contrast mixture in the syringe necessary for proper inflation at the time of deployment.

The RetroFlex catheter (see Fig. 53-3, *B*), an innovation that facilitates the passage of the mounted valve across the aortic arch from the retrograde approach, was initially evaluated by Webb and colleagues.[72] The catheter has a deflectable tip that changes direction when activated by the rotation of an actuator incorporated in the handle. The catheter is then used to direct the valve delivery system through the arterial system, around the aortic arch, and across the aortic valve, providing a less traumatic passage. The RetroFlex catheter assists in centering and supporting the valve as it crosses the calcified and stenotic native valve. This system also provides precise positioning at the aortic annulus.

The Sapien valve and deflecting guiding catheter are introduced through a 25-cm-long sheath with a hydrophilic coating that extends into the abdominal aorta to decrease vascular complications. The transfemoral delivery system requires a 22- and 24-Fr sheath for the 23- and 26-mm valves, respectively. The Ascendra catheter (Edwards LifeSciences, Irvine, CA) is the delivery system used for the transapical route (Fig. 53-5). The catheter allows easy valve manipulation to improve the prosthetic orientation.

Sapien XT Valve

The Edwards Sapien XT (see Fig. 53-2, *B*) is a modified and improved version of the Sapien prosthesis. It has been commercially available in Europe since 2009 and was approved in the United States in June 2014. It consists of a cobalt-chromium, balloon-expandable stent

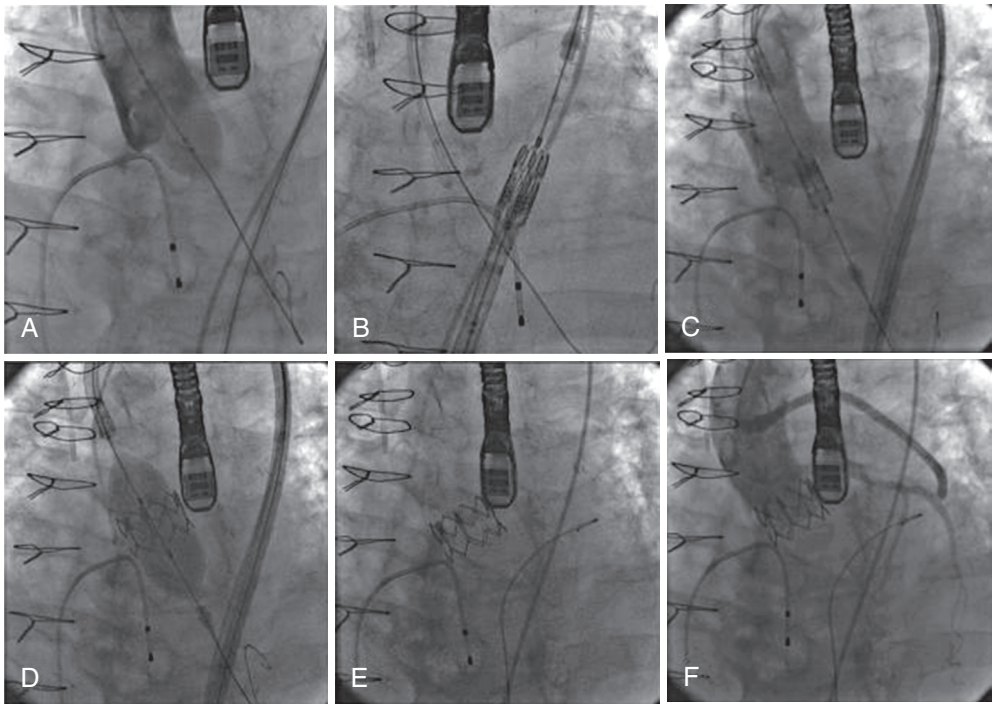
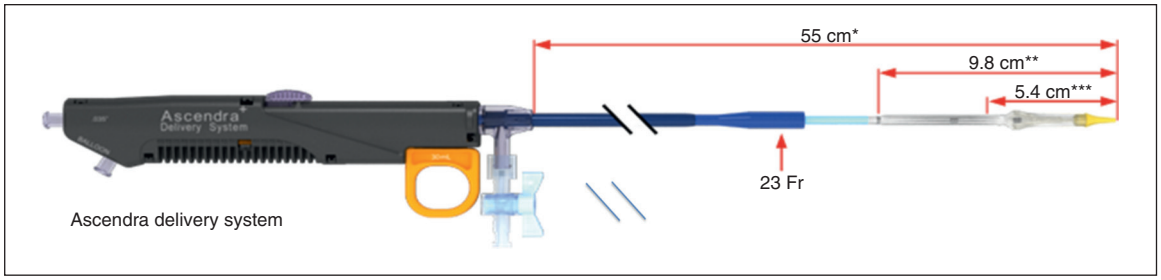


FIGURE 53-4 Transfemoral transcatheter aortic valve replacement. **A,** Balloon aortic valvuloplasty with simultaneous aortography. **B,** Delivery system and valve assembly advanced through the descending aorta. **C,** Correct valve positioning confirmed by angiography. **D,** Valve deployment under rapid ventricular pacing. **E,** Valve in place after delivery. **F,** Aortic angiography to confirm valve position, lack of aortic insufficiency, and unrestricted flow through the native coronary arteries and bypass grafts.



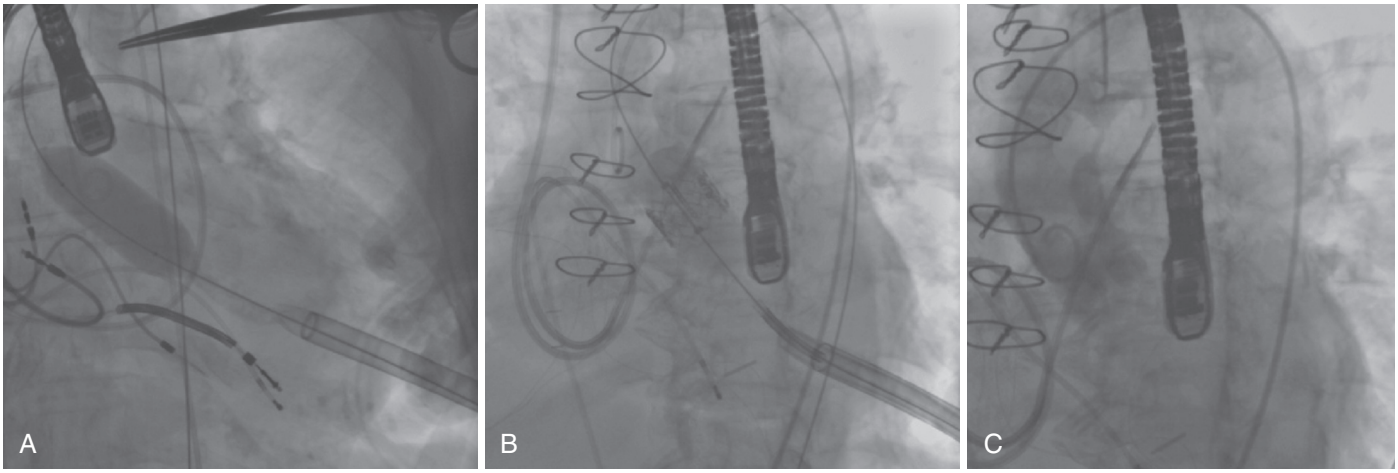


FIGURE 53-5 The Ascendra delivery system for transapical delivery of the Sapien valve *(top)*. **A,** Balloon valvuloplasty is performed under rapid pacing. The delivery sheath is inserted through the apex of the left ventricle after a lateral thoracotomy. **B,** Valve deployment under rapid ventricular pacing. **C,** Aortic angiography after valve implantation confirms the absence of aortic insufficiency.

Sapien XT Valve Sizing Chart

	23 mm	26 mm	29 mm
Annulus diameter (mm)	18 – 22	21 – 25	24 – 27
Annulus area (mm^2)	332 – 395	425 – 506	528 – 660
Expanded length (mm)	14	17	19

Sapien 3 Valve Sizing Chart

	20 mm	23 mm	26 mm	29 mm
Annulus diameter (mm)	16 – 19	18 – 22	21 – 25	24 – 28
Annulus area (mm^2)	273 – 345	338 – 430	430 – 546	540 – 680
Expanded height (mm)	15.5	18	20	22.5

FIGURE 53-6 Annular sizing charts for determining the valve size when using the Sapien XT and Sapien 3 devices.

with an integrated trileaflet bovine tissue valve and a polyethylene terephthalate fabric cuff. Its design renders it highly resistant to compression after implantation.

The valve's physical properties are similar to those of surgical bioprostheses. It has three sections of bovine pericardium and is manufactured with the ThermaFix anticalcification process. The transfemoral kit includes the NovaFlex delivery system (see Fig. 53-3), which consists of a deflectable balloon catheter with a distal nose cone and a handle consisting of a flexing wheel, a flex indicator, and an alignment wheel used to mount the crimped valve on the balloon that is advanced into the abdominal aorta. The system also includes a single-use crimper; a 35-cm hydrophilic coated introducer (i.e., expandable e-sheath) of 16, 18, or 20 Fr for the 23-, 26-, and 29-mm valve sizes, respectively (Fig. 53-6); 16-, 18-, 20-, and 22-Fr polyethylene iliofemoral arterial dilators (40 cm long); dedicated 20-, 23-, and 25-mm valvuloplasty balloons (40 mm long) for the 23-, 26-, and 29-mm valve sizes, respectively, for predilation of the native aortic valve; and two Atrion balloon inflation devices.

The transapical (or transaortic) kit includes the Ascendra 2 transapical delivery catheter (22 Fr) optimized for a single-hand operation, the Ascendra sheath (24 Fr), a single-use crimper, a 20-mm Ascendra custom-designed valvuloplasty balloon catheter, and two Atrion inflation devices. Dimensions and adequate requirements for the Sapien XT compared with other Edwards devices are shown in (Fig. 53-7).

Valve	Valve size (mm)	Sheath OD (mm)	Minimum vessel diameter (mm)
Sapien 3	20	6	5
Sapien THV	23	8.4	7.0
Sapien XT THV	23	6.7	6.0
Sapien 3	23	6	5.5
Sapien THV	26	9.2	8.0
Sapien XT THV	26	7.2	6.5
Sapien 3	26	6	5.5
Sapien XT THV	29	8.0	7.0
Sapien 3	29	6.7	6.0

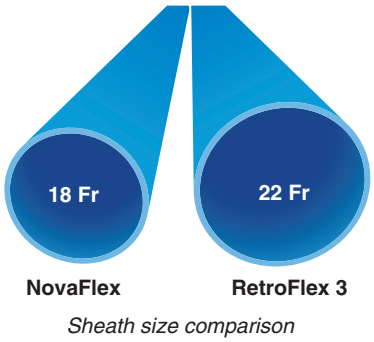


FIGURE 53-7 Outer sheath diameters (OD) and minimal internal vessel diameters required with the three generations of Edwards balloon-expandable valves.

Transfemoral Approach to Valve Implantation

Room Requirements

Transfemoral TAVR can be performed in the cardiac catheterization laboratory or in the hybrid operating room. The room must be equipped with a fixed fluoroscopy unit that provides high image quality and can store reference images for roadmapping. The room needs to be large enough to allow all operators to work comfortably and the circulators to move freely. A cardiopulmonary bypass machine should be accessible if complications arise. Equipment to treat vascular or coronary complications should be stocked in the room and available on demand.

Anesthesia

The procedure can be done under general anesthesia[92] or conscious sedation.[93] General anesthesia is preferred if TEE is performed simultaneously during the procedure. If not, conscious sedation and local anesthesia provide enough relief during the procedure and have been increasingly accepted since the launch of smaller devices (i.e., Sapien XT and Sapien 3).

Continuous invasive hemodynamic monitoring should be used throughout the procedure. Vasopressor support should be used judiciously because vasoconstrictors may interfere with the insertion and removal of the arterial sheath and predispose to vascular complications.

Infection and Antithrombotic Prophylaxis

To decrease the risk of prosthetic infection, patients are given intravenous antibiotics (i.e., vancomycin or cefazolin) on call to the procedure room, and they are continued for 48 hours. Aspirin (160 to 325 mg) and clopidogrel (300 mg) are administered at least 24 hours before the procedure. After the procedure, clopidogrel (75 mg/day) is continued for 1 month, and aspirin (75 mg/day) is continued indefinitely.

Venous and Arterial Access

Femoral arterial access is obtained for aortic angiography with a 5- to 6-Fr pigtail catheter, and a venous sheath is inserted for RVP. The contralateral artery is cannulated percutaneously or by surgical cutdown. If accessed percutaneously, it can be preclosed with suture-mediated devices. Preclosing with a single 10-Fr Prostar device or with two Proglide devices (Abbott Vascular, Abbott Park, IL) is regularly performed with use of the Sapien XT device[94] If surgical cutdown is performed, the common femoral artery should not be completely dissected in the posterior aspect because sheath insertion is easier when the vessel is partially anchored.

Aortic Angiography

Ascending aortic angiography is performed in a projection that places all aortic cusps in line and perpendicular to the image intensifier. Ideally, the best projection is previously determined to minimize the radiation and contrast exposure during CT. It can also be facilitated by the use of online three-dimensional reconstruction systems.

Temporary Pacemaker Placement

A ventricular stimulation lead such as the 6-Fr Soloist lead (Medtronic, Minneapolis, MN) is placed in the right ventricle. After testing for appropriate capture, a RVP test is performed at a rate of 180 to 220 beats/min as detailed in the BAV section.

Delivery Sheath Insertion

With the guidewire in the aorta, the previously inserted 8-Fr sheath is removed. Serial dilation of the femoral and iliac arteries is performed with arterial dilators of increasing size (16 to 22 Fr). The delivery sheath is then inserted and positioned in the descending aorta.

Crossing the Aortic Valve

After the patient is anticoagulated with heparin (100 IU/kg), the native aortic valve is crossed as described earlier using an AL-2 catheter and a straight guidewire. The previously shaped Amplatz 0.035-inch, 270-cm-long, extra-stiff guidewire is then exchanged through the AL-2, and the catheter is withdrawn while maintaining the distal wire position in the left ventricle. A pigtail catheter is advanced, and the valve pressure gradient is then obtained.

Prior Balloon Aortic Valvuloplasty

BAV is performed under RVP before TAVR with the technique described previously. A 20-, 23-, or 25-mm RetroFlex balloon (Edwards LifeSciences, Irvine, CA) is used for placement of a 23-, 26-, or 29-mm prosthesis, respectively. The valve prosthesis should be ready for insertion before the completion of BAV in case severe aortic insufficiency and hemodynamic instability develops. Using the pigtail catheter placed in the ascending aorta above the native aortic valve, contrast is administered at the time of full balloon inflation to assess the risk of coronary obstruction by displacement of the native valve leaflet over the left main ostium and to confirm optimal valve sizing (see Fig. 53-4, *A*).

Valve Insertion and Deployment

The prosthesis and delivery system are inserted in the sheath over the extra-stiff wire (see Fig. 53-4, *B*). After the delivery system reaches the aortic arch, the RetroFlex (or NovaFlex) catheter is activated, allowing safe passage of the delivery system across the aortic arch. The system is then advanced until it reaches the ascending aorta. In the predetermined reference projection, the valve is positioned in the aortic position.

After confirmation of the appropriate location with angiography (and TEE if available) (see Fig. 53-4, *C*), the valve is deployed under RVP (see Fig. 53-4, *D*) after confirming that the systemic blood pressure has reached and maintained its nadir. Balloon inflation is held 3 to 5 seconds before deflation, and RVP is stopped to avoid traction on the prosthesis while the balloon catheter is being withdrawn (see Fig. 53-4, *E*). The RVP run usually does not last longer than 15 seconds.

The delivery system is straightened and withdrawn. The transvalvular pressure gradient can be measured and paravalvular leaks evaluated by angiography (see Fig. 53-4, *F*) and echocardiography.

Sheath Removal and Arteriotomy Closure

The sheath is withdrawn with careful monitoring of the blood pressure and simultaneous contrast administration through a catheter placed at the level of the iliac bifurcation or into the iliac artery. A precipitous drop in blood pressure or extravasation of contrast indicates vascular rupture. This complication should be treated appropriately and expeditiously using a covered stent or surgical repair. Immediate tamponade of the ruptured vessel with the large sheath or closure of the iliac artery or abdominal aorta with a large balloon can be urgently performed before arterial repair. The arteriotomy site is then closed surgically or percutaneously with the previously placed preclosure device.

Transapical Approach to Valve Implantation

Because the procedural steps of valve deployment for the transapical approach are similar to those for the transfemoral route, only the differences are delineated (see Fig. 53-5).[95-100] Femoral arterial and venous accesses are obtained for aortic root angiography and RVP as previously described. RVP can also be obtained with an epicardial lead.

A small left lateral thoracotomy is performed. The planes are dissected until the LV apex is visualized. A purse-string suture is placed in a muscular segment of the apicolateral wall. After the patient is anticoagulated and the activated clotting time (ACT) reaches a therapeutic level, a direct puncture of the left ventricle is performed, and a 7- or 8-Fr sheath is inserted into the left ventricle. A 0.035-inch, J-tipped wire is then advanced through the valve into the descending aorta while guided with a Judkins right curve catheter. The wire must be free of the papillary muscles or mitral chordal structures to avoid complications with the insertion of the delivery sheath.

After the wire is in the descending aorta, it is exchanged for an extra-stiff wire, the Amplatz 0.035-inch, 270-cm-long guidewire, and the Judkins right catheter is removed. The sheath is exchanged for the large delivery sheath that is inserted 3 to 4 cm into the LV cavity. Under RVP, BAV is performed with a 20-mm RetroFlex balloon (see Fig. 53-5, *A*). The Ascendra delivery system is advanced into the sheath and deaired. The valve-catheter ensemble is advanced into the aortic position, maintaining a position midway between the aorta and ventricle.

After confirmation of the appropriate position by TEE and angiography, RVP and a breath hold by the patient are begun. The valve is deployed (see Fig. 53-5, *B*) as the blood pressure is at is nadir, and the balloon is deflated and withdrawn. After the degree of aortic insufficiency is assessed (see Fig. 53-5, *C*) and the valve position is confirmed by TEE, the ventricular sheath can be removed. If the valve needs to be postdilated, the procedure is done. If no further intervention is needed, the delivery sheath is removed,[96] the puncture site repaired, and the anticoagulation reversed. The thoracotomy is closed over a drain.

Direct Transaortic Approach to Valve Implantation

The retrograde direct transaortic approach is an interesting alternative to the transapical approach for patients in whom vascular access through the femoral artery cannot be considered.[101] It involves a 5-cm incision in the chest by a ministernotomy or minithoracotomy. CT is used to determine the anatomy and calcification of the aorta, to confirm a minimal distance of 7 cm between the insertion site and the annulus, and to select the best puncture site for optimizing coaxial alignment with the native valve. The advantage of this approach over the transapical route is to avoid any trauma to the left ventricle.

Outcomes

Historical Results

The initial report of a successful percutaneous implantation of an aortic bioprosthesis in a patient with severe, symptomatic AS who was admitted in cardiogenic shock in April 2002 was greeted with enthusiasm.[21] From 2003 to 2004, single-center registries that documented the feasibility of the procedure done on a compassionate basis were started under the names of Initial Registry of Endovascular Implantation of Valves in Europe (I-REVIVE) and Registry of Endovascular Critical Aortic Stenosis Treatment (RECAST).[68] These procedures used a 23-mm bioprosthesis made of equine pericardium mounted on a stainless steel balloon-expandable stent, and valve placement was primarily done through the antegrade (transseptal) approach.

Procedural success was achieved in 75% of cases. Aortic valve area increased consistently from 0.6 to 1.6 cm^2 and was accompanied by a fall in the mean transvalvular pressure gradient (37 to 9 mm Hg) and an increase in the left ventricular ejection fraction (LVEF) (45% ± 18% to 53% ± 14%). The 30-day mortality rate was 23%, and the 30-day major adverse cardiovascular and cerebrovascular event (MACCE) rate was 26%.[68] The survival rate was 63% at 6 months and was limited by the severity of patients' comorbidities.

Moderate to severe perivalvular aortic insufficiency, which occurred in 63% of patients, and valve embolization were procedural limitations imposed by the availability of a single valve size. Due to venous distensibility, sheath insertion was not limited by vessel size, tortuosity, or peripheral vascular disease. Valve placement was simple because the device crossed the smooth aspect of the aortic valve. However, the technique was challenging because it required a transseptal puncture, navigation of the catheter-valve ensemble across the mitral and aortic valve, and guidewire interaction with the mitral valve and subvalvular apparatus, contributing to poorly tolerated acute mitral insufficiency. The sum of these problems limited the diffusion of this approach, prompted technical improvements in the delivery system, and promoted the resurgence of the retrograde approach.

Significant technical and prosthetic modifications followed to solve the previously encountered limitations. To reduce the degree of perivalvular regurgitation, valves were oversized in relation to the aortic annulus, and a second prosthesis size (26 mm) became available. The perimeter and area of the aortic annulus at the level of aortic leaflet insertion was identified for appropriate valve sizing. Necessary landmarks for valve positioning were recognized, decreasing the risk of valve embolization. Catheters with a manually activated deflectable tip facilitated the valve delivery through the retrograde approach. Modifications in the delivery sheath also reduced vascular complications. Sheath length was increased to deliver the catheter-valve ensemble directly in the descending aorta, decreasing the risk of vascular injury.[98] Minimal arterial diameter, vessel tortuosity, and vessel calcification were the major limiting factors.

Multicenter registries in the United States, such as the second Transcatheter Endovascular Implantation of Valves (REVIVAL II); the European Union, such as the second Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE II); and Canada, such as the Canadian Special Access Program, continued to evaluate procedural safety and efficacy. New valve modifications were added to improve long-term function, which included the use of

bovine pericardium, elongation of the skirt to decrease perivalvular insufficiency, and the addition of an anticalcification treatment, culminating in the prosthesis that is currently used.

The series of retrograde implantations published by Webb and colleagues showed an initial procedural success rate of 78%, which increased to 96% after the first 25 cases, reflecting an important learning curve.[97] The observed 30-day mortality rate was 12%, whereas the expected 30-day mortality rate was 28%. At median follow-up, there was no evidence of valve deterioration, migration, restenosis, or valvular insufficiency. Moderate perivalvular leaks were seen in three cases at 1 month. Perivalvular aortic insufficiency was mild, clinically inconsequential, and stable during follow-up for most patients. This information led to approval and valve commercialization in Europe in the fall of 2007.

The initial experience of the transapical approach in the animal model was extrapolated to early human application and showed promising results.[98,99] The first publicaton from Lichtenstein and colleagues[98] consisted of data on seven high-risk patients with AS. Valve implantation was successful in all of them, and there were no procedural deaths. Transvalvular gradient and aortic valve area improvement was seen in all patients, and the results were consistent with those found after retrograde implantation. The observed 30-day mortality rate was lower than the expected mortality rate (14% vs. 35%).[95,98]

Published multicenter experience using this innovative approach has been growing. Walther and colleagues[102] reported a successful implantation rate of 93.2% and a conversion rate to SAVR of 6.8%. Trace to mild aortic insufficiency was seen in 23 patients. The 30-day mortality rate was 13.6%, whereas the predicted operative mortality rate was 26.8%. Extracorporeal circulatory support was used for 47% of patients during the initial procedures, but after familiarization with the technique, the rate dropped.

A U.S. feasibility study reported successful valve placement in 90% of cases and persistent improvement in symptoms, valve area, mean pressure gradient, aortic insufficiency, and quality of life (QOL).[100] Patient survival rates were 81.8% at 1 month, 71.7% at 3 months, and 58.7% at 6 months. MACCE was seen in 65% and included a 5% incidence of stroke, 2.5% need for emergent cardiac surgery, and 17.5% myocardial infarction rate.

Recent Results

Over the past 10 years, the Sapien valve and updated devices have been evaluated in several national and international registries[103-107] and in one evidence-based trial, the pivotal U.S. PARTNER trial.[22,23] A second randomized study—the PARTNER II trial, using the Sapien XT valve—has finished enrollment. Results from the inoperable arm are summarized below (Table 53-3). Results from the intermediate risk arm are expected in 2015. Results of the main series are summarized later.

Canadian Sapien Registry

The Canadian registry of the Sapien valve from 2005 to 2009 in six centers found very encouraging results.[107] There were 339 high-risk patients (STS-PROM 9.8% ± 6.4%) enrolled, with 49.6% transfemoral and 50.4% transapical cases. The procedural success rate was 93.3%, with a 30-day mortality rate of 10.4%. The mortality rate was 22% at a mean follow-up of 8 months, and periprocedural sepsis, need for hemodynamic support, chronic kidney disease, and chronic obstructive pulmonary disease were independent predictors of late mortality, regardless of the approach. Patients with porcelain aorta and those who were frail had acute outcomes similar to those of the overall cohort, and patients with porcelain aorta had as good or better survival at the 1-year follow-up.

PARTNER European Registry

Most short- and medium-term TAVR data have come from European and Canadian registries. The PARTNER European Registry,[108] whose results were published in 2010, is one of three major registries outside the U.S. with experience using the Sapien valve. Its primary safety end point was freedom from death from the index procedure to 30 days and to 6 months. The primary efficacy end point was hemodynamic status of the valve, QOL, and New York Heart Association (NYHA) class improvement at 12 months after implantation. Mean patient age was 82 years, and 84% and 85% of the transfemoral and transapical group had NYHA class III and IV heart failure, respectively. The EuroSCOREs were 26% and 34% for the transfemoral and transapical groups, respectively. The transapical cohort had more comorbidities.

After valve implantation, the mean aortic pressure gradient fell to 10 mm Hg, and the aortic valve area rose to 1.6 cm^2. These values remained the same at the 6-month and 1-year follow-up. Mean LVEF, which was reasonably well preserved at 54% before implantation, was unchanged. Patients who survived to the 1-year follow-up evaluation had a dramatic improvement in NYHA class (60% class I or II), and QOL scores improved at 1 year by 23 points. At the 18-month follow-up, patients in the transfemoral group had a 71% survival rate, and those in the transapical group had a 44% survival rate. However, comparisons between the transfemoral and transapical groups are not appropriate due to the major differences in comorbidities between the two groups, especially peripheral vascular disease, a marker of more severe atherosclerotic disease and poorer outcomes, in the transapical group.

SOURCE and SOURCE XT Registries

The SOURCE Registry, which catalogued Sapien aortic bioprosthesis outcomes, included 1123 consecutive patients who underwent transfemoral and transapical TAVR in 32 centers across Europe.[103] It was created for postmarketing surveillance. Each center provided 100% of the consecutive patients' data for analysis. Twenty-two of the 32 enrolling centers had no prior experience with the Sapien valve and underwent structured training and proctoring.

The mean logistic EuroSCOREs were 25.7% (transfemoral, $n = 463$) and 29.1% (transapical, $n = 575$). The overall procedural success rate was 93.8%, with 30-day mortality rates of 6.3% and 10.3% for the transfemoral and transapical approaches, respectively. At 30 days, functional improvement was dramatic (NYHA class I/II at baseline of 19% vs. 86% at 30 days, $P < .001$), and the mean survival rate at 224 days was 74%. The symptomatic improvement persisted during follow-up. The mean transaortic pressure gradient decreased from 46.1 ± 6.7 to 11.2 ± 4.9 mm Hg at 1 year. Most deaths and hospital readmissions were not valve related. Perivalvular aortic insufficiency remained constant during follow-up, and there was no structural deterioration of the valve.

Results from the transapical SOURCE registry confirm a similar procedural success (92.7%), with conversion to SAVR in 3.5% of cases. Although vascular injury was less common in the transapical group, it was associated with a higher mortality rate. Thirty-day and 1-year mortality rates for the transapical group were higher compared with those for the transfemoral group, but this likely reflects a selection bias. Patients who undergo the transapical approach are older, have more comorbidities, and have higher EuroSCOREs.

The SOURCE XT registry (December 2010 through May 2011)[110] included 2189 patients from 17 countries who received Sapien XT valves in 94 European centers. This registry, which monitored the new technology introduced into the European market, evaluated the results at 30 days and annually to 5 years of the Sapien XT valve and NovaFlex delivery system using various approaches (transfemoral, 62.7%; transapical, 33.3%; other, 3.7%).

Complications were assessed according to the Valve Academic Research Consortium 2 (VARC 2) standards.[112] The preliminary results were presented by Thomas at the 2012 Transcatheter Therapeutics Meeting. The STS-PROM was lower than in the SOURCE registry (8.4% vs. 12.7%). At 30 days, the all-cause mortality (6.3%), cardiac mortality (2.6%), and stroke (2.2%) rates were significantly lower than in the SOURCE registry ($P < .0001$). The rate of major vascular complications had decreased from 27.5% to 10.1% ($P < .0003$), and the rate of major bleeding decreased from 19.3% to 10.6% ($P < .01$).[112a]

FRANCE and FRANCE 2 Registries

After the results released in 2009 of the first French TAVR registry (FRANCE), 109 of a total of 3195 consecutive patients were enrolled

TABLE 53-3 Baseline and Follow-Up Characteristics of Patients Undergoing Transcatheter Aortic Valve Replacement With the Sapien and Sapien XT Valves

Study	*N*	Age (yr)	Logistic ES (%)	STS Score (%)	PS (%)	AVA Pre-P (cm^2)	AVA Post-P (cm^2)	Mean Gradient Pre-P (mm Hg)	Mean Gradient Post-P (mm Hg)	NYHA Class III/IV Pre-P (%)	NYHA Class III/IV at 1 Yr (%)	LVEF Pre-P (%)	LVEF Post-P (%)	Survival at 1 Yr (%)
Sapien Valve														
Canada[107]	339	81±8	NR	9.8	93.3	0.63±0.17	1.55±0.41	46±17	10±4	90.9	NR	55±14	NR	76
SOURCE (TF)[103]	463	81.7	25.8	NR	95.2	0.59	1.7	53.5	3.95	76	21.6	NR	NR	81.1
SOURCE (TA)[103]	575	80.7	29.1	NR	92.7	0.59	1.7	53.5	3.95	77	31	NR	NR	72.1
PARTNER cohort B[22]	358	83.1±8	26.4±17.2	11.6±6	96.6	0.6±0.2	1.5±0.5	44.5±15.7	11±6.9	92	16.7	53.9	57.2	69.3
PARTNER cohort A[23]	699	83.6	29.3±16	11.8±3.3	90.2	0.7±0.2	1.59±0.4	42.7±14	10.2±4	93	12	52.5±13	56±10	75.8
PARTNER EU (TF)[108]	61	82.3	25.7±11	11.3±6	96.4	0.6±0.2	1.5±0.5	48.9±19	12.7±4	82	10.4	52.9±17	56.3±13	79.7
PARTNER EU (TA)[108]	69	81.9±5	33.8±14	11.8±6	95.4	0.6±0.2	1.6±0.5	46.6±18	11.5±3	85.5	14.7	52.8±14	55.2±8	50.7
FRANCE (TF)[109]	95	83.2±7	25.6±11	17.4±11	92.6	0.66±0.1	1.74±0.4	45±16	10.7±5	70	NR	47±14	55.1±12	NR
FRANCE (TA)[109]	71	82.1±7	26.8±11	18.4±12	92.6	0.68±0.1	1.74±0.4	48±16	10.7±5	53	NR	54±12	55.1±12	NR
Sapien XT Valve														
SOURCE XT[110]	2166	81.4±6	20.5±12	8.4	NR	0.7	1.8	47.6	10.8	76.9	12.3	NR	NR	NR
FRANCE 2[110]	2107	82.9±7	22.2±14	15.6±12	96.9	0.7±.2	NR	48.6±16	NR	75.5	10.5	53.8±14	NR	76
PARTNER[111]	284	84±8.7	NR	103±5	96.3	0.6±0.2	1.6	45.2±14	10	96.8	12	52±13	NR	77.5

AVA, Aortic valve area; *ES,* EuroSCORE; *EU,* European Union; *LVEF,* left ventricular ejection fraction; *NR,* not reported; *N,* number of patients enrolled; *NYHA,* New York Heart Association classification; *Post-P,* after procedure; *Pre-P,* before procedure; *PS,* procedural success; *STS,* Society of Thoracic Surgeons, *TA,* transapical approach; *TF,* transfemoral approach.

from January 2010 to October 2011 at 34 centers in France in the FRANCE 2 registry.[112] As of November 2011, patients in this registry had baseline demographics similar to those in the European PARTNER registry, but they received the Edwards Sapien XT valve (67%) or the Medtronic CoreValve (33%).

The transfemoral approach was used in 75% of cases, and the overall procedural success rate was 96.9%. The mortality rates at 30 days and 1 year were 9.7% and 24%, respectively. Major stroke, major bleeding, and major vascular complications occurred in 2.3%, 4.5%, and 4.7% of patients, respectively. The only significant difference between the two valves was the rate of new pacemaker implantation, which was 11.5% for the Sapien XT and 24.2% for the CoreValve ($P < .001$). On multivariate analysis, the independent predictors of 1-year mortality were increased risk according to the logistic EuroSCORE, NYHA functional class III or IV, use of a transapical approach, and a periprosthetic regurgitation grade of 2 or more (scale of 0 to 4). At 1 year, 89.5% of surviving patients had NYHA functional class I or II heart disease.

PARTNER Trial

The U.S. and Canadian multicenter, randomized PARTNER trial[22,23] led to FDA approval of the Sapien valve. The primary end point of this pivotal trial was death from any cause at 1 year (see Fig. 53-6). The study design is shown in Figure 53-8.

Between 2007 and March 2009, it enrolled patients from 25 centers with severe, symptomatic AS who were poor surgical candidates. In one arm powered for noninferiority analysis, 699 patients with an elevated surgical risk (STS-PROM >10%) were randomized to SAVR or TAVR (transapical or transfemoral approach). In a second arm powered for superiority analysis, 358 patients with severe AS who were deemed inoperable were randomized to optimal medical treatment (including BAV) or TAVR.

Results of the inoperable arm were reported first.[22] Patients randomized to TAVR had lower rates of all-cause mortality (30.7% vs. 50.7%, $P < .001$), cardiovascular mortality (19.6% vs. 41.9%, $P < .001$), repeat hospitalization (22.3% vs. 44.1%, $P < .001$), and the composite end point of death or repeat hospitalization (42.5% vs.71.6%, $P < .001$). During up to 2 years of follow-up, there was no evidence of degeneration of the valvular prosthesis or restenosis.[113] Heart failure symptoms were less severe in patients treated with TAVR. Patients treated with TAVR had a higher incidence of major vascular complications (16.2% vs 1.1%, $P < .001$), major bleeding (22.3% vs. 11.2%, $P < .001$), and major strokes (5.0% vs.1.1%, $P = .06$). In patients with severe AS who are not suitable candidates for SAVR, TAVR should be the standard of care.

Results for the high-risk operative cohort were reported 1 year later.[23] The all-cause mortality rate at 30 days was slightly lower with TAVR than SAVR (3.4% vs. 6.5%, $P = .07$) but was similar at 1 year (24.2% vs. 26.8%), 2 years (33.9% vs. 35%), and 3 years (44.2% vs. 44.8%).[3,8] Although the rates of all neurologic events were higher after TAVR at 30 days and 1 year (5.5% vs. 2.4% and 8.3% vs. 4.3%, $P < .05$), rates of major strokes were not significantly different between TAVR and SAVR at 30 days (3.8% vs. 2.1%, $P = .2$) or at 1 year (5.1% vs. 2.4%, $P = .07$).

There were other important differences in periprocedural risks between the two groups, with more major vascular complications 30 days after TAVR (11.0% vs. 3.2%, $P < .001$) and more major bleeding (19.5% vs. 9.3%, $P < .001$) and new-onset atrial fibrillation (16.0% vs. 8.6%, $P = .006$) after SAVR. Marked improvement of symptoms was similar after TAVR and SAVR, and it was sustained at 3 years for both

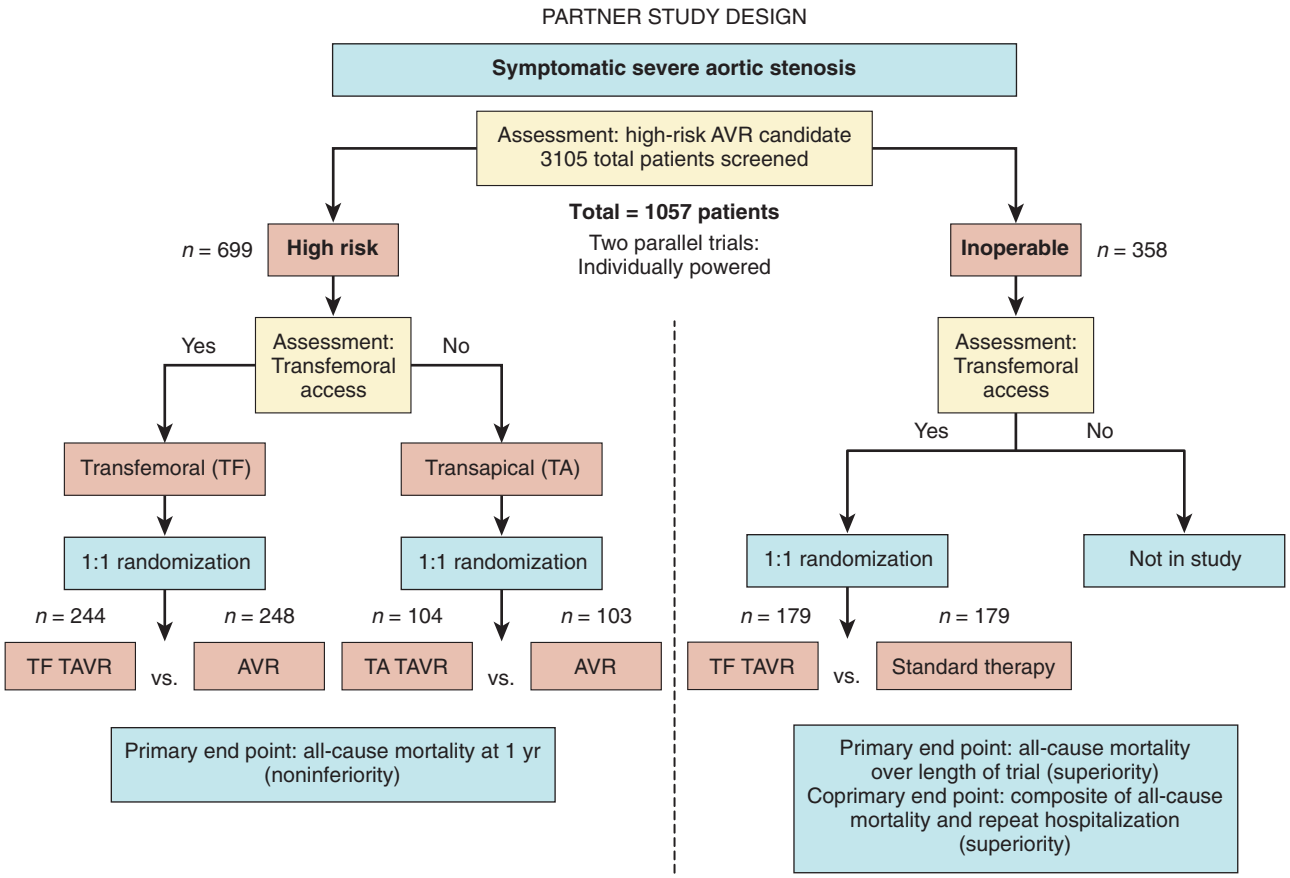


FIGURE 53-8 The PARTNER trial is a multicenter, randomized trial that evaluated the Sapien valve in the inoperable and high-risk operable population of patients with severe symptomatic aortic stenosis. *AVR,* Aortic valve replacement; *TAVR,* transcatheter aortic valve replacement.

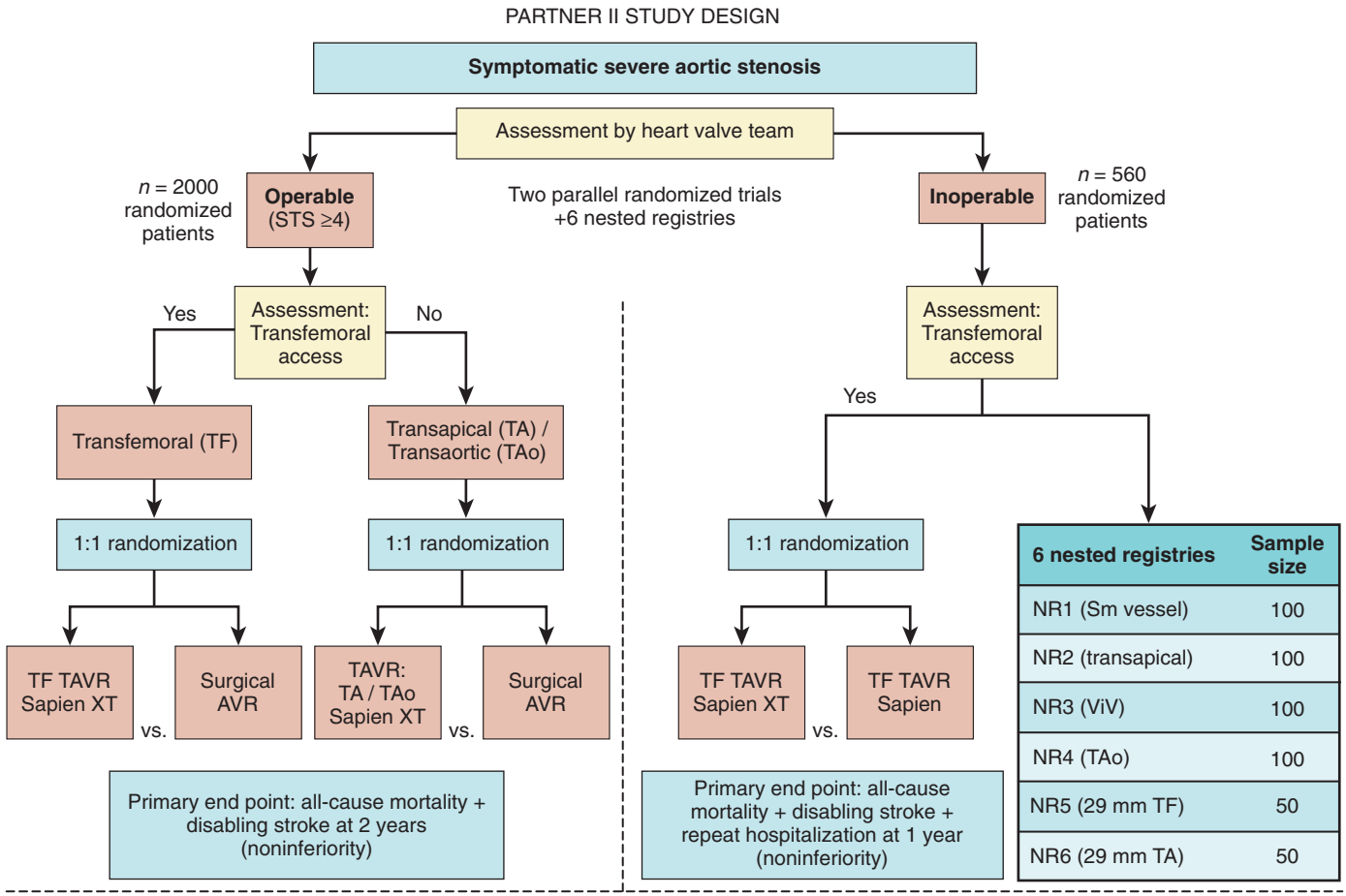


FIGURE 53-9 The PARTNER II trial evaluated the Sapien XT valve in an inoperable population randomized to Sapien XT or Sapien devices with multiple nonrandomized, nested registries and in an operable, intermediate-risk population randomized to transcatheter aortic valve replacement with the Sapien XT or to surgical aortic valve replacement. *AVR,* Aortic valve replacement; *NR,* nested registry; *SDS,* Society of Thoracic Surgery score; *TAVR,* transcatheter aortic valve replacement.

groups.[114] From these results, TAVR emerged as a viable alternative to SAVR for high-risk patients. The choice is made by the interdisciplinary heart team.

PARTNER II Trial

The PARTNER II trial compared the safety and effectiveness of the Sapien XT valve using the NovaFlex delivery system with the Sapien valve in a randomized controlled trial using rigorous trial methods, including the VARC 2 definitions[115] for clinical outcomes. The study design is shown in Figure 53-9. It had two independently randomized populations: the inoperable cohort of patients randomized to the Sapien XT or Sapien valve using a transfemoral approach and the moderate-risk cohort of patients randomized to SAVR or TAVR with the Sapien XT valve using the transapical, transaortic, or transfemoral approach (see Fig. 53-6). In addition to these populations, there were seven nonrandomized nested registries for the inoperable population: inoperable small vessel, inoperable transapical, valve in valve, transaortic, 29-mm Sapien XT transfemoral, 29-mm Sapien XT transapical, and 20-mm Sapien 3.

The primary end point for the inoperable cohort was a composite end point of death, disabling stroke, and repeat hospitalization. The results were presented at the American College of Cardiology meeting in 2013.[116] At 30 days, there was no significant difference in the incidence of the components of the composite end point or in the combined end point ($P = .6$), whereas major vascular events were more common among patients implanted with the Sapien system (15.5% vs. 9.6%, $P = .04$), reaching the noninferiority threshold. Valve performance was similar.[117] The 29-mm prosthesis had similar performances in the nonrandomized registries.

The intermediate-risk cohort included patients with an STS-PROM greater than 4% who were randomized to TAVR or SAVR. Its primary end point was the nonhierarchical incidence of stroke or death at 2 years. Enrollment has finished, and data are being adjudicated, but the results are not yet available. Results from the other nonrandomized registries are pending completion.

Complications

Stroke

The overall incidence of clinically significant stroke is 2.5% to 4.2%.[98-100,103-105,117] Stroke seriously affects the survival and QOL (Table 53-4).[23] Stroke has many causes, as shown by the occurrence of cardiovascular events during, shortly after, or distant from the TAVR procedure.[118] Strokes occur in 87% of patients within 24 hours after TAVR.

It was originally postulated that the rate of cerebrovascular accident (CVA) would be lower with the transapical approach because the aortic arch was not manipulated, but the incidence appears to be similar to that of other approaches. Studies suggest a higher incidence, with subclinical perfusion abnormalities documented by magnetic resonance imaging (MRI).[119] Cerebral embolization can occur during the passage of the valve across the aortic arch, while trying to traverse the aortic valve to gain access into the left ventricle, and during BAV and valve

TABLE 53-4 Procedural Characteristics and Complications of Patients Undergoing Transcatheter Aortic Valve Replacement With the Sapien and Sapien XT Valves

Study	Proc. MR (%)	30-Day MR (%)	Valve in Valve (%)	Conv. Open AVR (%)	AI >2+ (%)	Major CVA or TIA (%)	Major VC (%)	MI (%)	AKI (%)	PM (%)	Major Bleeding (%)
Sapien Valve											
Canada (TF)[107]	1.8	9.5	2.4	1.2	6	0.6	13.1	0.6	1.8	3.6	NR
Canada (TA)[107]	1.7	11.3	2.8	2.3	6	0.6	13	1.7	3.4	6.2	NR
Source (TA)[103]	NR	10.3	3.3	3.5	2.3	2.6	2.4	0.6	7.1	7	9.9
Source (TF)[103]	NR	6.3	0.6	1.7	1.5	2.4	10.6	0.6	1.3	7	8.9
SOURCE (XT)[110]	NR	4%			5.5						
PARTNER Cohort B[22]	1.1	5.0	1.7	0	12	5/0	16.2	0	1.1	3.4	16.8
Sapien XT Valve											
PARTNER Cohort A[23]	0.9	3.4	2	2.6	12.2	5.6	11	0	1.2	3.8	9.3
PARTNER EU (TF)[108]	1.6	8.2	NR	1.6	5	3.3	7.2	3.3	NR	1.8	NR
PARTNER EU (TA)[108]	1.4	18.8	1.4	3	5	1.5	NR	6	2%	3.8	NR
FRANCE TF[109]	NR	8.4	NR	NR	9	4.2	6.3	2	1	5.3	NR
FRANCE (TA)[109]	NR	16.9	NR	NR	9	1.4	5.6	0	2.8	5.6	NR
FRANCE 2 (TF)[112]	2.9	8.5	1.4	0.4%	13.9	1.9	2.7	NR	NR	11.5	2
FRANCE 2 (TA)[112]	4.1	13.9	2.9	0.7	9	4.4	1.9	NR	NR	13.6	3.4

AI, Aortic insufficiency; *AKI,* acute kidney injury; *Conv.,* conversion to; *CVA,* cerebrovascular accident; *EU,* European Union; *MI,* myocardial infarction; *MR,* mortality rate; *NR,* not reported; *PM,* pacemaker placement; *Proc.,* procedural; *TIA,* transient ischemic attack; V, vascular complications; *TA,* transapical approach; *TF,* transfemoral approach.

implantation. The use of cerebral embolic protection devices during TAVR is being evaluated.

Heart Block

Conduction abnormalities are commonly seen in patients undergoing TAVR due to the proximity of the aortic annulus to the left bundle branch and the AV node. The incidence of conduction abnormalities among patients undergoing TAVR with the Sapien prosthesis is relatively low and not significantly different from that after SAVR.

In the PARTNER trial, the incidence of complete heart block requiring a permanent pacemaker (PPM) was 4.7% (cohort B) and 5.7% (cohort A), left bundle branch block occurred in 12% of patients, and first-degree AV block occurred in 15%. Preexisting right bundle branch block and the degree of oversizing of the prosthesis in relation to the left ventricular outflow tract are predisposing factors for pacemaker dependency.[120,121]

Conduction defects related to trauma of the conduction tissue are transient. However, if there is myocyte necrosis in the interventricular septum, a new AV block will likely develop. With the CoreValve Revalving System, the insertion depth into the LV cavity is associated with more frequent complete heart block.[122]

Renal Dysfunction

Acute kidney injury after TAVR has an incidence of 12% to 28%, and it may progress and require renal replacement therapy for 1.4% of patients. Hypertension (odds ratio [OR] = 4.66), chronic obstructive pulmonary disease (OR = 2.64), and transfusion requirement (OR = 3.47) are important risk factors for development of acute kidney injury. It is associated with a higher mortality rate (28% vs. 7%).[111,123] Compared with surgery, acute kidney injury (9.2% vs. 25%) and the need for dialysis (2.5% vs. 8.7%) are less common in patients undergoing TAVR. Development of advanced renal dysfunction after the procedure is associated with high mortality rates.[123]

Severe Aortic Insufficiency

Severe aortic insufficiency is a rare event. It is categorized as valvular or perivalvular. Valvular (central) insufficiency is most commonly caused by the guidewire and disappears after the wire is removed. It is rarely caused by prosthetic malfunction or native leaflets that interfere with prosthetic function. This is treated with placement of a new valve inside the previously placed valve.

Perivalvular insufficiency results from incomplete coverage of the annulus by the stent frame or malposition of the prosthesis (too aortic or too ventricular). It is a serious concern because more than mild aortic insufficiency has been associated with impaired midterm outcomes.[115] All efforts must be made to prevent paravalvular aortic insufficiency by rigorous assessment of the annulus shape and dimension by CT. Paravalvular insufficiency may result from inappropriate sizing, valve malposition, or stent underexpansion. Dilation of the implanted valve may be performed cautiously by adding 1 or 2 mL of saline and contrast mixture to the balloon catheter, which must be centered in the valve. Because the stent has a skirt that does not allow further expansion, postimplantaton dilation with a larger balloon may cause flaring of the aortic portion of the stent, changing the conformation of the ventricular portion and worsening aortic insufficiency.

The incidence of paravalvular aortic insufficiency continues to decrease as new valve sizes become available, valves are sized appropriately, and valve skirts are modified. As newer types of valves appear, it is likely that aortic insufficiency will be further reduced.

Valve Embolization

Valve embolization usually results from malposition, an undersized prosthesis, or inappropriate capture during RVP. Valve embolization to the LV cavity requires urgent thoracotomy for removal of the prosthesis and replacement of the aortic valve.

If aortic embolization occurs, the guidewire must not be removed from across the prosthetic valve until it is anchored in the distal aorta to prevent the valve from turning. A balloon catheter is placed in the proximal end of the valve, and the valve is pulled until it can be deployed or fully expanded distal to the left subclavian artery. After the embolized valve is fixed, a new valve can be placed in the aortic position while correcting the original cause of the complication. If the guidewire is removed before fixing the valve in place, the valve may become inverted, preventing the passage of blood through it. This complication is often fatal unless the valve can be opened with a stent or surgically. Aortic angiography is recommended after valve manipulation because it can cause aortic dissection.

Vascular Complications

Vascular complications occur in 6.6% of cases. They more commonly occur in procedures using the transfemoral approach than the transapical approach (8% vs. 3.6%),[103] but they are more likely to be fatal in

those using the transapical approach. Vascular complications include small dissection, vascular perforation, and vessel avulsion. Prevention requires vascular screening and determination of the appropriate luminal diameter and absence of luminal calcification.

Although vascular complications have been associated with higher mortality rates, increasing procedural experience has spawned effective prevention and intervention strategies, decreasing the associated mortality. Complications may arise from difficult sheath insertion or prolonged sheath time because the adluminal surface adheres to the endothelium. They are easily recognized by the sudden onset of hypotension.

Aortic occlusion balloons should be accessible to minimize bleeding while stabilizing the patient. With the availability of expandable sheaths, catheter modifications that allow passage through a smaller arteriotomy site, availability of alternative access routes, and multidisciplinary approaches for device implantation, the frequency of vascular complications will continue to fall, as observed in the PARTNER II inoperable arm.[111]

Aortic Root Dissection and Annular Rupture

Aortic root dissections may occur if the native valve is not appropriately predilated and passage of the prosthesis is vigorous or occurs after attempts to capture an embolized valve. Aortic annular tear is seen in patients with a heavily calcified aortic root and can be avoided by limiting the degree of prosthesis oversizing. These rare complications require urgent conversion to surgery and are often fatal.

Coronary Obstruction

The Sapien prosthesis is placed in the subcoronary position and should not interfere with the coronary ostia or future attempts at percutaneous revascularization.[124] Coronary obstruction occurs in 0.6% of cases and is seen in patients with effacement of the sinotubular junction, which causes the coronary ostia to migrate.[104]

The distance between the ostia and the aortic annulus is routinely determined by CT angiography (CTA) during patient screening. Coronary obstruction may be inconsequential if patients have functioning coronary artery bypass grafts. If occlusion occurs, emergency revascularization can be performed.

COREVALVE TRANSCATHETER AORTIC VALVE REPLACEMENT

Three generations of the CoreValve transcatheter heart valve have been developed. The first-generation CoreValve was composed of a 25-Fr delivery catheter that housed a self-expanding nitinol frame supporting a bovine pericardial valve.[125,126] The second-generation, 21-Fr delivery catheter used lower-profile porcine pericardial tissue and a scalloped inflow portion of the valve to provide better flow hemodynamics.[126,127]

The third-generation 18-Fr CoreValve percutaneous aortic valve achieved its lower profile by cutting the skirt and leaflet into six independent sections and sewing these sections onto the nitinol frame. The third-generation CoreValve received Conformiteé Européenne (CE mark) approval in March 2007 and was approved by the FDA for extreme-risk patients in January 2014 and for high-risk patients in April 2014.

The CoreValve has three components: a self-expanding nitinol support frame with cells configured in a diamond design, which anchors a trileaflet porcine pericardial tissue valve; an 18-Fr Accutrek delivery catheter; and a disposable loading system. CoreValve frames are available in 23-mm (annular diameter of 18 to 20 mm), 26-mm (aortic annular diameter of 20 to 23 mm), 29-mm (annular diameter of 24 to 26 mm), and 31-mm (annular diameter of 26 to 29 mm) sizes.

The nitinol frame and has three levels of radial and hoop strength (Fig. 53-10). The frame inflow exerts a high radial expansive force to secure the frame in the aortic annular location. The strength of this portion of the frame prevents annular recoil and allows the frame to partially conform to the noncircular shape of the aortic annulus, preventing frame migration and minimizing the occurrence of paravalvular leaks. The constrained center portion of the frame has high hoop strength that resists size and shape deformation, which is critical because this portion of the frame contains the supraannular valve leaflets. The frame is concave at this location to avoid the coronary ostium with the native valve, and it allows coronary cannulation after implantation. The outflow portion of the frame exerts low radial forces and orients the frame to the aorta parallel to flow through the valve.

Porcine pericardium was selected due to its lower profile compared with bovine pericardium and its durability. The three leaflet elements are constructed with long commissures that are similar to a suspension bridge and more uniformly distribute the aortic pressure load to the valve leaflets and the commisural posts. An angled takeoff of the posts further reduces the stress and optimizes leaflet motion. The ability to maintain functionality in a nonround shape at the inflow is a critical feature of the CoreValve Revalving System because the constrained portion of the frame that supports the valve remains in a circular configuration.[128]

Patient Selection

Selection of patients suitable for CoreValve TAVR is best facilitated by a multidisciplinary team that includes cardiac surgeons, interventional cardiologists, imaging specialists, and geriatricians. The multidisciplinary team reviews the clinical, anatomic, and vascular information for the individual patient and determines his or her suitability for CoreValve TAVR.

Clinical Criteria

The multidisciplinary team evaluates the overall surgical risk of patients being evaluated for CoreValve TAVR. Risk assessment includes standard scoring criteria, such as the STS-PROM[129] and EuroSCORE,[130] along with other assessments for comorbidities, frailty, and disability.[131,132] Patients who have debilitating comorbidities that prevent recovery after TAVR should not treated with the procedure. Extreme-risk patients are those who have an expected risk of death or irreversible comorbidities greater than 50% within 30 days after surgery.[24] High-risk patients have a greater than 10% risk of death within 30 days after surgery, although a slightly higher threshold (>15%) was used in a randomized study.[25] Moderate- or intermediate-risk patients have an estimated surgical risk greater than 3%; the benefit of CoreValve TAVR compared with surgery in this subgroup is being evaluated in an ongoing study.[133]

Clinical contraindications to CoreValve placement include sepsis (including active endocarditis), recent myocardial infarction or CVA, left ventricular or atrial thrombus, uncontrolled atrial fibrillation, and severe mitral, pulmonary, or tricuspid regurgitation. Relative contraindications include active gastritis or peptic ulcer disease, uncontrolled bleeding diathesis, symptomatic carotid artery disease, and abdominal or thoracic aortic aneurysm.

Anatomic Criteria

The aortoannular complex should be carefully evaluated with imaging studies before the procedure. Multidetector CT is the gold standard for CoreValve size selection,[24,25,134-137] and anatomic factors are included in the CoreValve selection matrix. Paramount to the reduction of paravalvular regurgitation after CoreValve TAVR is selection of the appropriate valve size based on end-systole perimeter measurements by multidetector CT.

Vascular Criteria

The 18-Fr CoreValve Revalving System is advanced through an 18-Fr sheath, which requires the access vessel diameter to be larger than 6 mm. In cases of severe calcification and vessel tortuosity, the access vessel diameter should be at least 7 mm. Although initial studies used aortography to select patients for CoreValve placement, later screening procedures included CTA of the torso, including the ascending and descending aorta and the subclavian, iliac, and femoral arteries.[138]

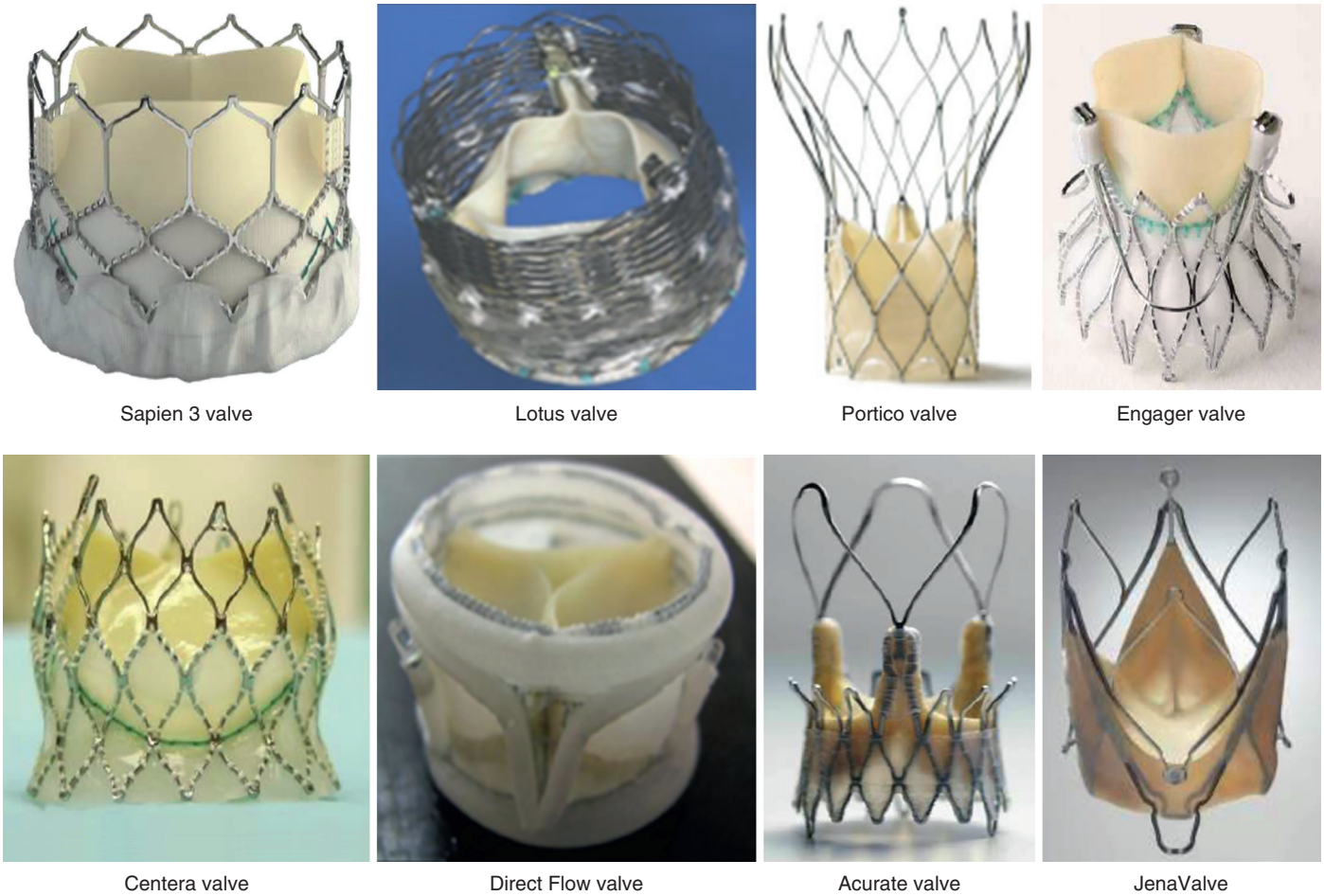


FIGURE 53-10 Significant improvements have occurred in the prostheses for transcatheter aortic valve replacement, minimizing paravalvular insufficiency, facilitating coaxiality, and allowing repositioning.

Procedure

Patients are pretreated with aspirin and clopidogrel. Depending on the clinical status of the patient, general anesthesia or conscious sedation can be used. A temporary 5-Fr pacing wire is positioned within the right ventricle. Arterial access is then obtained on the side contralateral to the planned 18-Fr sheath for CoreValve TAVR. Angiography-guided and ultrasound-guided methods have been used for arterial puncture.[139] After access has been obtained, anticoagulation is administered to achieve an ACT of 250 seconds or longer.

A 6-Fr pigtail catheter is advanced to the ascending aorta, and the distal tip of the catheter is positioned in the noncoronary sinus. A long sheath may be use to stabilize the injection catheter. The gantry position is optimized to allow visualization of all three coronary sinuses in the same plane. An angiographic catheter is then advanced over a standard, J-tip guidewire through the primary access sheath and advanced to the ascending aorta. The J-tip guidewire is exchanged for a 0.035-inch, straight-tip guidewire, which is used to cross the aortic valve.

After the guidewire is across the aortic valve, the catheter is advanced into the ventricle, and hemodynamic measurements are obtained. A 0.035-inch, super-stiff or extra-stiff guidewire is advanced through the angiographic catheter and positioned in the apex of the left ventricle. Careful shaping of the distal portion of the wire prevents inadvertent perforation. If severe valvar calcification is present, balloon valvuloplasty may be performed using a balloon sized to the minor axis of the multidetector CT.

The CoreValve device is advanced over the 0.035-inch guidewire and positioned across the native valve. Aortography is used to identify the most inferior aspect of the valvular plane in the noncoronary sinus. The CoreValve bioprosthesis is then positioned with the inflow portion within the aortic annulus, which is approximately 4 mm below the annulus. The 0.035-inch super-stiff or Lunderquest wire is used to stabilize the CoreValve along the greater curvature of the aorta. Deployment of the CoreValve device then begins.

As the inflow aspect of the device begins to flare outward, aortography is performed sequentially, and final positioning is obtained. After the CoreValve frame has been deployed, aortography is performed to assess the degree of residual stenosis within the frame and the degree of aortic regurgitation. Hemodynamic measurements are obtained to ensure adequate separation of the left ventricular and aortic diastolic contours.[140] TEE or TTE is performed to assess the degree of aortic regurgitation. Concordance of the angiographic, hemodynamic, and echocardiographic findings is critical for determining the need for balloon dilation after insertion. After a satisfactory result has been achieved, the vascular sheath is removed, and percutaneous or open closure is performed.

The patient should be observed with temporary pacemaker placement in a cardiovascular ICU for 24 to 48 hours to monitor for conduction system disturbances. If they not are observed, the patient is monitored for an additional 72 hours and discharged. The patient is continued on the combination of aspirin and clopidogrel for 3 months after the procedure.

Alternative Vascular Access Sites

Several alternative access sites have been used to facilitate CoreValve implantation in patients with suboptimal iliofemoral access.[141,142] The left subclavian (or axillary) artery may be used if there is an adequate lumen caliber (>6.0 mm or >6.5 mm in the absence of a patent left internal mammary graft) and an aortoventricular angle of less than 70 degrees. The right subclavian artery can be used with an adequate lumen caliber (>6.0 mm) and an aortoventricular angle of less than 30 degrees.

Clinical Series

Several single-center and multicenter series have reported the results of CoreValve implantation.[109,126,143-150] The CoreValve Advance International Post-Market Study was a prospective, observational, international study that enrolled 1015 patients with an average age of 81 ± 6 years and mean logistic EuroSCORE of 19.4% ± 12.3%.[151] Thirty days after CoreValve implantation, the all-cause mortality rate was 4.5%, the cardiovascular mortality rate was 3.4%, and the rate of stroke was 3.0%.[151] The 12-month rates of all-cause mortality, cardiovascular mortality, and stroke were 17.9%, 11.7%, and 4.5%, respectively.[151] The 12-month rates of all-cause mortality were 11.1%, 16.5%, and 23.6% for patients with a logistic EuroSCORE of 10% or less, EuroSCORE between 10% and 20%, and EuroSCORE greater than 20% ($P < .05$), respectively.[151]

The U.S. CoreValve Extreme-Risk Pivotal Trial was a prospective, multicenter, nonrandomized investigation evaluating the safety and efficacy of a self-expanding TAVR in patients with severe, symptomatic AS who had risks prohibiting surgery.[24] The primary end point was a composite of all-cause mortality or major stroke at 12 months, which was compared with a prespecified objective performance goal.[24] A total of 506 patients were recruited, and 489 underwent attempted treatment with the CoreValve.[24] The rate of all-cause mortality or major stroke at 12 months was 26.0%, compared with 43.0% for the performance goal ($P < .0001$). Individual 30-day and 12-month events included all-cause mortality (8.4% and 24.3%, respectively) and major stroke (2.3% and 4.3%, respectively).[24] Procedural events at 30 days included life-threatening or disabling bleeding (12.7%), major vascular complications (8.2%), and the need for a PPM (21.6%).[24] The frequency of moderate or severe paravalvular aortic regurgitation was lower 12 months after self-expanding TAVR (4.2%) than at discharge (10.7%, $P = .004$ for paired analysis).[24]

In the U.S. High-Risk Pivotal Trial, patients were recruited with severe AS who were at increased risk for surgery as determined by the heart team at each study center.[25] A total of 795 patients were randomly assigned in a 1:1 ratio to TAVR with the self-expanding transcatheter valve (TAVR group) or to surgical aortic valve replacement (surgical group). In the as-treated analysis, the rate of death from any cause at 1 year was significantly lower for the TAVR group than for the surgical group (14.2% vs. 19.1%), with an absolute reduction in risk of 4.9% (upper boundary of the 95% confidence interval [CI], −0.4; $P < .001$ for noninferiority; $P = .04$ for superiority).[25] The results were similar in the intention-to-treat analysis. In a hierarchical testing procedure, TAVR was noninferior with respect to echocardiographic indices of valve stenosis, functional status, and QOL.[25] Exploratory analyses suggested a reduction in the rate of MACCEs and no increase in the risk of stroke.[25]

Valve Performance After Implantation

Sustained reductions in aortic valve pressure gradients and improvements in effective orifice areas have been reported after CoreValve implantation (see Fig. 53-8).[24,25] Improvements in aortic valve areas and reductions in mean aortic valve pressure gradients have been sustained at the 1- and 2-year follow-up evaluations.[24,25,143,145] One series showed an improvement in left ventricular function after CoreValve implantation.[152] In patients with an LVEF of less than 50%, the LVEF improved from 37.3% ± 7.6% at baseline to 46.0% ± 11.3% after the procedure and to 51.4% ± 11.0% at late follow-up ($P < .001$). No worsening of mitral valve function has been found after CoreValve implantation.[153]

Patient-prosthesis mismatch is an important predictor of outcome after traditional SAVR.[154] The indexed effective orifice area (EOA) was measured after CoreValve implantation in 74 patients with severe, symptomatic AS.[155] Patient-prosthesis mismatch was classified as severe (indexed EOA <0.65 cm^2/m^2) or moderate (indexed EOA = 0.65 to 0.85 cm^2/m^2). The indexed EOA increased from 0.35 ± 0.13 to 0.97 ± 0.34 cm^2/m^2 after aortic valve implantation ($P < .001$) and was accompanied by significant clinical improvement. Severe and moderate patient-prosthesis mismatches were found in 16% and 23% of patients, respectively. Patients with a severe patient-prosthesis mismatch were more symptomatic and had a smaller indexed EOA at baseline than those with a moderate or no patient-prosthesis mismatch (0.28 ± 0.09 vs 0.36 ± 0.12 cm^2/m^2, $P < .05$). Functional status and mortality at 30 days and 6 months were not significantly different for patients with severe patient-prosthesis mismatch and those with moderate or no patient-prosthesis mismatch.

A sustained improvement in NYHA class has been demonstrated 12 to 24 months after CoreValve implantation.[143,145] In the 18-Fr CoreValve Safety and Efficacy Registry analysis, the NYHA class improved by at least one class for 72% of patients, and 18% had no change 2 years after the procedure ($P < .001$) (see Fig. 53-9).[143] In a single-center series of 126 patients, improvement of QOL scores was demonstrated at 5 months, and gains were sustained 24 months after the procedure.[145] In a series of 30 patients who underwent CoreValve implantation, QOL assessments and scales for physical and mental health were improved 5 months after the procedure.[156] The NYHA class was improved at discharge and after 5 months. Preprocedural evaluation showed severe impairment of perceived QOL by patients compared with the general population of those older than 75 years as evidenced by physical and mental scores; there were striking improvements in both scores 5 months after the procedure.[156]

Complications

Unique complications have been reported after TAVR,[88] necessitating a refinement of the end points used for traditional SAVR.[157] The VARC developed standardized definitions for outcomes after TAVR, and these criteria will form the evidence base for future studies.

Strokes and Transient Ischemic Attacks

Stroke has been reported in approximately 5% of patients after traditional SAVR[158]; similar stroke rates have been reported after CoreValve placement and SAVR.[25] The CVAs after TAVR are likely caused by embolization of atherothrombotic material during advancement of the device to and across the aortic valve.[159] Microembolization demonstrated by MRI is common after TAVR,[160,161] but clinically detectable strokes are uncommon (2.9% to 5.1%).[126,144] A broader definition of stroke that includes transient ischemia attacks (<24 hours) with new structural defects seen on imaging studies may increase the reporting of this complication in contemporary series.[162] Novel embolic protection devices to protect the cerebral circulation are being developed.

Aortic Regurgitation

The significance and treatment of aortic regurgitation after CoreValve placement are determined by its cause.[163] Significant aortic regurgitation due to paravalvular leaks is uncommon after CoreValve TAVR and primarily results from low positioning of the CoreValve frame, incomplete expansion of the frame into the eccentrically shaped annulus, rigidity of the underlying aortic annulus due calcification, or undersizing of the valve relative to the aortic annular size. When the CoreValve frame is underexpanded, postdeployment valvuloplasty may useful. When the CoreValve frame is positioned too low after deployment, retraction of the frame loops using a retrieval snare may allow appropriate positioning within the annulus.[164-166]

Higher degrees of postimplantation aortic regurgitation (≥2+) have been associated with worse clinical outcomes, including low cardiac output, respiratory failure, delirium, new left bundle branch block, and in-hospital death.[134] Moderate to severe aortic regurgitation improved in more than 80% of patients in the first year after CoreValve implantation, likely due to annular remodeling and CT-based valve sizing.[24]

Vascular Access Complications

Due to the relatively large (18-Fr) caliber sheath required for placement, vascular complications may occur during and after CoreValve placement. In a series of 91 consecutive patients who were treated with TAVR using the 18-Fr Medtronic CoreValve System, vascular events occurred in 13 patients (13%), and 7 (54%) of these cases were related to incomplete arteriotomy closure with the Prostar device.[167]

Depending on how major vascular complications were defined, the incidence varied from 4% to 13%.[167] Meticulous preprocedural screening using CTA, the use of vascular ultrasound guidance for arterial access,[139] and the use of alternative (e.g., subclavian) access have improved case selection and prevented vascular complications.

Conduction System Disturbances

AS is commonly associated with latent and manifest conduction disease in the His bundle and the trifascicular conduction system.[168,169] Conduction system disease is more extensive in cases with calcified valves and greater valve obstruction.[168] Because of the location of the AV node and origin of the left bundle adjacent to the junction of the right coronary and noncoronary cusps, irritation of the membranous septum can affect AV conduction.

Paired electrophysiologic studies of patients undergoing BAV showed that a new intraventricular conduction defect (i.e., QRS complex duration greater than 100 msec) or bundle branch block occurred in 5 of 13 patients who had a normal QRS duration before the procedure.[170] In four patients, the newly acquired intraventricular conduction defect was still seen on follow-up electrocardiographic tracing.[170]

SAVR is associated with an almost sixfold increased risk of PPM placement compared with other cardiac operations.[171] In a series of 354 patients undergoing SAVR, 29 (8.5%) patients required early PPM placement.[172] Preoperative conduction system disease was the only independent predictor of PPM placement ($P < .01$); the relative risk for PPM placement in this group was 2.88 (95% CI, 1.31 to 6.33).[172]

Conduction disturbances and heart block occur in some patients after percutaneous placement of the CoreValve.[173] In an initial series of 30 patients undergoing CoreValve placement, the incidence of new, postoperative conduction system disturbances diagnosed by 12- to 24-hour Holter monitoring was 68.0%.[174] Left bundle branch block occurred in 45.8% to 55%,[173,174] and complete AV block requiring PPM implantation occurred in approximately 20% of patients.[174]

In another series of 30 patients who underwent CoreValve placement, 10 underwent PPM implantation during the same admission (33.3%).[175] PPM placement was performed for prolonged, high-grade AV block in four cases, episodic high-grade AV block in five, and sinus node disease in one.[175] The need for a PPM correlated with a left axis deviation at baseline and left bundle branch block with a left axis deviation ($P = .002$).[175] Baseline right bundle branch block is an important predictor of the need for a PPM.[173] It was also related to a diastolic interventricular septal dimension greater than 17 mm on transthoracic echocardiography ($P = .045$, $r = 0.39$) and the baseline thickness of the native noncoronary cusp ($P = .002$, $r = 0.655$).[175] Attention to avoiding septal trauma during balloon valvuloplasty before CoreValve implantation and higher CoreValve positioning (<6 mm below the sinus) may decrease the need for a PPM after CoreValve placement.

Coronary Artery Occlusion

Coronary occlusion after CoreValve TAVR is rare. Multidetector CTA has shown that the distance between the aortic annulus and the coronary arteries is reduced in patients with AS, likely due to longitudinal remodeling of the aortic root in cases of degenerative AS.[176] Because the degenerative native aortic valve is not removed but is circumferentially displaced during TAVR, patients with a narrow sinus of Valsalva and low origin of the native coronary arteries may be predisposed to coronary occlusion by displacement of the native valve.[177]

Coupled with the constrained CoreValve frame diameter in the region of the coronary ostia and better preprocedural screening using aortography and CTA to ensure an adequate sinus of Valsalva width and height, coronary occlusion now occurs in less than 1% of cases. When it does occur, rescue percutaneous coronary intervention can be performed to reestablish coronary perfusion.[178]

Ongoing Investigations

The SURTAVI trial is a multicenter, randomized study primarily based in Europe. It is designed to evaluate the safety and efficacy of CoreValve TAVR compared with SAVR in a broader patient population, including approximately 2500 patients at intermediate risk for SAVR. Intermediate or moderate risk for this study has been defined as a greater than 3% risk of death within 30 days of valve implantation.

EMERGING VALVE TECHNOLOGIES

Sapien 3 Valve

The Sapien 3 device, the latest generation of balloon-expandable valve developed by Edwards LifeSciences, has been approved and commercialized in several European countries and is under investigation in the United States (see Fig. 53-10). It is a modified and improved version of the Sapien XT valve. It consists of a trileaflet bovine pericardial tissue valve with an optimized shape for hemodynamics and durability. It is mounted into a cobalt-chromium frame with enhanced geometry for an ultralow delivery profile. Four sizes are available: 20, 23, 26, and 29 mm (see Fig. 53-6). A polyethylene terephthalate outer skirt minimizes paravalvular leaks.

The Edwards Commander Delivery System was designed for the transfemoral approach and offers a dual articulation for coaxiality. The device can be used in 14-Fr, ultralow-profile introducer e-sheaths for the 23- and 26-mm valves and 16-Fr sheaths for the 29-mm valve. The Edwards Certitude Delivery System (18 Fr) with articulation features was designed for the transapical approach.

Centera Valve

The Centera valve is the first self-expanding model of a transcatheter valve developed by Edwards LifeSciences with the goal of improving deliverability and allowing valve repositioning. The device consists of a treated, trileaflet bovine pericardial valve mounted into a nitinol stent and delivered by a motorized, low-profile delivery system (14 Fr) requiring a single operator for delivery. The device is under investigation in Europe.

Lotus Valve

The Lotus aortic valve replacement system (Boston Scientific, Natick, MA) is a bioprosthetic valve with three bovine pericardial leaflets mounted into a braided nitinol frame that can be delivered through a transfemoral approach. The valve is fully repositionable and retrievable before detachment, does not require rapid pacing for deployment, and has an adaptive seal that minimizes paravalvular regurgitation.

The Lotus valve has been evaluated in the Repositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of the Lotus Valve System (REPRISE) family of trials. Initial feasibility was evaluated in the first REPRISE trial, which included patients with severe AS at high risk for operative mortality (STS-PROM >8%) and showed a procedural success rate of 81%, absence of procedural 30-day and 1-year mortality, no evidence of moderate or severe paravalvular

insufficiency, and a stroke in one patient (9.1%).[179] After the procedure, the mean transvalvular pressure gradient was 13.7 mm Hg, and all patients had significant improvement. The PPM placement rate was 36.4%.[179]

Reprise II included a second valve size (23 and 27 mm). It showed 100% procedural success, a 4.2% all-cause mortality rate at 30 days, CVA rate of 5.9%, moderate aortic insufficiency or greater paravalvular aortic insufficiency in 1% of patients, and a need for new PPM placement in 28.6% of patients that was mostly associated with valve oversizing.[180]

The Reprise III trial began enrollment in the United States in 2014 to evaluate the Lotus valve in patients with severe AS who are at high or extreme risk for SAVR. The study includes 23-, 25-, and 27-mm valve sizes.

Direct Flow Valve

The Direct Flow Medical (DFM) transcatheter aortic valve is a unique prosthesis with a nonmetallic design and an inflatable support structure that allows precise valve placement and manipulation.[181,182] It is placed through a transfemoral approach and uses an 18-Fr delivery system.

In a multicenter, 100-patient cohort of high-risk patients with severe AS, use of the DFM valve showed a 99% rate of freedom from all-cause mortality at 30 days, a 99% rate of no or mild aortic insufficiency, and a mean transvalvular pressure gradient of 12.6 mm Hg.[181] Data from up to a 2-year follow-up showed appropriate valve function, no evidence of structural deterioration, and no change in aortic insufficiency.[183]

The Transcatheter Aortic Valve Replacement System U.S. Feasibility (SALUS) trial in the United States is evaluating the use of the DFM valve in inoperable patients. An ongoing trial is actively recruiting high-risk or inoperable patients with severe aortic stenosis, randomizing participants to DFM or CoreValve systems.

Portico Valve

The Portico transcatheter heart valve (St. Jude Medical, Minneapolis, MN) is a self-expanding, nitinol prosthesis with bovine pericardial leaflets and a porcine pericardial sealing cuff that can be delivered through a transfemoral, transaortic, subclavian, or transapical approach. The valve is repositionable and resheathable, allowing a greater degree of manipulation before valve deployment. Its positioning does not require RVP.

The U.S. Portico trial was designed to compare the Portico valve with other commercially available valves implanted in high-risk and inoperable cohorts using a transfemoral or alternative access approach. Initial data showed successful device implantation in all patients and demonstrated the ability to recapture. Its hemodynamic profile was comparable to that of other newer prostheses, with a postprocedural mean transvalvular pressure gradient of 10 mm Hg and mild or trace aortic insufficiency in 90% of patients.[184] The study temporarily halted enrollment due to concerns of reduced leaflet mobility, but is now actively enrolling.

JenaValve

The JenaValve (JenaValve Technology, Munich, Germany) consists of a self-expanding, nitinol stent designed to be placed in the subcoronary position. Its leaflets are made of porcine root valve tissue fitted with a porcine pericardial skirt. It is placed by the transapical route and has a set of "feelers" that allows the valve to be implanted in the correct orientation and prevents coronary obstruction. Sizes range from 23 to 27 mm.[185,186]

Results from a pivotal trial demonstrated a procedural success rate of 89.6%, CVA rate of 3%, and 30-day mortality rate of 7.6%. No patients had severe paravalvular aortic insufficiency, and mild or trace aortic insufficiency was seen in 86.4%.[186]

Symetis Acurate Valve

The Acurate aortic heart valve (Symetis, Écublens, Switzerland) is a self-positioning, self-expanding valve placed by the transapical and transfemoral route. The unique design has three stabilization arms that allow the valve to maintain coaxiality while being deployed. The stent body is not covered, which minimizes the risk of coronary obstruction. Sizes range from 23 to 27 mm.

A small study of the valve in high-risk patients with severe, symptomatic AS who were not considered surgical candidates for open heart surgery demonstrated 100% valve implantation, a 12% 30-day mortality rate, and a 2% PPM placement rate.[187] The 6-month follow-up showed appropriate valve function.[187] In 2014, the Accurate valve was approved for use in Europe. Results from a first-in-man series of a new transfemoral delivery system (Acurate-neo) showed successful procedures in 14 of 15 patients with no procedural deaths or pacemaker placements, a mean postprocedural gradient of 7.7 + 3.1 mmHg. Postprocedural paravalvular AI was none/trace in 50%, and no patients had moderate or severe AI.[188]

Engager Valve

The Engager aortic valve (Medtronic, Minneapolis MN) is a self-expanding, repositionable bioprosthesis for TAVR with a special stent design that minimizes paravalvular aortic insufficiency and allows rotational positioning. It accommodates an aortic annulus of 19 to 26 mm.

Initial studies show appropriate valve function, with a mean pressure gradient of 17 mm Hg, no coronary obstruction, and trace or mild aortic insufficiency in all patients. It is available in sizes of 23 and 26 mm.[189]

Other Valve Prostheses

Numerous other TAVR prostheses are being evaluated. Their availability will depend on the results of initial feasibility trials and how they perform against the older-generation devices.

OTHER USES FOR TRANSCATHETER AORTIC VALVE REPLACEMENT

TAVR has been evaluated for the treatment of degraded bioprosthetic valves in patients unsuitable for repeat surgery.[190] The transcatheter procedure is performed by the previously described approaches, but the valve prosthesis is positioned at various heights depending on the type of valve degeneration. Sizing is determined by the internal diameter of the valve.

Initial reports are encouraging, with important residual pressure gradients found in smaller prostheses.[191] Although the hemodynamic performance of the valve-in-valve implants were similar to those in reports of surgical valves, it remains to be seen whether underdeployment will accelerate degradation of the transcatheter heart valves and lead to earlier valve failure. Early data have shown that valve-in-valve treatment is a safe and feasible alternative for treating high-risk patients with failing bioprostheses.[192]

The CoreValve Revalving System has also been used to treat degenerated bioprosthetic valves.[193-195] In the first-reported valve-in-valve procedure, the CoreValve was used to treat a stenotic 21-mm aortic bioprothesis.[194] The CoreValve also has been successfully implanted in patients with a prior mechanical mitral valve prosthesis.[158]

CONCLUSIONS

Catheter-based treatment of AS is rapidly expanding. With the development of TAVR, restenosis after valvuloplasty has been overcome. Medium- and long-term follow-up data on patients treated with TAVR are slowly becoming available, and as more patients reach significant

milestones and valve durability is confirmed, indications for TAVR may be expanded.

Successful TAVR depends on patient selection and the cooperation of cardiac surgeons, interventional cardiologists, anesthesiologists, and all individuals who participate in the care of these patients, many of whom are frail. Centers interested in performing TAVR need specific training in this procedure in addition to a commitment to appropriate imaging equipment and personnel required to perform the procedures safely. A concentrated effort by industry, physicians, and governing medical bodies is needed to facilitate technologic diffusion in a safe and effective manner.

DISCLOSURES

Dr. Cribier is a consultant for Edwards LifeSciences. Dr. Popma receives research grants from Medtronic and is a consultant for Boston Scientific. Dr Zajarias is a consultant for Edwards LifeSciences.

REFERENCES

1. Lindroos M, Kupari M, Heikkila J, Tilvis R: Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol* 21:1220–1225, 1993.
2. Ross J, Jr, Braunwald E: Aortic stenosis. *Circulation* 38:61–67, 1968.
3. Varadarajan P, Kapoor N, Bansal RC, Pai RG: Clinical profile and natural history of 453 nonsurgically managed patients with severe aortic stenosis. *Ann Thorac Surg* 82:2111–2115, 2006.
4. Edwards FH, Peterson ED, Coombs LP, et al: Prediction of operative mortality after valve replacement surgery. *J Am Coll Cardiol* 37:885–892, 2001.
5. Reference deleted in review.
6. Otto CM: Valvular aortic stenosis: disease severity and timing of intervention. *J Am Coll Cardiol* 47:2141–2151, 2006.
7. Iung B, Baron G, Butchart EG, et al: A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. *Eur Heart J* 24:1231–1243, 2003.
8. Cribier A, Savin T, Saoudi N, et al: Percutaneous transluminal valvuloplasty of acquired aortic stenosis in elderly patients: an alternative to valve replacement? *Lancet* 1:63–67, 1986.
9. Schwarz F, Baumann P, Manthey J, et al: The effect of aortic valve replacement on survival. *Circulation* 66:1105–1110, 1982.
10. Kolh P, Kerzmann A, Lahaye L, et al: Cardiac surgery in octogenarians; peri-operative outcome and long-term results. *Eur Heart J* 22:1235–1243, 2001.
11. Bridges CR, Edwards FH, Peterson ED, et al: Cardiac surgery in nonagenarians and centenarians. *J Am Coll Surg* 197:347–356, 2003.
12. Chukwuemeka A, Borger MA, Ivanov J, et al: Valve surgery in octogenarians: a safe option with good medium-term results. *J Heart Valve Dis* 15:191–196, 2006.
13. Connolly HM, Oh JK, et al: Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction: result of aortic valve replacement in 52 patients. *Circulation* 101:1940–1946, 2000.
14. Tarantini G, Buja P, Scognamiglio R, et al: Aortic valve replacement in severe aortic stenosis with left ventricular dysfunction: determinants of cardiac mortality and ventricular function recovery. *Eur J Cardiothorac Surg* 24:879–885, 2003.
15. Vaquette B, Corbineau H, Laurent M, et al: Valve replacement in patients with critical aortic stenosis and depressed left ventricular function: predictors of operative risk, left ventricular function recovery, and long term outcome. *Heart* 91:1324–1329, 2005.
16. Iung B, Cachier A, Baron G, et al: Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J* 26:2714–2720, 2005.
17. Kapoor N, Varadajan P, Pai R: Survival patterns in conservatively treated patients with severe aortic stenosis: prognostic variables in 457 patients. *Circulation* 110(Suppl III):548, 2004.
18. O'Neill WW: Predictors of long-term survival after percutaneous aortic valvuloplasty: report of the Mansfield Scientific Balloon Aortic Valvuloplasty Registry. *J Am Coll Cardiol* 17:193–198, 1991.
19. Registry N: Percutaneous balloon aortic valvuloplasty. Acute and 30-day follow-up results in 674 patients from the NHLBI Balloon Valvuloplasty Registry. *Circulation* 84:2383–2397, 1991.
20. Nishimura RA, Otto CM, Bonow RO, et al: 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 129:2440–2492, 2014.
21. Cribier A, Eltchaninoff H, Bash A, et al: Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation* 106:3006–3008, 2002.
22. Leon MB, Smith CR, Mack M, et al: Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 363:1597–1607, 2010.
23. Smith CR, Leon MB, Mack MJ, et al: Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 364:2187–2198, 2011.
24. Popma JJ, Adams DH, Reardon MJ, et al: Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol* 63:1972–1981, 2014.
25. Adams DH, Popma JJ, Reardon MJ: Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 371:967–968, 2014.
26. Vahanian A, Iung B: The new ESC/EACTS guidelines on the management of valvular heart disease. *Arch Cardiovasc Dis* 105:465–467, 2012.
27. Letac B, Cribier A, Koning R, Bellefleur JP: Results of percutaneous transluminal valvuloplasty in 218 adults with valvular aortic stenosis. *Am J Cardiol* 62:598–605, 1988.
28. Letac B, Cribier A, Koning R, Lefebvre E: Aortic stenosis in elderly patients aged 80 or older. Treatment by percutaneous balloon valvuloplasty in a series of 92 cases. *Circulation* 80:1514–1520, 1989.
29. Berland J, Cribier A, Savin T, et al: Percutaneous balloon valvuloplasty in patients with severe aortic stenosis and low ejection fraction. Immediate results and 1-year follow-up. *Circulation* 79:1189–1196, 1989.
30. Letac B, Cribier A, Eltchaninoff H, et al: Evaluation of restenosis after balloon dilatation in adult aortic stenosis by repeat catheterization. *Am Heart J* 122:55–60, 1991.
31. Koning R, Cribier A, Asselin C, et al: Repeat balloon aortic valvuloplasty. *Cathet Cardiovasc Diagn* 26:249–254, 1992.
32. Eltchaninoff H, Cribier A, Tron C, et al: Balloon aortic valvuloplasty in elderly patients at high risk for surgery, or inoperable. Immediate and mid-term results. *Eur Heart J* 16:1079–1084, 1995.
33. Agatiello C, Eltchaninoff H, Tron C, et al: Balloon aortic valvuloplasty in the adult. Immediate results and in-hospital complications in the latest series of 141 consecutive patients at the University Hospital of Rouen (2002-2005). *Arch Mal Coeur Vaiss* 99:195–200, 2006.
34. Eltchaninoff H, Durand E, Borz B, et al: Balloon aortic valvuloplasty in the era of transcatheter aortic valve replacement: acute and long-term outcomes. *Am Heart J* 167:235–240, 2014.
35. Litvack F, Jakubowski AT, Buchbinder NA, Eigler N: Lack of sustained clinical improvement in an elderly population after percutaneous aortic valvuloplasty. *Am J Cardiol* 62:270–275, 1988.
36. Lieberman EB, Bashore TM, Hermiller JB, et al: Balloon aortic valvuloplasty in adults: failure of procedure to improve long-term survival. *J Am Coll Cardiol* 26:1522–1528, 1996.
37. Freeman RV, Otto CM: Spectrum of calcific aortic valve disease: pathogenesis, disease progression, and treatment strategies. *Circulation* 111:3316–3326, 2005.
38. Dare AJ, Veinot JP, Edwards WD, et al: New observations on the etiology of aortic valve disease: a surgical pathologic study of 236 cases from 1990. *Hum Pathol* 24:1330–1338, 1993.
39. Roberts WC, Ko JM: Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation* 111:920–925, 2005.
40. O'Brien KD: Pathogenesis of calcific aortic valve disease: a disease process comes of age (and a good deal more). *Arterioscler Thromb Vasc Biol* 26:1721–1728, 2006.
41. Inoue K, Owaki T, Nakamura T, et al: Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg* 87:394–402, 1984.
42. Letac B, Gerber LI, Koning R: Insights on the mechanism of balloon valvuloplasty in aortic stenosis. *Am J Cardiol* 62:1241–1247, 1988.
43. Lembo NJ, King SB, 3rd, Roubin GS, et al: Fatal aortic rupture during percutaneous balloon valvuloplasty for valvular aortic stenosis. *Am J Cardiol* 60:733–736, 1987.
44. Bashore TM, Davidson CJ: Follow-up recatheterization after balloon aortic valvuloplasty. Mansfield Scientific Aortic Valvuloplasty Registry Investigators. *J Am Coll Cardiol* 17:1188–1195, 1991.
45. Feldman T, Glagov S, Carroll JD: Restenosis following successful balloon valvuloplasty: bone formation in aortic valve leaflets. *Cathet Cardiovasc Diagn* 29:1–7, 1993.
46. van den Brand M, Essed CE, Di Mario C, et al: Histological changes in the aortic valve after balloon dilatation: evidence for a delayed healing process. *Br Heart J* 67:445–449, 1992.
47. Soyer R, Bouchart F, Bessou JP, et al: Aortic valve replacement after aortic valvuloplasty for calcified aortic stenosis. *Eur J Cardiothorac Surg* 10:977–982, 1996.
48. Agarwal A, Kini AS, Attanti S, et al: Results of repeat balloon valvuloplasty for treatment of aortic stenosis in patients aged 59 to 104 years. *Am J Cardiol* 95:43–47, 2005.
49. Gorlin R, Gorlin SG: Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. I. *Am Heart J* 41:1–29, 1951.
50. McKay RG: The Mansfield Scientific Aortic Valvuloplasty Registry: overview of acute hemodynamic results and procedural complications. *J Am Coll Cardiol* 17:485–491, 1991.
51. Lababidi Z, Wu JR, Walls JT: Percutaneous balloon aortic valvuloplasty: results in 23 patients. *Am J Cardiol* 53:194–197, 1984.
52. Block PC, Palacios IF: Comparison of hemodynamic results of anterograde versus retrograde percutaneous balloon aortic valvuloplasty. *Am J Cardiol* 60:659–662, 1987.
53. Orme EC, Wray RB, Barry WH, et al: Comparison of three techniques for percutaneous balloon aortic valvuloplasty of aortic stenosis in adults. *Am Heart J* 117:11–17, 1989.
54. Sakata Y, Syed Z, Salinger MH, Feldman T: Percutaneous balloon aortic valvuloplasty: antegrade transseptal vs. conventional retrograde transarterial approach. *Catheter Cardiovasc Interv* 64:314–321, 2005.
55. Omran H, Schmidt H, Hackenbroch M, et al: Silent and apparent cerebral embolism after retrograde catheterisation of the aortic valve in valvular stenosis: a prospective, randomised study. *Lancet* 361:1241–1246, 2003.
56. Monin JL, Quere JP, Monchi M, et al: Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. *Circulation* 108:319–324, 2003.
57. Dauterman KW, Michaels AD, Ports TA: Is there any indication for aortic valvuloplasty in the elderly (review)? *Am J Geriatr Cardiol* 12:190–196, 2003.
58. Feldman T: Proceedings of the TCT: balloon aortic valvuloplasty appropriate for elderly valve patients. *J Interv Cardiol* 19:276–279, 2006.
59. Davies H: Catheter mounted valve for temporary relief of aortic insufficiency. *Lancet* 1:250, 1965.
60. Moulopoulos SD, Anthopoulos L, Stamatelopoulos S, Stefadouros M: Catheter-mounted aortic valves. *Ann Thorac Surg* 11:423–430, 1971.
61. Phillips SJ, Ciborski M, Freed PS, et al: A temporary catheter-tip aortic valve: hemodynamic effects on experimental acute aortic insufficiency. *Ann Thorac Surg* 21:134–137, 1976.
62. Matsubara T, Yamazoe M, Tamura Y, et al: Balloon catheter with check valves for experimental relief of acute aortic regurgitation. *Am Heart J* 124:1002–1008, 1992.
63. Andersen HR, Knudsen LL, Hasenkam JM: Transluminal implantation of artificial heart valves. Description of a new expandable aortic valve and initial results with implantation by catheter technique in closed chest pigs. *Eur Heart J* 13:704–708, 1992.
64. Bonhoeffer P, Boudjemline Y, Saliba Z, et al: Transcatheter implantation of a bovine valve in pulmonary position: a lamb study. *Circulation* 102:813–816, 2000.
65. Bonhoeffer P, Boudjemline Y, Saliba Z, et al: Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. *Lancet* 356:1403–1405, 2000.
66. Cribier A, Eltchaninoff H, Letac B: Advances in percutaneous techniques for the treatment of aortic and mitral stenosis. In Topol E, editor: *Textbook of Interventional Cardiology*, ed 4, Philadelphia, 2003, WB Saunders, pp 941–953.
67. Eltchaninoff H, Nusimovici-Avadis D, Babaliaros V, et al: Five month study of percutaneous heart valves in the systemic circulation of sheep using a novel model of aortic insufficiency. *EuroIntervention* 1:438–444, 2006.
68. Cribier A, Eltchaninoff H, Tron C, et al: Early experience with percutaneous transcatheter implantation of heart valve prosthesis for the treatment of end-stage inoperable patients with calcific aortic stenosis. *J Am Coll Cardiol* 43:698–703, 2004.
69. Bauer F, Eltchaninoff H, Tron C, et al: Acute improvement in global and regional left ventricular systolic function after percutaneous heart valve implantation in patients with symptomatic aortic stenosis. *Circulation* 110:1473–1476, 2004.
70. Cribier A, Eltchaninoff H, Tron C, et al: Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. *J Am Coll Cardiol* 47:1214–1223, 2006.
71. Hanzel GS, Harrity PJ, Schreiber TL, O'Neill WW: Retrograde percutaneous aortic valve implantation for critical aortic stenosis. *Catheter Cardiovasc Interv* 64:322–326, 2005.

72. Webb JG, Chandavimol M, Thompson CR, et al: Percutaneous aortic valve implantation retrograde from the femoral artery. *Circulation* 113:842–850, 2006.
73. Grube E, Laborde JC, Gerckens U, et al: Percutaneous implantation of the CoreValve self-expanding valve prosthesis in high-risk patients with aortic valve disease: the Siegburg first-in-man study. *Circulation* 114:1616–1624, 2006.
74. Collart F, Feier H, Kerbaul F, et al: Valvular surgery in octogenarians: operative risks factors, evaluation of Euroscore and long term results. *Eur J Cardiothorac Surg* 27:276–280, 2005.
75. Roques F, Michel P, Goldstone AR, Nashef SA: The logistic EuroSCORE. *Eur Heart J* 24:881–882, 2003.
76. Pinna-Pintor P, Bobbio M, Colangelo S, et al: Inaccuracy of four coronary surgery risk-adjusted models to predict mortality in individual patients. *Eur J Cardiothorac Surg* 21:199–204, 2002.
77. Shroyer AL, Coombs LP, Peterson ED, et al: The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models. *Ann Thorac Surg* 75:1856–1864, 2003.
78. Grossi EA, Schwartz CF, Yu PJ, et al: High-risk aortic valve replacement: are the outcomes as bad as predicted? *Ann Thorac Surg* 85:102–106, 2008.
79. Dewey TM, Brown D, Ryan WH, et al: Reliability of risk algorithms in predicting early and late operative outcomes in high-risk patients undergoing aortic valve replacement. *J Thorac Cardiovasc Surg* 135:180–187, 2008.
80. Makkar RR, Jilaihawi H, Mack M, et al: Stratification of outcomes after transcatheter aortic valve replacement according to surgical inoperability for technical versus clinical reasons. *J Am Coll Cardiol* 63:901–911, 2014.
81. Lee DH, Buth KJ, Martin BJ, et al: Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. *Circulation* 121:973–978, 2010.
82. Afilalo J, Eisenberg MJ, Morin JF, et al: Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. *J Am Coll Cardiol* 56:1668–1676, 2010.
83. Green P, Woglom AE, Genereux P, et al: The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. *JACC Cardiovasc Interv* 5:974–981, 2012.
84. Arnold SV, Reynolds MR, Lei Y, et al: Predictors of poor outcomes after transcatheter aortic valve replacement: results from the PARTNER (Placement of Aortic Transcatheter Valve) trial. *Circulation* 129:2682–2690, 2014.
85. Piazza N, Grube E, Gerckens U, et al: Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) CoreValve Revalving System: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. *EuroIntervention* 4:242–249, 2008.
86. Fraccaro C, Napodano M, Tarantini G, et al: Expanding the eligibility for transcatheter aortic valve implantation the transsubclavian retrograde approach using: the III generation CoreValve revalving system. *JACC Cardiovasc Interv* 2:828–833, 2009.
87. Khalique OK, Kodali SK, Paradis JM, et al: Aortic annular sizing using a novel 3-dimensional echocardiographic method: use and comparison with cardiac computed tomography. *Circ Cardiovasc Imaging* 7:155–163, 2014.
88. Masson JB, Kovac J, Schuler G, et al: Transcatheter aortic valve implantation: review of the nature, management, and avoidance of procedural complications. *JACC Cardiovasc Interv* 2:811–820, 2009.
89. Eltchaninoff H, Kerkeni M, Zajarias A, et al: Aorto-iliac angiography as a screening tool in selecting patients for transfemoral aortic valve implantation with the Edwards SAPIEN bioprosthesis. *EuroIntervention* 5:438–442, 2009.
90. Joshi SB, Mendoza DD, Steinberg DH, et al: Ultra-low-dose intra-arterial contrast injection for iliofemoral computed tomographic angiography. *JACC Cardiovasc Imaging* 2:1404–1411, 2009.
91. Clavel MA, Webb JG, Pibarot P, et al: Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. *J Am Coll Cardiol* 53:1883–1891, 2009.
92. Ruggeri L, Gerli C, Franco A, et al: Anesthetic management for percutaneous aortic valve implantation: an overview of worldwide experiences. *Minerva Anestesiol* 76:100–108, 2010.
93. Durand E, Borz B, Godin M, et al: Transfemoral aortic valve replacement with the Edwards SAPIEN and Edwards SAPIEN XT prosthesis using exclusively local anesthesia and fluoroscopic guidance: feasibility and 30-day outcomes. *JACC Cardiovasc Interv* 5:461–467, 2012.
94. Sharp AS, Michev I, Maisano F, et al: A new technique for vascular access management in transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 75:784–793, 2010.
95. Ye J, Cheung A, Lichtenstein SV, et al: Six-month outcome of transapical transcatheter aortic valve implantation in the initial seven patients. *Eur J Cardiothorac Surg* 31:16–21, 2007.
96. Dumont E, Rodes-Cabau J, De LaRochelliere R, et al: Rapid pacing technique for preventing ventricular tears during transapical aortic valve replacement. *J Card Surg* 24:295–298, 2009.
97. Webb JG, Pasupati S, Humphries K, et al: Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. *Circulation* 116:755–763, 2007.
98. Lichtenstein SV, Cheung A, Ye J, et al: Transapical transcatheter aortic valve implantation in humans: initial clinical experience. *Circulation* 114:591–596, 2006.
99. Dewey TM, Walther T, Doss M, et al: Transapical aortic valve implantation: an animal feasibility study. *Ann Thorac Surg* 82:110–116, 2006.
100. Svensson LG, Dewey T, Kapadia S, et al: United States feasibility study of transcatheter insertion of a stented aortic valve by the left ventricular apex. *Ann Thorac Surg* 86:46–54, 2008.
101. Bapat V, Khawaja MZ, Attia R, et al: Transaortic transcatheter aortic valve implantation using Edwards Sapien valve: a novel approach. *Cathet Cardiovasc Diagn* 79:733–740, 2012.
102. Walther T, Simon P, Dewey T, et al: Transapical minimally invasive aortic valve implantation. Multicenter experience. *Circulation* 116:I-240, 2007.
103. Thomas M, Schymik G, Walther T, et al: One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation* 124:425–433, 2011.
104. Webb JG, Altwegg L, Boone RH, et al: Transcatheter aortic valve implantation: impact on clinical and valve-related outcomes. *Circulation* 119:3009–3016, 2009.
105. Walther T, Schuler G, Borger MA, et al: Transapical aortic valve implantation in 100 consecutive patients: comparison to propensity-matched conventional aortic valve replacement. *Eur Heart J* 31:1398–1403, 2010.
106. Zierer A, Wimmer-Greinecker G, Martens S, et al: Is transapical aortic valve implantation really less invasive than minimally invasive aortic valve replacement? *J Thorac Cardiovasc Surg* 138:1067–1072, 2009.
107. Rodes-Cabau J, Dumont E, De LaRochelliere R, et al: Feasibility and initial results of percutaneous aortic valve implantation including selection of the transfemoral or transapical approach in patients with severe aortic stenosis. *Am J Cardiol* 102:1240–1246, 2008.
108. Lefevre T, Kappetein AP, Wolner E, et al: One year follow-up of the multi-centre European PARTNER transcatheter heart valve study. *Eur Heart J* 32:148–157, 2011.
109. Eltchaninoff H, Prat A, Gilard M, et al: Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry. *Eur Heart J* 32:191–197, 2011.
110. Schmyk G, Lefevre T, Bartorelli AL, et al: European experience with the second generation Edwards Sapien XT transcatheter heart valve in patients with severe aortic stenosis: 1-year outcomes from the SOURCE XT registry. *J Am Coll Cardiol Cardiovasc Interv* 8:657–669, 2015.
111. Leon M, van Dijk L: True percutaneous implantation of CoreValve aortic valve prosthesis by the combined use of ultrasound guided vascular access, Prostar XL and the Tandem Heart. Presented at Transcatheter Cardiovascular Therapeutics, San Francisco, November 7, 2011.
112. Van Belle E, Juthier F, Susen S, et al: Postprocedural aortic regurgitation in balloon-expandable and self-expandable transcatheter aortic valve replacement procedures: analysis of predictors and impact on long-term mortality: insights from the FRANCE2 Registry. *Circulation* 129:1415–1427, 2014.
112a. Thomas M, Schymik G, Walther T, et al: Thirty day outcome of the SAPIEN aortic biopsothesis European Outcomes (SOURCE) Registry. *Circulation* 122:62–69, 2010.
113. Makkar RR, Fontana GP, Jilaihawi H, et al: Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med* 366:1696–1704, 2012.
114. Kodali SK, Williams MR, Smith CR, et al: Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 366:1686–1695, 2012.
115. Kappetein AP, Head SJ, Genereux P, et al: Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Thorac Cardiovasc Surg* 145:6–23, 2013.
116. Leon M: A randomized evaluation of the SAPIEN XT transcatheter valve system in patients with aortic stenosis who are not candidates for surgery: PARTNER II, inoperable cohort: late breaking clinical trials. American College of Cardiology conference, San Francisco, March 10, 2013.
117. Bapat VV, Attia R: Transaortic transcatheter aortic valve implantation using the Edwards Sapien valve. *Multimed Man Cardiothorac Surg* 2012. doi: 10.1093/mmcts/mms017.
118. Daneault B, Kirtane AJ, Kodali SK, et al: Stroke associated with surgical and transcatheter treatment of aortic stenosis: a comprehensive review. *J Am Coll Cardiol* 58:2143–2150, 2011.
119. Ghanem A, Muller A, Nahle CP, et al: Risk and fate of cerebral embolism after transfemoral aortic valve implantation: a prospective pilot study with diffusion-weighted magnetic resonance imaging. *J Am Coll Cardiol* 55:1427–1432, 2010.
120. Sinhal A, Altwegg L, Pasupati S, et al: Atrioventricular block after transcatheter balloon expandable aortic valve implantation. *JACC Cardiovasc Interv* 1:305–309, 2008.
121. Nazif TM, Williams MR, Hahn RT, et al: Clinical implications of new-onset left bundle branch block after transcatheter aortic valve replacement: analysis of the PARTNER experience. *Eur Heart J* 35:1599–1607, 2014.
122. Bleiziffer S, Ruge H, Horer J, et al: Predictors for new-onset complete heart block after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 3:524–530, 2010.
123. Yamamoto M, Hayashida K, Mouillet G, et al: Prognostic value of chronic kidney disease after transcatheter aortic valve implantation. *J Am Coll Cardiol* 62:869–877, 2013.
124. Zajarias A, Eltchaninoff H, Cribier A: Successful coronary intervention after percutaneous aortic valve replacement. *Catheter Cardiovasc Interv* 69:522–524, 2007.
125. Ruiz CE, Laborde JC, Condado JF, et al: First percutaneous transcatheter aortic valve-in-valve implant with three year follow-up. *Catheter Cardiovasc Interv* 72:143–148, 2008.
126. Grube E, Buellesfeld L, Mueller R, et al: Progress and current status of percutaneous aortic valve replacement: results of three device generations of the CoreValve Revalving system. *Circ Cardiovasc Interv* 1:167–175, 2008.
127. Buellesfeld L, Gerckens U, Grube E: Percutaneous implantation of the first repositionable aortic valve prosthesis in a patient with severe aortic stenosis. *Catheter Cardiovasc Interv* 71:579–584, 2008.
128. Schultz CJ, Weustink A, Piazza N, et al: Geometry and degree of apposition of the CoreValve Revalving System with multislice computed tomography after implantation in patients with aortic stenosis. *J Am Coll Cardiol* 54:911–918, 2009.
129. O'Brien S, Shahian D, Filardo G, et al: The Society of Thoracic Surgeons 2008 cardiac surgery risk models: Part 2—isolated valve surgery. *Ann Thorac Surg* 88:S23–S42, 2009.
130. Nashef SA, Roques F, Michel P, et al: European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 16:9–13, 1999.
131. Afilalo J, Alexander K, Mack M, et al: Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol* 63:747–762, 2014.
132. Kim CA, Rasania SP, Afilalo J, et al: Functional status and quality of life after transcatheter aortic valve replacement: a systematic review. *Ann Intern Med* 160:243–254, 2014.
133. Van Mieghem NM, Head SJ, van der Boon RM, et al: The SURTAVI model: proposal for a pragmatic risk stratification for patients with severe aortic stenosis. *EuroIntervention* 8:258–266, 2012.
134. Abdel-Wahab M, Zahn R, Sheri M, et al: In-hospital outcome of aortic regurgitation after transcatheter aortic valve implantation: results from the prospective multicentre German TAVI registry. *Eur Heart J* 31:I-160, 2010.
135. Tops LF, Wood DA, Delgado V, et al: Noninvasive evaluation of the aortic root with multislice computed tomography implications for transcatheter aortic valve replacement. *JACC Cardiovasc Imaging* 1:321–330, 2008.
136. Wood DA, Tops LF, Mayo JR, et al: Role of multislice computed tomography in transcatheter aortic valve replacement. *Am J Cardiol* 103:1295–1301, 2009.
137. Litmanovich DE, Ghersin E, Burke DA, et al: Imaging in transcatheter aortic valve replacement (TAVR): role of the radiologist. *Insights Imaging* 5:123–145, 2014.
138. Leipsic J, Wood D, Manders D, et al: The evolving role of MDCT in transcatheter aortic valve replacement: a radiologists' perspective. *AJR Am J Roentgenol* 193:W214–W219, 2009.
139. de Jaegere P, van Dijk L, Laborde J, et al: True percutaneous implantation of the CoreValve aortic valve prosthesis by the combined use of ultrasound guided vascular access, Prostar XL, and the TandemHeart. *EuroIntervention* 2:500–505, 2007.
140. Sinning JM, Hammerstingl C, Vasa-Nicotera M, et al: Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. *J Am Coll Cardiol* 59:1134–1141, 2012.
141. Ramlawi B, Bedeir K, Barker C, et al: Direct aortic and subclavian access for transcatheter aortic valve replacement: decision making and technique. *J Thorac Cardiovasc Surg* 148:353–356, 2014.
142. Reardon MJ, Adams DH, Coselli JS, et al: Self-expanding transcatheter aortic valve replacement using alternative access sites in symptomatic patients with severe aortic stenosis deemed extreme risk of surgery. *J Thorac Cardiovasc Surg* 148:2869–2876e1-e7, 2014.
143. Schuler G, Bonan R, Kovac J, et al: Effectiveness and durability at two years with CoreValve transcatheter aortic valve (abstract). *Eur Heart J* 31(Suppl):159–160, 2010.
144. Bleiziffer S, Ruge H, Mazzitelli D, et al: Results of percutaneous and transapical transcatheter aortic valve implantation performed by a surgical team. *Eur J Cardiothorac Surg* 35:615–620, discussion 620–621, 2009.
145. Barbanti M: Two-year outcomes of transcatheter aortic valve implantation: a single center experience. Presented at EuroPCR, Paris, May 26, 2010, Paris.
146. Meredith I: A snapshot from the ongoing Australia-New Zealand Medtronic CoreValve® Registry. Presented at Transcatheter Cardiovascular Therapeutics, San Francisco, September 21-25, 2009.
147. Fiorina C, Barbanti M, De Carlo M, et al: One year clinical outcomes in patients with severe aortic stenosis and left ventricular systolic dysfunction undergoing transcatheter aortic valve implantation: results from the Italian CoreValve Registry. *Int J Cardiol* 168:4877–4879, 2013.
148. Avanzas P, Munoz-Garcia A, Segura J: Percutaneous implantation of the CoreValve® self-expanding aortic valve prosthesis in patients with severe aortic stenosis: early experience in Spain. *Rev Esp Cardiol* 63:141–148, 2010.
149. Mohr FW, Holzhey D, Mollmann H, et al: The German Aortic Valve Registry: 1-year results from 13,680 patients with aortic valve disease. *Eur J Cardiovasc Thorac Surg* 46:808–810, 2014.
150. Ludman P: The UK transcatheter aortic valve implantation registry; one of the suite of registries hosted by the National

Institute for Cardiovascular Outcomes Research (NICOR). *Heart* 98:1787–1789, 2012.
151. Linke A, Wenaweser P, Gerckens U, et al: Treatment of aortic stenosis with a self-expanding transcatheter valve: the international multi-centre ADVANCE study. *Eur Heart J* 35:2672–2684, 2014.
152. Ewe S, Ajmone-Marsan N, Delgado V, et al: Clinical and echocardiographic outcomes after transcatheter aortic valve implantation: comparison between patients with normal and impaired left ventricular systolic function (abstract). *Eur Heart J* 31 (Suppl):957–958, 2010.
153. Tzikas A, Piazza N, van Dalen BM, et al: Changes in mitral regurgitation after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 75:43–49, 2010.
154. Yap CH, Mohajeri M, Yii M: Prosthesis-patient mismatch is associated with higher operative mortality following aortic valve replacement. *Heart Lung Circ* 16:260–264, 2007.
155. Tzikas A, Piazza N, Geleijnse ML, et al: Prosthesis-patient mismatch after transcatheter aortic valve implantation with the Medtronic CoreValve system in patients with aortic stenosis. *Am J Cardiol* 106:255–260, 2010.
156. Ussia GP, Mule M, Barbanti M, et al: Quality of life assessment after percutaneous aortic valve implantation. *Eur Heart J* 30: 1790–1796, 2009.
157. Akins CW, Miller DC, Turina MI, et al: Guidelines for reporting mortality and morbidity after cardiac valve interventions. *J Thorac Cardiovasc Surg* 135:732–738, 2008.
158. Bruschi G, De Marco F, Oreglia J, et al: Percutaneous implantation of CoreValve aortic prostheses in patients with a mechanical mitral valve. *Ann Thorac Surg* 88:e50–e52, 2009.
159. Berry C, Cartier R, Bonan R: Fatal ischemic stroke related to nonpermissive peripheral artery access for percutaneous aortic valve replacement. *Catheter Cardiovasc Interv* 69:56–63, 2007.
160. Kahlert P, Knipp SC, Schlamann M, et al: Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. *Circulation* 121:870–878, 2010.
161. Blazek S, Vollmann R, Simbrunner J, et al: Cerebral magnetic resonance imaging unmasks microembolic cerebral lesions after transcatheter aortic valve implantation (abstract). *Eur Heart J* 31(Suppl):145–146, 2010.
162. Easton JD, Saver JL, Albers GW, et al: Definition and evaluation of transient ischemic attack. *Stroke* 40:2276–2293, 2009.
163. Zahn R, Schiele R, Kilkowski C, Zeymer U: Severe aortic regurgitation after percutaneous transcatheter aortic valve implantation: on the importance to clarify the underlying pathophysiology. *Clin Res Cardiol* 99:193–197, 2009.
164. Hoffmann R, Rieck B, Dohmen G: Correction of CoreValve position using snare traction from a right brachial artery access. *J Invasive Cardiol* 22:E59–E60, 2010.
165. Vavuranakis M, Vrachatis D, Stefanadis C: CoreValve aortic bioprosthesis: repositioning techniques. *JACC Cardiovasc Interv* 3:565, 2010.
166. Vavouranakis M, Vrachatis DA, Toutouzas KP, et al: "Bail out" procedures for malpositioning of aortic valve prosthesis (CoreValve). *Int J Cardiol* 145:154–155, 2009.
167. Van Mieghem NM, Nuis RJ, Piazza N, et al: Vascular complications with transcatheter aortic valve implantation using the 18 Fr Medtronic CoreValve System: the Rotterdam experience. *EuroIntervention* 5:673–679, 2010.
168. Dhingra RC, Amat-y-Leon F, Pietras RJ, et al: Sites of conduction disease in aortic stenosis: significance of valve gradient and calcification. *Ann Intern Med* 87:275–280, 275, 1977.
169. Friedman HS, Zaman Q, Haft JI, Melendez S: Assessment of atrioventricular conduction in aortic valve disease. *Br Heart J* 40:911–917, 1978.
170. Carlson MD, Palacios I, Thomas JD, et al: Cardiac conduction abnormalities during percutaneous balloon mitral or aortic valvotomy. *Circulation* 79:1197–1203, 1989.
171. Gordon RS, Ivanov J, Cohen G, Ralph-Edwards AL: Permanent cardiac pacing after a cardiac operation: predicting the use of permanent pacemakers. *Ann Thorac Surg* 66:1698–1704, 1998.
172. Dawkins S, Hobson AR, Kalra PR, et al: Permanent pacemaker implantation after isolated aortic valve replacement: incidence, indications, and predictors. *Ann Thorac Surg* 85:108–112, 2008.
173. Piazza N, Onuma Y, Jesserun E, et al: Early and persistent intraventricular conduction abnormalities and requirements for pacemaking after percutaneous replacement of the aortic valve. *JACC Cardiovasc Interv* 1:310–316, 2008.
174. Calvi V, Puzzangara E, Pruiti GP, et al: Early conduction disorders following percutaneous aortic valve replacement. *Pacing Clin Electrophysiol* 32(Suppl 1):S126–S130, 2009.
175. Jalaihawi H, Chin D, Vasa-Nicotera M, et al: Predictors for permanent pacemaker requirement after transcatheter aortic valve implantation with the CoreValve bioprosthesis. *Am Heart J* 157:860, 2009.
176. Akhtar M, Tuzcu EM, Kapadia SR, et al: Aortic root morphology in patients undergoing percutaneous aortic valve replacement: evidence of aortic root remodeling. *J Thorac Cardiovasc Surg* 137:950–956, 2009.
177. Bombien R, Humme T, Schunke M, Lutter G: Percutaneous aortic valve replacement: computed tomography scan after valved stent implantation in human cadaver hearts. *Eur J Cardiothorac Surg* 36:592–594, 2009.
178. Gerckens U, Latsios G, Mueller R, et al: Left main PCI after trans-subclavian CoreValve implantation. Successful outcome of a combined procedure for management of a rare complication. *Clin Res Cardiol* 98:687–690, 2009.
179. Meredith IT, Worthley SG, Whitbourn RJ, et al: Transfemoral aortic valve replacement with the repositionable Lotus Valve System in high surgical risk patients: the REPRISE I study. *EuroIntervention* 9:1264–1270, 2014.
180. Meredith I, Dumonteil N: Data presented at Transcatheter Cardiovascular Therapeutics, San Francisco, 2013.
181. Schofer J, Colombo A, Klugmann S, et al: Prospective multicenter evaluation of the direct flow medical transcatheter aortic valve. *J Am Coll Cardiol* 63:763–768, 2014.
182. Low RI, Bolling SF, Yeo KK, Ebner A: Direct flow medical percutaneous aortic valve: proof of concept. *EuroIntervention* 4:256–261, 2008.
183. Bijuklic C, Tuebler T, Reichenspurner H, et al: Mid-term stability hemodynamics performance of a transfemorally implantable nonmetallic and repositionable aortic valve in patients with severe aortic stenosis—2 year results of the Direct Flow Medical valve. *J Am Coll Cardiol* 58:B197, 2011.
184. Willson AB, Rodes-Cabau J, Wood DA, et al: Transcatheter aortic valve replacement with the St. Jude Medical Portico valve: first-in-human experience. *J Am Coll Cardiol* 60:581–586, 2012.
185. Treede H, Baldus S, Figulla HR, et al: 3-Month results of the JenaValve multicenter study evaluating a second generation transcatheter aortic valve implantation system. *J Am Coll Cardiol* 58:B210, 2011.
186. Treede H, Mohr FW, Baldus S, et al: Transapical transcatheter aortic valve implantation using the JenaValve system: acute and 30-day results of the multicentre CE-mark study. *Eur J Cardiothorac Surg* 41:e131–e138, 2012.
187. Kempfert J, Treede H, Rastan AJ, et al: Transapical aortic valve implantation using a new self-expandable bioprosthesis (ACURATE TA): 6-month outcomes. *Eur J Cardiothorac Surg* 43:52–56, discussion 57, 2012.
188. Maeda K, Kuratani T, Torikai K, et al: New Self expandin catheter aortic valve devce for transfemoral implantation-Earlu results of the first in man Acurate Neo/TF(™) system. *Circ J* 79:1037–1104, 2015.
189. Falk V, Walther T, Schwammenthal E, et al: Transapical aortic valve implantation with a self-expanding anatomically oriented valve. *Eur Heart J* 32:878–887, 2011.
190. Dvir D, Barbanti M, Tan J, Webb JG: Transcatheter aortic valve-in-valve implantation for patients with degenerative surgical bioprosthetic valves. *Curr Probl Cardiol* 39:7–27, 2014.
191. Webb JG, Wood DA, Ye J, et al: Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. *Circulation* 121:1848–1857, 2010.
192. Bapat V, Attia R, Redwood S, et al: Use of transcatheter heart valves for a valve-in-valve implantation in patients with degenerated aortic bioprosthesis: technical considerations and results. *J Thorac Cardiovasc Surg* 144:1372–1379, 2012.
193. Wenaweser P, Buellesfeld L, Gerckens U, Grube E: Percutaneous aortic valve replacement for severe aortic regurgitation in degenerated bioprosthesis: the first valve in valve procedure using the Corevalve Revalving system. *Catheter Cardiovasc Interv* 70:760–764, 2007.
194. Giannini C, De Carlo M, Guarracino F, et al: Dysfunction of a 21-mm aortic bioprosthesis treated with percutaneous implantation of a CoreValve prosthesis. *J Cardiovasc Med (Hagerstown)* 14:541–544, 2013.
195. Khawaja MZ, Haworth P, Ghuran A, et al: Transcatheter aortic valve implantation for stenosed and regurgitant aortic valve bioprostheses CoreValve for failed bioprosthetic aortic valve replacements. *J Am Coll Cardiol* 55:97–101, 2010.

54 Pulmonary and Tricuspid Valve Interventions

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KEY POINTS

- Transcatheter pulmonary valve implantation (TPVI) is suitable for patients with dysfunctional right ventricle–to–pulmonary artery conduits and for patch reconstructed outflow tracts in selected cases.
- Two stent-mounted valves, the Melody for right ventricular outflow tracts of less than 22 mm and the Sapien for those less than 29 mm, are approved for use within and outside the United States.
- TPVI is performed with the patient under general anesthesia, and a femoral approach is used. The procedure results in early symptomatic improvement and reduction of right ventricular volumes.
- TPVI can be complicated by device displacement, homograft rupture, or coronary artery compression at the time of implantation; these should be avoidable by careful assessment of anatomy and correct prestenting procedures.
- TPVI has become part of routine clinical practice, with more than 3000 procedures performed worldwide in the past decade. It prolongs conduit life and may reduce the number of operations required by patients with congenital heart disease during their lifetimes.
- Percutaneous tricuspid valve implantation into a dysfunctional biologic prosthesis has been successfully performed in small numbers of patients.
- Percutaneous tricuspid valve implantation is mainly reserved for high-risk patients with conditions that preclude surgery.

Isolated pulmonary and tricuspid valve dysfunction, whether acquired or in the context of congenital heart disease, can be clinically asymptomatic and tolerated for a long time.[1] In Western countries, acquired tricuspid or pulmonary valve diseases are rare and mostly related to conditions such as rheumatic fever, infective endocarditis, and carcinoid syndrome. In cases of congenital heart disease, valve dysfunction is a primary component of many anatomic defects and a common secondary consequence of several early repair strategies.

Increasing knowledge about potential harmful effects of chronic pulmonary regurgitation has made surgical revision of the right ventricular outflow tract (RVOT) a frequently performed operation in this population.[2] Typically, most patients require several repeat operations during their lifetime to halt the detrimental effects of valvular dysfunction. Since the techniques of transcatheter pulmonary valve implantation (TPVI) were first described by Philipp Bonhoeffer and colleagues more than a decade ago, the procedure has gained worldwide acceptance and has become a routine interventional procedure.[3]

Several devices have been investigated for purposes of interventional pulmonary valve implantation, but only the Melody transcatheter pulmonary valve (Medtronic, Minneapolis, MN) has obtained European and American regulatory approval. Interventional procedures focusing on percutaneous tricuspid valve replacement or interventional treatment of severe tricuspid regurgitation are evolving but remain at a much earlier stage of clinical practice and have not obtained the level of a standard procedure.[4]

This chapter explores the clinical applications of this revolutionary technology. Indications, patient selection, updated clinical results, and future directions of pulmonary and tricuspid valve interventions are discussed.

TRANSCATHETER PULMONARY VALVE IMPLANTATION

Background and Clinical Indications

Over the past decades, advances in cardiac surgery, interventional procedures, intensive care, and noninvasive imaging have led to a substantial increase in life expectancy for many patients with congenital heart disease. This challenging, heterogeneous population of patients who were treated by corrective, semicorrective, or palliative surgical procedures, sometimes decades ago, is growing inexorably. Comparing birth registries for the years 1950 to 1959 and 1990 to 1999, the life expectancy of patients with congenital heart disease expressed by 18-year survival rates has increased from 10% to 70%.[5]

Studies have shown that the numbers of adult patients with congenital heart disease are already similar to those for the pediatric population and will continue to grow.[6] For approximately 20% of these adults and children late after neonatal repair of complex congenital heart disorders such as tetralogy of Fallot, pulmonary atresia, persistent trunk, or D-transposition with RVOT obstruction, RVOT dysfunction manifesting as an obstructive lesion or as pulmonary regurgitation becomes clinically evident.

Surgical pulmonary valve replacement using valved homograft or porcine (e.g., Medtronic Hancock) and bovine xenograft conduits (e.g., Medtronic Contegra) helps to treat RVOT dysfunction. Undeniably the most frequent mode of repeat operation in patients with congenital heart disease, surgical pulmonary valve replacement is a safe procedure and is performed with low morbidity and mortality rates.[2] However, an important drawback is the limited life span of the conduits. Due to growth-related undersizing and degeneration of the conduit causing obstruction or pulmonary regurgitation, conduit life span is about 10 years.[7-10] Most patients must undergo several open heart procedures during their lives that raise potential risks for bleeding, adhesions, and sternal or cutaneous related complications.

To minimize the number of open heart operations, delaying surgical interventions for as long as possible has been the strategy of choice. This policy risks delaying necessary treatment beyond the point of no return, when right ventricular (RV) dysfunction, impaired exercise capacity, and increased risk of sudden cardiac death, which can result from chronic adverse RV loading conditions,[11-13] may be irreversible.

The correct timing for surgical pulmonary valve replacement is unknown and remains a highly controversial issue among cardiologists who take care of children and adults with congenital heart disease.[2,14] Using magnetic resonance imaging (MRI), attempts have been made to establish RV volume thresholds as predictors of outcome after conduit placement. Cutoff points for RV end-systolic and end-diastolic volumes (EDV) have been reported, with some suggesting values (EDV = 150 to 170 mL/m^2)[14-16] above which normalization of RV dimensions is less likely after pulmonary valve replacement. However, the impact of the timing of pulmonary valve replacement on RV function, exercise performance, and particularly, long-term survival remains undefined.

To postpone and potentially reduce the number of operations patients have to undergo throughout their lives, transcatheter stent

implantation into stenotic conduits has been carried out,[17-19] although bare-metal stenting can potentially convert a pressure overload due to obstruction into a volume overload due to free pulmonary incompetence. With the introduction of percutaneous valve implantation, a nonsurgical technique has become available. It enables treatment of conduit obstruction and regurgitation. This minimally invasive method can potentially avoid open heart surgery for RVOT dysfunction in children and adults by restoring acceptable RV loading conditions.

Since the first description of a percutaneously implanted heart valve in 2000,[3] more than 3000 TPVIs have been performed worldwide.[20] The Melody device became commercially available in Europe and Canada in 2006. It was certified by Conformité Européenne (CE) in 2006 and approved by the U.S. Food and Drug Administration (FDA) for clinical use in the United States in 2010, making the new percutaneous strategy available to a broader population.

TPVI is performed to prolong the life span of conduits from the right ventricle to the pulmonary artery (RV-PA) and therefore postpone open heart surgery in children and adults with congenital heart disease. Over the past 10 years, increasing operator experience with TPVI has resulted in improved safety, efficacy, and outcomes, including freedom from transcatheter or surgical reintervention for pediatric or adult patients who underwent this procedure.[21-28]

Indications, technical aspects, and early and late results of TPVI using the Melody valve and the Sapien valve (Edwards Lifesciences, Irvine, CA) as nonsurgical treatment options for RVOT dysfunction are reviewed in the following sections.

Devices and Delivery Systems

Melody Transcatheter Pulmonary Valve

The Melody transcatheter pulmonary valve is composed of a segment of bovine jugular vein with a central valve (Figs. 54-1 and 54-2) sutured inside an expanded platinum-iridium stent. The currently used Cheatham platinum stent (CP Stent CP8Z34, NuMed, Hopkinton, NY) is 34 mm long it can be crimped to minimum of 6 mm in diameter and reexpanded up to 22 mm. It consists of an eight-crown zigzag pattern with six segments along its length that are reinforced at each strut intersection with a gold weld. The venous segment is attached to the frame by continuous 5-0 polypropylene sutures around the entire circumference at the inflow and outflow and also discretely at each strut intersection. The suture is clear for all points except the outflow line, which is blue to signify the outflow end of the device. The valve is packaged and sterilized in a solution containing 1% glutaraldehyde and 20% isopropyl alcohol (see Fig. 54-1). The delivery system (EnsembleTM, Medtronic, MN) contains a balloon in balloon (BiB) deployment design.

The Ensemble delivery system (Medtronic, Minneapolis, MN) contains a balloon-in-balloon deployment design. At its distal end, the valved stent is front-loaded and crimped (see Fig. 54-2). The system is available with outer balloon diameters of 18, 20, and 22 mm to fit different outflow tract diameters. To avoid incorrect implantation and potential failure, the tip of the delivery system is blue to correspond to the outflow suture of the device as described previously.

The body of the system is composed of a one-piece, 22-Fr Teflon sheath containing a braided-wire, elastomer-reinforced lumen. The retractable sheath that covers the stented valve during delivery is pulled back just before deployment. Contrast can be delivered through the retracted sheath from a side port to confirm positioning of the device before deployment. The proximal portion of the system has three ports, one for the *g*uidewire (*g*reen), one to deploy the *i*nner balloon (*i*ndigo), and one to deploy the *o*uter balloon (*o*range) (see Fig. 54-2).

Sapien Pulmonic Transcatheter Heart Valve

The Edwards Sapien valve is radiopaque and made of a trileaflet bovine pericardial valve that is sewn by hand into a stainless steel stent (14 or 16 mm long) (Fig. 54-3). A fabric polyethylene terephthalate sealing cuff covers the proximal part of the stent and is designed to prevent paravalvular leakage. The valve tissue is fabricated from three equal sections of bovine pericardium that have been preserved in glutaraldehyde to crosslink the xenograft tissue and preserve its flexibility and strength.

The device was initially designed for aortic valve replacement and obtained CE certification for TPVI in 2010.[29] The valve is commercially available in 23- and 26-mm diameter sizes and is crimped onto the designated balloon delivery system (Retroflex). A 29-mm diameter valve is also available for the aortic position (Sapien XT, Edwards Lifesciences, Irvine, CA).

In 2013, the third generation of the Retroflex III delivery system (Edwards Lifesciences, Irvine, CA.) was FDA approved. It consists of a balloon catheter and a deflectable guiding catheter. The system

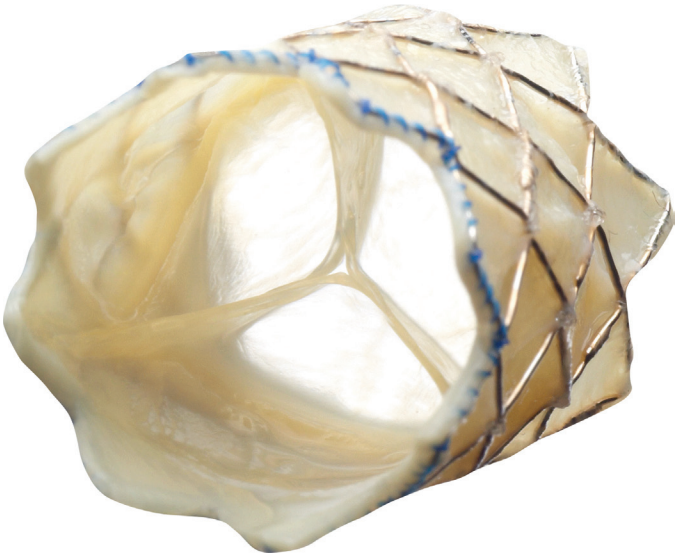

FIGURE 54-1 Melody transcatheter pulmonary valve in an oblique view. Notice the blue line that identifies the outflow end of the device. (Courtesy Medtronic, Minneapolis, MN.)

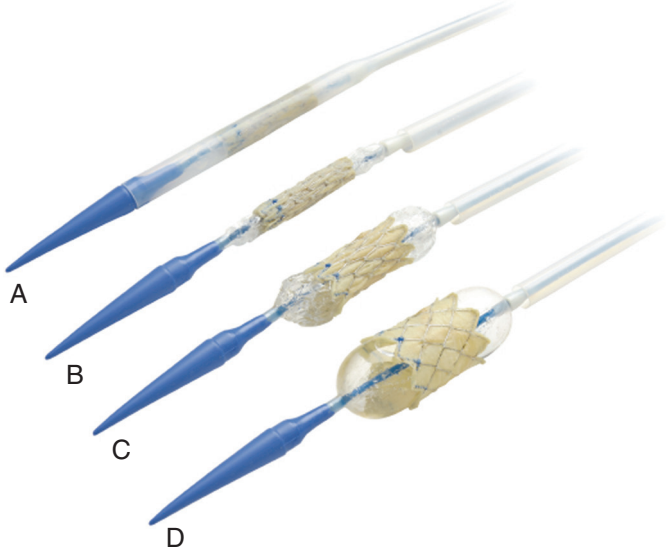

FIGURE 54-2 Melody device and its delivery system. **A,** Crimped device on the delivery system with a retractable sheath covering the device to protect it during the delivery. **B,** Retracted sheath. **C,** Deployment of the *i*nner balloon (*i*ndigo access). **D,** Deployment of the *o*uter balloon (*o*range access). (Courtesy Medtronic, Minneapolis, MN.)

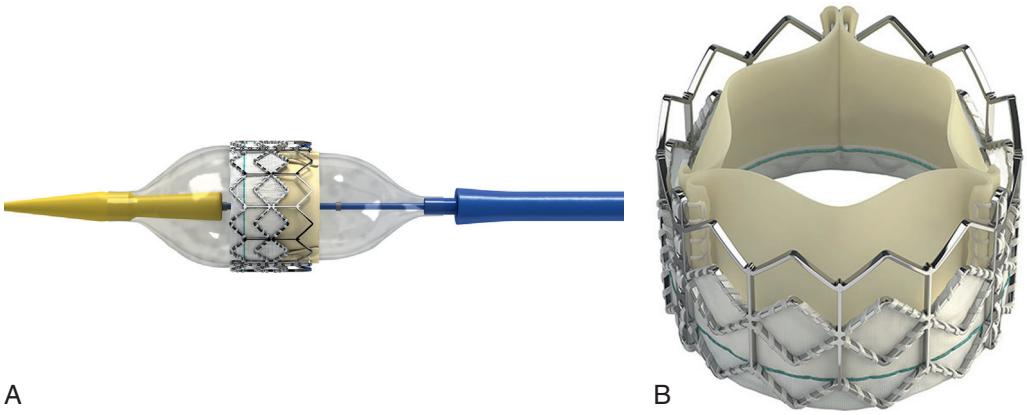

FIGURE 54-3 **A,** Top view of the Sapien pulmonic transcatheter heart valve **B,** The Retroflex III delivery system. (Courtesy Edwards Lifesciences LLC, Irvine, CA. Edwards, Edwards Lifesciences, RetroFlex, RetroFlex II, RetroFlex 3, RF3, Edwards SAPIEN, SAPIEN, SAPIEN XT and SAPIEN 3 are trademarks of Edwards Lifesciences Corporation.)

requires a 22-Fr sheath (for the Sapien 23-mm valve) or 24-Fr hydrophilic sheath (for the Sapien 26-mm and Sapien XT 29-mm valve) (see Fig. 54-3). According to the manufacturer's data, improvements in design (e.g., Edwards eSheath) offer smaller sheath sizes for the 23-mm valve (18 Fr), the 26-mm valve (19 Fr), and the 29-mm XT model (16 Fr). The guiding catheter has a control handle on the catheter hub, which can be rotated to deflect the catheter passing through the tricuspid aperture to the RVOT. The Retroflex III system also contains a retractable nose cone catheter, which facilitates atraumatic delivery.

Patient Selection Criteria

Clinical Criteria

Clear-cut guidelines do not exist for treating RVOT dysfunction caused by obstruction or regurgitation. This issue is slightly less complex in the setting of RVOT obstruction because patients with significant obstruction tend to develop symptoms early. According to the 2010 European Society of Cardiology (ESC) and Association for European Pediatric Cardiology (AEPC) guidelines for the management of grown-up congenital heart disease[30] include indications for surgical intervention or TPVI in patients with RV-PA conduits, patients with RVOT obstruction should be treated if the gradient exceeds 60 mm Hg or with symptoms due to RVOT obstruction regardless of the RVOT gradient.

In the clinical setting, indications for TPVI can be adapted from the indications for RVOT bare metal stenting.[18] In cases of RV pressure overload due to RVOT obstruction, symptomatic patients should undergo TPVI if the RV systolic pressure exceeds 65% of systemic pressures. In the absence of symptoms, patients should undergo treatment if RV pressures exceed 75% of systemic pressures as estimated by echocardiography and noninvasive blood pressure measurement.[21]

Pulmonary regurgitation can be clinically asymptomatic and be tolerated for a long time. When to intervene is the subject of ongoing discussions. It is common sense to base the indication criteria for transcatheter or surgical treatment on a combined assessment of MRI-derived RV end-diastolic volume and systolic function, cardiopulmonary exercise testing (as an objective measure of the patient's exercise capacity), and atrial or ventricular dysrhythmia. According to the 2010 ESC recommendations of the ESC grown-up congential heart disease task force, TPVI may be indicated if the patient has severe pulmonary regurgitation (assessed by echocardiography or MRI) and one of the following: severe RV dilation, severe RV dysfunction, symptoms, or impaired exercise capacity.[30]

In 2011, the American Heart Association (AHA) stated, "It is reasonable to consider the percutaneous pulmonary valve replacement in patient with RV-PA conduits with moderate to severe pulmonary regurgitation or stenosis provided the patient meets inclusion/exclusion criteria for the available valve." The AHA writing committee recommended this procedure based on class IIa evidence (evidence level B).[31]

There is no absolute lower age limit, but an adequate body size (e.g., weight >20 kg) is required to accommodate femoral placement of the introducer.[24] Table 54-1 summarizes clinical indications for Melody and Sapien TPVI.

TABLE 54-1 Clinical and Morphologic Requirements for Percutaneous Pulmonary Valve Implantation

Clinical indications in the context of RV pressure overload or pulmonary stenosis:
RV systolic pressure >65% of systemic pressure in symptomatic patients
RV systolic pressure >75% of systemic pressure in asymptomatic patients
Clinical indications in the context of RV volume overload or pulmonary regurgitation:
Severe pulmonary regurgitation on echocardiography or MRI *and*
One or more of the following:
• Severe RV dilatation >150 mL/m^2 or the RV/LV end-diastolic ratio of >1.5 *and/or*
• Rapidly progressive RV dilation *and/or*
• Severe RV dysfunction *and/or*
• Symptoms *and/or*
• Sustained atrial or ventricular arrhythmia *and/or*
• Impaired exercise capacity (<65% compared with normal peak oxygen consumption)

LV, Left ventricular; *MRI,* magnetic resonance imaging; *RV,* right ventricular.

Morphologic Criteria

Size and shape of the implantation site, also called the *landing zone*, and its anatomic relation to the coronary arteries are decisive morphologic criteria. They must be correct when considering patients as candidates for TPVI.

Size and Shape of the Implantation Site

The Melody device cannot be dilated to a diameter of more than 22 mm. Patients with nondilated conduits between the RV and PA of 22 mm or less offer an ideal environment for TPVI with this device. In contrast, native or patched outflow tracts after surgical repair for tetralogy of Fallot tend to be dilated and too large (>22 mm) and therefore do not provide a secure landing zone for Melody valves. In these cases or if the conduit size at surgical implantation is at least 18 mm but no larger than 29 mm with significant discrete narrowing, the Sapien valve may be used for treatment.[32-34]

In our experience, the RVOT shape after prestenting is important because of the engineered nature of sutured pericardial tissue. Optimal

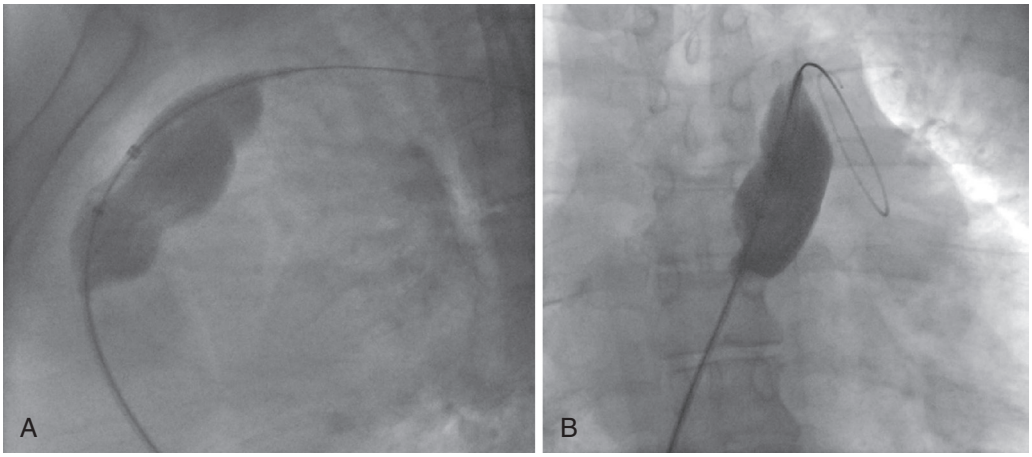

FIGURE 54-4 Balloon sizing for the right ventricular outflow tract. Fluoroscopy shows the balloon sizing maneuver from 90-degree (**A**) and 0-degree (**B**) left anterior oblique views.

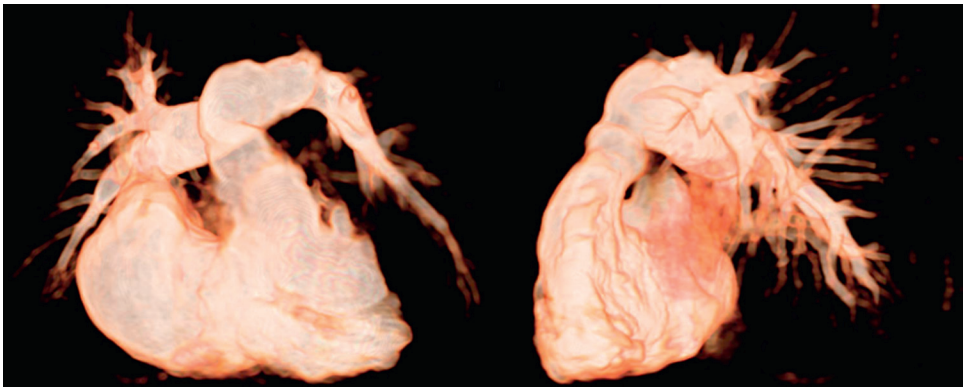

FIGURE 54-5 Noninvasive, three-dimensional, whole heart imaging by magnetic resonance tomography was performed in a patient with pulmonary atresia with an intact ventricular septum after repair by pulmonic homograft implantation. The patient had ventricular outflow tract dysfunction before percutaneous pulmonary valve implantation.

valved stent function in Sapien procedures is guaranteed by a circular RVOT shape. In TPVI procedures with the Melody valve, the RVOT shape has much less impact on the hemodynamic outcome.

Studying the patient's operative reports in detail and, unless contraindicated, using MRI before the procedure help to understand the anatomy of the outflow tract and to avoid implantation failure. Cine MRI can determine the maximal and minimal dimensions of the RVOT and its shape throughout the cardiac cycle. If there is doubt about the reliability of MRI-derived measurements, balloon sizing of the RVOT at the time of catheterization is recommended and is discussed later (Fig. 54-4). The minimal diameter for TPVI is not less than 16 mm to avoid unacceptable residual gradients. Rare exceptions to this rule include cases in which three-dimensional imaging and echocardiographic assessment suggest that sufficient space is available to deploy a valve to a reasonable diameter.

Assessment of Coronary Artery Anatomy

Coronary artery anatomy varies according to the type of congenital heart defect and is affected by surgical reinsertion into the aorta. In some cases, one or more of the relevant coronary artery branches are near the main PA. This configuration exposes patients who undergo RVOT interventions to the risk of fatal coronary artery obstruction due to expansion of the RVOT.[18,35]

The course of proximal coronary arteries in relation to the RVOT must be assessed before percutaneous valve deployment. Some centers prefer three-dimensional MRI of the whole heart to assess the anatomic relationship of the coronary arteries and the proposed implantation site (Fig. 54-5). We recommend selective coronary angiography and particularly aortic root angiography and simultaneous high-pressure balloon inflation within the landing zone (discussed later) at the time of catheterization in all patients to rule out the risk of coronary compression (Fig. 54-6).

Procedure

Laboratory Setup

TPVI should be performed in a catheterization laboratory with a monoplane or, preferably, biplane fluoroscopy setup. Procedures must be performed under sterile conditions meeting the standards for surgical valve implantations. Autotransfusion kits (e.g., pleural drainage kits, cell saver) should be available in cases of acute bleeding. Although simultaneous surgical backup is not required, TPVI should be performed at institutions with a (congenital disease) surgical program. Ideally, the surgical team has access to and experience with extracorporeal circulation equipment.

TPVI is usually performed using general endotracheal anesthesia, although use of conscious sedation is feasible. Peripheral, central venous, and 5-Fr arterial line access is needed for continuous hemodynamic monitoring and anesthesia management. Femoral access is preferred because it allows an easier working position in the

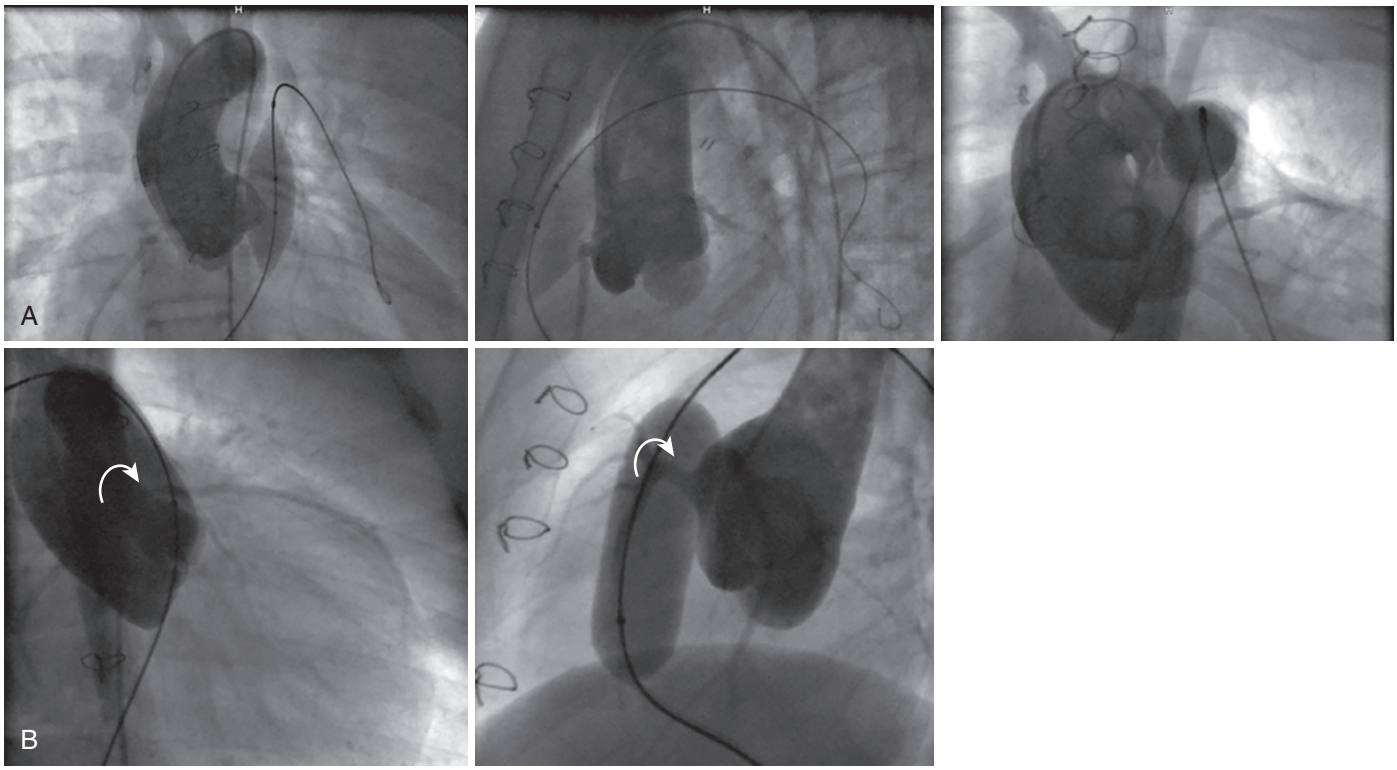

FIGURE 54-6 Assessment of risk for coronary compression. **A,** The 0-degree and 90-degree left anterior oblique (LAO) and 0-degree with 45-degree caudal angulation aortic root angiograms show high-pressure balloon inflation within the eligible landing zone, which is performed to rule out coronary compression. **B,** The 0-degree and 90-degree LAO aortic root angiograms show compression of the left anterior descending coronary artery *(arrow)* during balloon inflation in the conduit. The procedure was therefore abandoned in this patient, and no percutaneous pulmonary valve implantation was performed.

catheterization laboratory. Preparation of both groins for vascular access allows a quick change in case of problems. Jugular vein access can also be obtained if required. Use of a 10-Fr sheath (maximum) for initial venous access is appropriate.

Recommendations include aseptic technique meeting surgical standards, initiation of effective heparinization at the beginning of the procedure (100 IU/kg of heparin or a standard dose of 5000 IU in adults, repeated as required), and a single dose of broad-spectrum intravenous antibiotics for endocarditis prophylaxis.

Hemodynamic Assessment

Right heart catheterization is performed using standard techniques to assess pressures and saturation levels. Routine measurements are made for the RV, PA, and aorta, and additional measurements (e.g., branch PAs) are made as appropriate. To provide a stable position before advancing the delivery system, a stiff guidewire (e.g., Amplatz Ultra Stiff guidewire [0.035 inch × 260 cm]; Lunderquist [0.035 inch × 260 cm], Cook, Bloomington, IN) is positioned in a distal branch PA, which preferably has few curves and is as distal as possible. In an endeavor to maintain the guidewire's tip at the level of the diaphragm, the operators must not interfere with the tricuspid valve chordae.

Pulmonary artery (biplane) angiography is performed using appropriate catheters (e.g., balloon-tipped, pigtail, Multi-Track [NuMed, Hopkinton, NY]). The catheter's tip should be placed just beyond the expected position of the pulmonary valve to allow assessment of the proposed landing zone and estimation of pulmonary regurgitation.

Morphologic Assessment

Assessing the suitability of the size and shape of the landing zone is a crucial part of preparation before the final TPVI procedure. Invasive morphologic assessment during catheterization is often necessary, especially in cases of borderline dimensions derived by MRI. Distensibility of the site can be assessed only by balloon interrogation and is therefore strongly recommended in cases of expected high distensibility of the RVOT (i.e., patch-extended or native outflow tracts). Soft sizing balloon catheters (e.g., PTS, NuMed, Hopkinton, NY) are commonly used for balloon interrogation. They should be partially inflated when positioned distally to the supposed landing zone and then slowly retracted across the RVOT back into the RV. The use of biplane orthogonal fluoroscopy allows accurate two-dimensional measurements.

The anterior-posterior imaging plane with cranial tilt is ideal for visualizing the pulmonary bifurcation and distal end of the stented valve. The anterior-posterior cranial view with or without left anterior oblique angulation is used to assess the bifurcation. The lateral plane visualizes the anterior chest and landing zone for the transcatheter pulmonary valve and seems to be the ideal view during stent positioning.

The risk of coronary compression should be minimized before implanting a Melody or Sapien valve. The preferred stepwise approach includes noninvasive, three-dimensional MRI of the whole heart to judge the proximity of the proximal coronary arteries to the RVOT (see Fig. 54-5). For all patients at the time of catheterization, aortic root and selective coronary artery angiography should be performed along with simultaneous high-pressure balloon inflation in the landing zone and selective coronary angiography (see Fig. 54-6).[18,21,35]

The Medtronic guidelines for Melody valve Implantation[36] recommend a combined aortic root angiogram and balloon dilation to outline the coronary anatomy and exclude the risk of coronary ostium or coronary compression. For larger distances between the landing zone and the coronary arteries, a low-pressure balloon can be used. If coronary arteries are close, full inflation is indicated to avoid false-negative screening results and ensure that valve insertion is adequately

mimicked by the balloon position. An aortic root angiogram may be preferable to a selective coronary artery angiogram because intubation of the coronary artery by the catheter may lead to a false-negative test result. If evidence of coronary artery compression is found, the procedure must be abandoned.

Device Setup

Before implantation, preparations include checking and removing the manufacture's identification label and flushing, crimping, and loading the valved stent onto the delivery system. The valved stent should be flushed by hand at least two times in bowls filled with sterile, isotonic sodium chloride solution for approximately 30 seconds each time to remove residues of the glutaraldehyde preservative and to test leaflet function.

The device is then crimped using hand tools over the barrel of a sterile 2-mL syringe before being front-loaded onto the delivery system. The blue stitching on the distal portion of the device must match the blue portion of the delivery system (*the carrot*), which is then verified by an independent observer to guarantee correct device orientation. Further crimping is performed while advancing the sheath carefully over the device during saline flushing through the side port to exclude air bubbles from the system and facilitating uncovering of the device (see Fig. 54-2).

Device Implantation

After removing the angiography catheter (e.g., Multi-Track catheter), the femoral vein is dilated to 22 or 24 Fr. This is unnecessary if an 18-Fr sheath is used for periprocedural interventions (discussed later) because the outer diameter is about 22 Fr.

The delivery system is introduced into the access site and advanced into the landing zone under fluoroscopic guidance. The tip of the guidewire must be seen at all times. If its position has been lost, advancement of the delivery system must stop because the risk of peripheral vascular rupture is high when trying to push the wire back into position while carrying the delivery system. The delivery system can be safely removed and repositioned as long as the valve is at least partially covered.

The operator must reestablish a stable wire position with the use of catheters before advancing the delivery system. Coordination between first and second operator is necessary to safely advance the system into the desired position. Pushing the system in the groin moves it forward or backward; turning is impossible. Driving the wire will determine how the delivery system's end moves up to the landing zone. If the carrot makes turns well, the wire is kept fixed. If the carrot hesitates at the entry into the RVOT, the operator may push the delivery system while fixing the guidewire, causing the tip to move backward.

In another maneuver, the delivery system is pushed while slightly pulling on the guidewire to make the carrot come loose from the conduit's wall and allow advancement. Additional maneuvers can be used by experienced operators to advance the delivery system when it is at the entrance to the conduit. Partial uncovering of the device provides more flexibility of the tip of the delivery system, facilitating crossing of tortuous and stenotic outflow tracts. Looping the system within the right atrium generates a forward force that often overcomes resistance and aids passage into the conduit.

If the delivery system has been placed too distally, forward pushing of the guidewire rather than backward pulling of the delivery system often helps to withdraw the delivery system slightly. After the most distal part of the delivery system has passed the landing zone, the wire should be first straightened in the right atrium (the loop keeps the tricuspid valve open) before continuing the implantation process. The outer sheath is retracted, uncovering the stented valve, which sometimes results in forward movement. Because there are no radiopaque markers on the outer sheath, complete uncovering of the delivery system can be confirmed only by checking the double markers placed on the proximal portion of the system (i.e., balloon shaft). It must be completely uncovered before balloon inflation. Contrast injection into the side arm of the delivery system can offer further confirmation.

Deployment of the Melody valve is achieved by hand-inflating the *i*nner (*i*ndigo) balloon. After confirmation of the position, the *o*uter (*o*range) balloon is inflated to complete deployment. The inner balloon is then deflated, followed by deflation of the outer balloon while recording the deflation.

The delivery system is removed with great care through the implanted valve to avoid leaflet damage. Sheath closure should not be attempted before careful and slow withdrawal of the balloon and delivery system into the inferior vena cava. Repeat angiography of the RVOT can rule out extravasations for confirmation of valvar competence. The RV pressure and RV-PA pressure gradient are measured to assess the outcome. After removing all catheters and the venous sheath, hemostasis is achieved with a single Z-stitch on the skin over the venous access and with manual compression of the arterial access.

Periprocedural Interventions

PREDILATION OF THE LANDING ZONE. Over time, RVOT anatomy evolves in response to the repair strategies and RV-PA conduits used. Besides the hemodynamic problems related to stenosis, aberrant anatomy may challenge cannulation when using a large delivery system. Predilation of heavily calcified or tortuous conduits can facilitate positioning of the system.

Observational studies have found that prestenting the conduit before TPVI is associated with a lower risk of developing Melody stent fractures.[37] It provides an unmistakable landmark for correct valve positioning and can produce superior immediate hemodynamic results because it enhances rigidity of the landing zone.[24,27] Prestenting of the conduit before TPVI has become standard practice in most centers. Because of the short length (14 to 16 mm) of the valve and better stability, prestenting before Edwards Sapien implantation is preferred.[38]

For prestenting with bare-metal stents, the balloon-expandable IntraStent (Max LD, EV3, Plymouth, MN) can be used on a balloon-in-balloon dilation catheter (BiB catheter, NuMed, Hopkinton, NY). They are chosen because they have smaller nominal balloon diameters than those subsequently used in the TPVI delivery system. This approach leaves some degree of residual outflow tract obstruction but reduces the risk of conduit rupture and facilitates safer anchoring of the valved stent.

Typically, an uncovered stent is used if obstruction ("jailing") of the origin of a pulmonary branch artery is expected after deployment of the preimplantation stent. Covered bare-metal stents (e.g., CP stent, NuMed, Hopkinton, NY) are preferred in small conduits that require dilation to diameters larger than their original sizes. This approach can reduce the risk of bleeding due to conduit rupture.

The optimal timing of prestenting in relation to definitive TPVI is unknown. Some centers allow stent ingrowth for 2 to 3 months, especially if inadequate sealing by covered stents is expected. In our experience, a combined procedure and a two-stage procedure are valid options. For the latter, temporal free pulmonary regurgitation after prestenting is well tolerated in most patients (Fig. 54-7).

POSTDILATION OF THE VALVED STENT. According to the Medtronic proctors' guidelines, postdilation of the valved stent is indicated if there is a gradient of more than 20 mm Hg caused by the valve's diameter; preimplantation or postimplantation residual valve stenosis should be ruled out or treated separately when applicable.[36] A residual RVOT gradient of more than 25 mm Hg is associated with a significantly higher rate of reintervention and reoperation during follow-up.[21]

An aggressive approach to residual RVOT obstruction is required to improve the long-term outcome after TPVI. High-pressure dilation to a maximum balloon size of 24 mm is needed for the valved stent. The covered Melody device is thought to be the safest option with regard to conduit rupture. Ultra-high-pressure balloons such as the Mullins-X ultra-high-pressure dilation catheter (NuMed, Hopkinton, NY) or Atlas PTA dilation catheter (CR Bard, Murray Hill, NJ) are suitable. Multiple postimplantation dilations can be considered in cases of residual gradients to achieve further expansion of the device

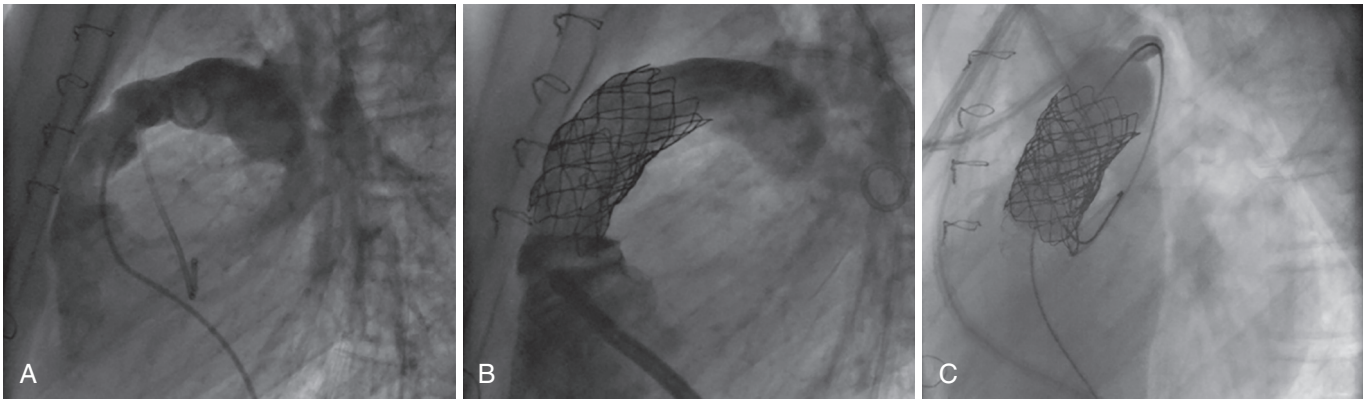

FIGURE 54-7 Two-staged procedure with prestenting before transcatheter pulmonary valve implantation (TPVI). A two-stage procedure with prestenting of a mixed dysfunctional xenograft (**A**) was performed to allow ingrowth of the right ventricular outflow tract (RVOT) stents (**B**) before TPVI with a Melody valve was performed 3 months later (**C**). The temporally free RVOT regurgitation after prestenting was accepted.

TABLE 54-2 Hemodynamic Outcome Immediately After Transcatheter Pulmonary Valve Implantation (TPVI)

	U.S. MELODY VALVE TRIAL ($N = 124$)		LONDON MELODY EXPERIENCE ($N = 151$)		MUNICH/BERLIN MELODY EXPERIENCE ($N = 102$)		PHILADELPHIA MELODY EXPERIENCE ($N = 104$)		EARLY SAPIEN EXPERIENCE ($N = 7$)		LATER SAPIEN EXPERIENCE ($N = 36$)	
Parameter*	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
RV systolic pressure (mm Hg)	65	41†	63	45‡	NA	NA	72	47‡	NA	NA	55	42‡
Peak RV to PA gradient (mm Hg)	37	12†	37	17‡	37	14	39	11‡	NA	NA	27	12‡
RV to systemic pressure (%)	0.74	0.42†	0.69	0.45‡	0.62‡	0.36‡	NA	NA	0.78	0.39‡	0.60	0.40‡

*Invasively measured pressures and gradients were reported before and after TPVI in the largest trials ($N > 100$) of the Melody[20,21,24,39] and Sapien implants[32,34] in the pulmonary artery (PA) position. In all studies, a profound improvement in right ventricular (RV) to systemic pressure ratio in response to TPVI was seen (†$P = .001$, ‡$P < .001$). Some data were not available (NA). All parameters are expressed as medians.

and optimize the hemodynamic result without damaging the bovine venous valve.[21]

Results

Immediate Hemodynamic Outcome

The hemodynamic outcome after TPVI in the largest published reports using the Melody[20,21,24,27,39] or the Sapien device[32,34] is summarized in Table 54-2.

Significant reductions in RV pressure, RVOT gradient, and ratio of RV to systemic pressure were demonstrated with both devices. Diastolic pulmonary arterial pressures rise after deployment, indicating restoration of valvar competence.[20,21,34] Angiography before and after insertion shows a significant reduction in pulmonary regurgitation in most patients. Paravalvar leaks after the procedure occur in approximately 2% of the interventions.[27] Data from the Melody Registry involving 40 international centers that treated more than 1000 patients by TPVI were reviewed.[40] Invasively measured RV systolic pressure fell from 62 ± 18 mm Hg to 43 ± 12 mm Hg ($P < .0001$), and percentage of patients with RVOT regurgitation of greater than grade 2 decreased (49% to 1%, $P < .0001$).[40]

Immediate Procedural Complications

Several single-center and multicenter trials consistently reported a low periprocedural complication rate using the Melody pulmonic valve. The London experience with 155 patients[21] and the U.S. Melody valve trial that enrolled 124 patients[39] found similar procedural complication rates of 6%. Smaller trials showed an overall early complication rate of up to 11%.[28] Analysis of the Melody Registry data found a major procedural complication rate of 2.7% and minor complication rate of 11.9% for 1003 Melody procedures.[40] Major procedural complications related to Melody TPVI include homograft rupture (2.2%), perforation of branch pulmonary arteries or guidewire injury to the PA (1.7%), damage to the tricuspid valve (1.6%), device dislodgment (0.5%), compression of coronary arteries (0.3%), and PA obstruction (0.3% in the London experience).

Early phase 1 results from an international multicenter clinical trial of Sapien TPVI in 36 patients demonstrated successful valve deployment in 97%, but 7 patients (20.5%) experienced adverse events.[34] The major complication was device dislodgment. Homograft rupture occurred in none of the patients. All of the Sapien patients underwent prestenting (33.3%) or periprocedural stenting procedures (66.6%). Risk factors for homograft ruptures are still not understood. The complication is difficult to avoid. No recommendations regarding patient selection and risk reduction can be given except for the avoidance of aggressive dilation of the RVOT before deployment of a covered stent or a valved stent, which is covered by nature.

Intervention-related coronary compression is a well-described complication in the setting of bare-metal stenting of the RVOT.[18] Approximately 5% to 6% of patients who are candidates for TPVI have coronary artery anatomy that increases the risk of coronary obstruction.[27] Several reports have described this potentially catastrophic complication,[41,42] which is strongly associated with early procedural death.[24]

Although coronary compression is avoidable in most patients, it remains a complex issue, and ruling out the risk for this complication is one of the most difficult steps in preprocedural planning for TPVI. Using a stepwise approach can minimize the risk. In case of doubt

about the risk of coronary compression, we recommend abandoning the Melody or Sapien valve procedure. In experienced hands, careful technique and attention to the recommended instructions for use help to avoid fatal complications.

Follow-Up and Outcomes

Clinical Consequences

The success of TPVI depends on device function during follow-up. Short- and medium-term results of TPVI with the Melody or Sapien valve are thought to be similar, although more data are available for the former. Long-term outcome data for both valved stents are not yet available.

The overall mortality rate for TPVI during follow-up procedures was 0% to 5% and was not related to the device itself. Failure of the Melody or Sapien device may be related to malfunction of the stent or sewn valve. Although failure of the valve leading to pulmonary regurgitation occurs rarely and only in the context of endocarditis,[43-46] the most common reason for reoperation and reintervention is repeat stenosis of the stent portion of the device. Restenosis of the stent can be caused by late recoil or loss of radial strength of the device due to stent fractures.

We have demonstrated rates of freedom from reoperation of 93% ± 2%, 86% ± 3%, 84% ± 4%, and 70% ± 13% and rates of freedom from transcatheter reintervention (second TPVI or balloon dilation) of 95% ± 2%, 87% ± 3%, 73% ± 6%, and 73% ± 6% at 10, 30, 50, and 70 months, respectively (median follow-up of 28 months).[47] Initially, the most common reason for reintervention was occurrence of the hammock effect, in which the venous wall of the bovine valve hangs into the stented valve's lumen.[48] This effect occurred with the first design of devices that had only proximal and distal sutures. After device modification with sutures placed at all struts of the stent, no further cases of the hammock effect have been seen.

Stent fractures now represent the most common reason for reintervention after Melody implantation. Without prestenting the RVOT, stent fractures occur in 20% to 21%[21,39] of valve placements, compared with 5% to 16% of cases after prestenting.[24,28] Nordmeyer and colleagues reported a stent fracture rate of 11%.[40]

In the U.S. Melody trial,[39] the rate of survival free from RVOT reintervention was 95.4% ± 2.1% at 1 year and 87.6% ± 4.5% at 2 years. The rate of freedom from a second TPVI was 96.9% ± 2.0% at 1 year and 90.4% ± 4.4% at 2 years. The rate of freedom from pulmonary valve dysfunction was 93.5% ± 2.4% at 1 year and 85.6% ± 4.7% at 2 years. By multivariable Cox regression analysis, a higher mean RVOT gradient on discharge echocardiography and younger age were associated with shorter freedom from transcatheter pulmonary valve dysfunction. The association between high RVOT gradients on echocardiography after TPVI and increased risk for reintervention draws a parallel to the London findings that a residual RVOT gradient of more than 25 mm Hg (invasively measured) results in higher rates of reintervention during follow-up.[21] It is thought that aggressive postprocedure dilation should be performed, especially in very stenotic conduits, to improve the long-term outcomes for these patients.

Data are available from the major four short- and medium-term observational studies with a total of more than 450 patients with 1 to 5 years of follow-up.[21,24,28,39] The rate of freedom from valve dysfunction or reintervention was approximately 94% at the 1-year follow-up assessment. The patients who did not require reintervention had consistently mild or less pulmonic valve regurgitation at the 1-year follow-up. Pulmonary regurgitation decreased from median values of 16% to 27% to 1% to 2%. Median peak velocity over the RVOT was 1.9 to 2.7 m/sec at thee 1-year echocardiographic follow-up. Nordmeyer and coworkers reported preliminary but promising Melody Registry data with a rate of 92.5% for 1-year freedom for all case events and 94.2% for TPVI-related events.[40]

There are no comparison studies with conventional surgery regarding pulmonary valve replacement by Sapien valves. Data on function of the Sapien valve are limited and available from smaller short- and medium-term observational studies with a total of fewer than 100 patients with RV-PA conduits,[32,34] these conduits and native RVOT,[38] or native RVOT interventions only.[49] In the largest series of 36 patients (Congenital Multicenter Trial of Pulmonic Valve Regurgitation Studying the Sapien Interventional Transcatheter Heart Valve [COMPASSION]) involving only patients with RV-PA conduits, successful valve deployment was achieved in 33 of 34 attempts.[34] In cases of native RVOT dysfunction after transannular repair of tetralogy of Fallot, a successful valve implantation was achieved in 9 of 10 eligible patients.[49] The COMPASSION trial reported an early complication rate of 7 of 34 deployed valves primarily due to device migration (three cases, with two requiring surgical retrieval). Other complications included pulmonary hemorrhage (two cases), ventricular fibrillation (one case), and stent migration (one case).

In the report by Boone and colleagues of seven patients with a median follow-up of 10 months (range, 30 days to 3.5 years), no stent fractures were described.[32] In this series, recatheterization was necessary in one patient 9 months after the initial implantation due to restenosis of the bare-metal stent. The rate of freedom from reintervention at 6 months of follow-up was 97% in the COMPASSION trial, and one patient underwent elective placement of a second valve due to conduit-induced distortion of the initial implant. Haas and colleagues demonstrated a significant reduction of the RVOT-to-PA gradient, reduction in RV systolic pressure, and an increase in diastolic pulmonary pressure from 6.3 to 14.5 mm Hg, which was a sign of tremendously decreased pulmonary regurgitation with freedom from reintervention after 6 months.[38] However, studies including more patients with longer follow-up times are required to assess performance of the Sapien device in the pulmonary position.

Nature and Management of Stent Fractures

Stent fractures may lead to stent embolization and especially to restenosis.[21] Observational data suggest that prestenting reduces the risk of stent fractures.[37,50] Prestenting the conduit with a bare-metal stent before TPVI is therefore standard practice in most centers. Stent fractures most commonly affect one or more struts, do not impact stent integrity (type I), and have no significant hemodynamic effect.[51] In cases of radiologic evidence of multiple strut fractures and increased RVOT velocity (measured by echocardiography), the fractures do impact stent integrity and can lead to restenosis (type II).

Implantation of a second device within the index device (i.e., valve-in-valve procedure) is indicated and can be performed successfully.[4,52] This strategy relieves RVOT obstruction effectively, enhances stent integrity, and minimizes the risk of stent embolization. Technically, the second TPVI procedure corresponds to the initial implantation. The first valved stent provides a perfect landmark for positioning the second device, facilitating the valve-in-valve procedure.

There has been only one reported case of device embolization into the PA. Stent disintegration resulted from stent fractures (type III).[51] This complication is avoidable as long as stent fractures are diagnosed quickly and a valve-in-valve procedure is performed. Stent fractures are significantly associated with dynamic RVOTs, as seen in noncalcified RVOT or noncircumferential homografts.[53] This information is useful for patient counseling and confirms the prestenting strategy to support the landing zone before TPVI. To detect stent fractures and plan reinterventions, patients must be closely followed after TPVI with repeated chest radiography and echocardiography.

Valved Stent Endocarditis

Infective endocarditis after TPVI has been observed in approximately 1% to 3% of patients during 1- to 4-year follow-up.[24,43-46,50] The Melody Registry preliminary data reveal a 1-year post-TPVI rate of 2.7%.[40] At first glance, the rate of endocarditis after TPVI seems to be similar to the observed rate of endocarditis after surgical RVOT reconstruction, which ranges from approximately 0% to 5% of patients during 1- to 4-year follow-up. However, Villafañe and coworkers stated that a risk comparison between TPVI and surgically implanted bioprosthetic valves is impossible. Infective endocarditis is not the primary objective in larger surgical series and is therefore underestimated.[46] Trials

directly comparing the incidence of endocarditis with the two techniques are lacking.

Factors predisposing to endocarditis reported in the literature include prior episodes of endocarditis,[21,43,44] male gender,[43] multiple stents,[43] dental treatment,[21,43] previous fungal infection,[21] and septic wounds.[21,43] Relevant residual RV-PA gradients were related to an increased risk of endocarditis.[44] Turbulence across the valve (e.g., due to stent fracture) can predispose to endothelial damage and thrombus formation with subsequent infection.[46]

Villafañe and colleagues recommend early surgical treatment in the setting of restenosis or regurgitation and in patients with no clinical improvement in response to medical treatment.[46] McElhinney and coworkers suggest that Melody valve replacement is not required during the acute treatment as long as there is no involvement of the valve system.[44] All patients with prosthetic valves, including those who have undergone Melody or Sapien TPVI, are at highest risk for endocarditis, and prophylaxis for bacterial endocarditis is strongly recommended for these procedures.[54]

Functional Outcome

Several studies have shown a significant improvement in the New York Heart Association (NYHA) functional class after TPVI.[20,21,39] Improvement has largely been maintained for the duration of follow-up, irrespective of the type of lesion (i.e., predominantly stenosis or predominantly regurgitation).[27]

Although symptomatic improvement beyond NYHA classification (i.e., quality of life) has not been systematically investigated, Gillespie and McElhinney observed that even patients who were in NYHA class I before intervention frequently report better performance of daily routines and improved exercise tolerance after intervention.[27]

Due to a variety of factors, exercise cardiopulmonary function is frequently abnormal in patients with complex congenital heart disease and is often assessed to guide decision making about interventions in patients with RVOT dysfunction. Peak oxygen consumption related to body weight ($\dot{V}O_2$/kg) and other metabolic parameters such as ventilatory efficiency and anaerobic oxygen consumption has been evaluated in studies of patients undergoing pulmonary valve replacement.[23,55-57] Exercise testing data show that patients with a predominantly stenotic lesion had a different response to TPVI compared with patients with a predominantly regurgitant lesion. Only patients with a predominantly stenotic lesion showed an improvement in peak $\dot{V}O_2$/kg.

It is assumed that significant RVOT obstruction limits augmentation of cardiac output, which is elicited by exercise, reducing exercise capacity. Lurz and colleagues demonstrated that reduction of the RVOT gradient was the only independent predictor of improved exercise capacity early after TPVI.[23] Pulmonary regurgitation may be reduced to a minimum (as a percentage and an absolute value) at peak exercise and may not be the limiting factor for cardiac output augmentation during exercise. This may reflect the shortening of diastole and reduced pulmonary vascular resistance during exercise.[23] By relieving only pulmonary regurgitation without improving the RV ejection fraction, peak $\dot{V}O_2$/kg may not be affected much in this subgroup, explaining differences in exercise capacity for the two groups.

Functional and morphologic MRI with analysis of biventricular function and calculation of great vessel blood flow is performed before and within 1 month after TPVI. The data are mixed regarding changes in the RV ejection fraction after pulmonary valve replacement. Some studies found no change,[24,39] and others reported improvements in the acute period or short term.[26,55,56] We found an improvement in the effective RV stroke volume in patients with predominantly pulmonary stenosis (40.6 ± 11.0 vs. 46.8 ± 8.0 mL/m^2, $P < .001$) and with a predominantly regurgitant lesion (37.1 ± 6.2 vs. 44.7 ± 7.5 mL/m^2, $P < .001$).[23] In the stenotic subgroup, improvement resulted from a decreased RV end-systolic volume and enhanced RV ejection fraction after relief of the pressure overload. In contrast, the RV ejection fraction remains unchanged in the regurgitant subgroup, with improvement in the RV and LV effective stroke volume due to abolishment of pulmonary regurgitation (reduction in pulmonary regurgitation fraction as assessed by MRI: 39.0% ± 8.6% vs. 3.0% ± 4.7%, $P < .001$). As in the surgical series of pulmonary valve replacement, relief of the RV volume overload resulted in a reduction in RV end-diastolic volume and the total RV stroke volume in patients with predominantly pulmonary regurgitation.[12,14]

Remarkably, there is no further reduction of RV size or improvement of RV function on MRI and exercise capacity parameters 1 year after TPVI compared with the early functional outcome.[57] The ideal timing of a surgical or percutaneous RVOT intervention remains unknown because long-term data are lacking. However, these functional results suggest treating patients with pulmonary regurgitation before the onset of RV dysfunction or impaired exercise capacity.

Because of the right-to-left ventricular interaction, an important physiologic consequence of RV enlargement and dysfunction is secondary left ventricular dysfunction in some patients, which can influence exercise capacity. The impact of TPVI on left ventricular systolic and diastolic function is not trivial. Improved systolic function due to TPVI as estimated by the ejection fraction on myocardial velocity imaging has been reported in several studies.[23,55] Improvement in left ventricular diastolic function has also been reported.[22,47,56]

Extended Indications and Future Directions

Approximately 15% of patients with dysfunction of the RVOT are eligible for the approved implantable valves.[29] Many patients are poor candidates because of their small physical size, limited vascular access, or the size and shape of the RVOT. It is not surprising that TPVI has moved beyond the original indications for off-label use in conditions with less than ideal hemodynamic and anatomic circumstances.

Case series report of effective and safe TPVI in patients with pulmonary hypertension[22] or failed bioprosthetic valves.[20] Most patients with RVOT dysfunction had patch enlargement of the RVOT as part of the initial surgical repair strategy. This clinical challenge prompted novel and sometimes creative approaches to treat RVOT failure using existing interventional pulmonic valve technology. Reports have described TPVI in native, stent-augmented RVOTs, which provided a landing zone that was nondistensible or could not distend beyond 22 mm for the Melody or 26 mm for the Sapien device.[25,51]

A small case series by Cheatham and coworkers described implantation or postimplantation dilation for the Melody valve using a 24-mm balloon.[58] This approach appeared not to compromise valve function, and it may effectively expand the pool of eligible patients.[58]

Patients with RVOT dysfunction with a predominantly regurgitant lesion and an enlarged outflow tract may not be eligible for TPVI. Several treatment strategies, including Melody valve implantation into the branch pulmonary arteries[59,60] or anchoring by a bare-metal stent implanted across the main pulmonary artery into a pulmonary branch ("jailing"), have been described as potential options.[61] A hybrid approach combining intraoperative TPVI with simultaneous conduit downsizing[62] or direct exposure of the RV or RVOT (i.e., bailout procedure after a failed percutaneous attempt) showed feasibility.[63]

Innovative, experimental technologies include the self-expanding Medtronic Native Outflow Tract device,[64] infundibular reducer devices,[65] and low-profile pulmonary valves such as the Colibri heart valve (Broomfield, CO), which requires 12- to 16-Fr delivery systems.[48] They offer treatment alternatives to surgery to a much broader patient population.

TRANSCATHETER TRICUSPID VALVE IMPLANTATION

Background and Clinical Indications

Patients with tricuspid regurgitation may be asymptomatic for prolonged periods before RV dysfunction or failure occurs. Surgical treatment is often reserved for advanced stages of tricuspid disease when dysfunction, particularly in the setting of congestive heart failure, has led to atrial arrhythmias, hepatic congestion, ascites, peripheral edema,

and failure to thrive.[66] For that reason, patients undergoing tricuspid repair or replacement procedures tend to be at higher risk and have poorer outcomes.[66]

Primary tricuspid valve disease is rare. The underlying cause can be congenital (e.g., Ebstein's anomaly, primary tricuspid dysplasia) or acquired (e.g., rheumatic disease, endocarditis, carcinoid disease). RV volume or pressure overload, left heart systolic, and diastolic failure or mitral valve dysfunction can result in secondary RV enlargement, geometric distortion, and tricuspid annular dilation. These circumstances can promote concomitant tricuspid regurgitation (i.e., functional tricuspid regurgitation).[67]

Approximately 80% of cases of significant tricuspid regurgitation are functional in nature.[68] The incidence of tricuspid regurgitation is likely to increase with the rising numbers of elderly patients with congenital or acquired left or right heart defects or failure. In 2012, the European Society of Cardiology and the European Association for Cardiothoracic Surgery (ESC/EACTS) updated the guidelines on the management of valvular heart disease and raised the indication level of class I and IIa for most situations of functional tricuspid regurgitation.[69] These more assertive recommendations were confirmed by the American College of Cardiology and American Heart Association (ACC/AHA) in 2014.[68]

Tricuspid valve surgery has become the third most frequently performed valve surgery in the United States.[66] Although patients undergoing surgery for tricuspid failure have demonstrated aggravation of risk factors, the perioperative mortality rate has declined but nonetheless remains significant.[66] With evolving percutaneous mitral valve repair techniques, as shown in the Endovascular Valve Edge-to-Edge Repair Study II (EVEREST II),[70] a transcatheter approach for tricuspid valve repair or replacement seems to be fundamental and may have significant benefits for this high-risk population.

Patient Selection Criteria in Selected Series

Van Garsse and coworkers reported the first percutaneous transcatheter valve-in-valve implantation in stenosed tricuspid valve bioprosthesis in 2011.[71] Tanous and colleagues described the use of a Melody valve for creation of a functional tricuspid valve in a patient with a right atrial–to–right ventricle conduit for a palliative Fontan procedure of tricuspid atresia.[72] Later, two extended series reported successful implantation of the Melody valve into failed tricuspid prostheses,[4,73] along with other case reports with smaller patient numbers.[74,75]

In the international multicenter series by Roberts and coworkers,[73] of the 15 patients with failed tricuspid prostheses who were enrolled, 10 underwent implantation into various failing bioprosthetic valves. Five cases included implantation into dysfunctional conduits forming part of a Fontan palliation procedure. The median NYHA class was III, and all patients were considered to be at too high a risk for conventional surgery for tricuspid prosthesis failure. The primary lesion was predominantly stenosis (mean gradient >5 mm Hg), although a few patients had significant regurgitation.

Cullen and colleagues reported a single-center series of transvenous Melody valve-in-valve implantations for bioprosthetic valve dysfunction that enrolled 10 patients with failing tricuspid prostheses.[4] Nine other patients with dysfunctional mitral protheses where enrolled for valve-in-valve implantation in the mitral position. After discussion with an interdisciplinary board and consultation with a cardiac surgeon, patients were considered candidates for the interventional procedure if they had significant bioprosthetic tricuspid valve dysfunction (i.e., stenosis or regurgitation, or both) with comorbid conditions that precludes a repeat sternotomy and valve replacement. Informed consent was obtained after detailed instruction on the potential risks of the procedure, including the off-label use of the Melody valve and discussion of therapeutic options (i.e., repeat open surgery and medical therapy). The median NYHA class was III, with 7 of the 10 patients suffering from moderate or worse tricuspid valve regurgitation with a mean inflow gradient of 10 ± 4.3 mm Hg.

Roberts and colleagues stated that a careful evaluation of the inner dimension of the tricuspid bioprosthesis by echocardiography was necessary.[73] They thought it was essential to determine a suitable anchor point and to ensure that adequate expansion of the stented-valve would be achievable.[73]

In summary, selection for valve-in-valve implantation should follow the ESC, EACTS, or the ACC/AHA guidelines for valve surgery. This is essential for patients at high risk for conventional surgery.[76]

Devices for Tricuspid Valve Implantation

Two percutaneous devices have been described for transcatheter valve implantation in failing bioprosthetic valves. They are the Edwards Sapien valve and its iterations and the Medtronic Melody valve. Their technical profiles are described in the "Devices and Delivery Systems" section.

If appropriate to the underlying size of the dysfunctional bioprosthesis, the Melody valve is thought to be preferable. The valve is longer (NuMed CP Stent CP8Z34 is 34 mm long) than the Edwards Sapien valve (14 or 16 mm long), facilitating coaxial alignment (Fig. 54-8). The longer length of the Melody device allows it to cover the entire

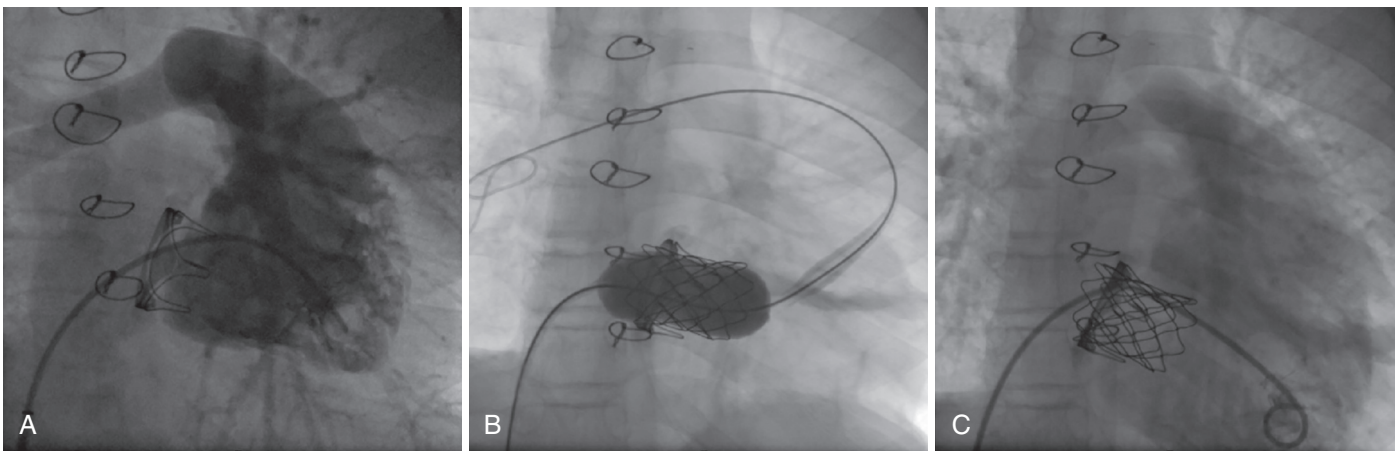

FIGURE 54-8 A Melody device was used for a valve-in-valve implantation in the tricuspid position in a patient with severe stenosis of a prosthetic biologic tricuspid valve. Angiograms show a right ventricle in systole before implantation (**A**), a guidewire in the right pulmonary artery and stable device positioning after inflating both balloons of the balloon-in-balloon delivery system (**B**), and the stent position within the biologic prosthesis and relative to the right ventricle. There is no tricuspid regurgitation.

dysfunctional bioprosthetic valve. Prestenting the deployment site before implantation is not necessary. Advantages of the Edwards Sapien valve for the tricuspid area include the larger available diameter (up to 29 mm) and the relatively shorter stent length, which ensures that the stent does not protrude significantly into the right ventricle, particularly in smaller hearts.[34,74]

No valve has been approved or certified to be implanted in the tricuspid position. Implantation in the tricuspid position remains an off-label use.

Procedure

Like TPVI, tricuspid valve-in-valve procedures should be performed in hybrid operating rooms that provide catheterization laboratory equipment with a monoplane or, preferably, biplane fluoroscopy setup. Procedures are performed in sterile conditions and usually under general anesthesia. Recommended hemodynamic monitoring is the same as for TPVI. Periprocedural imaging by intracardiac echocardiography (ICE) or transesophageal echocardiography with optional three-dimensional support may be helpful for safer device deployment (Fig. 54-9).[4,77]

Femoral venous access is preferred because it provides an easier working position in the catheterization laboratory. Jugular vein access can be performed if required.[4,73,76] Right heart hemodynamic measurements and angiography of the caval system and right ventricle should be completed if applicable (see Fig. 54-8).

An extra-stiff guidewire (i.e., Amplatz Ultra Stiff guidewire [0.035 inch × 260 cm] or Lunderquist [0.035 inch × 260 cm]) is advanced into the distal PA through a balloon wedge catheter. Balloon sizing of the tricuspid prosthesis is performed (e.g., 22-mm Z-Med II balloon, NuMed, Hopkinton, NY).[4] The desired stent-mounted valve is prepared and mounted onto the delivery system (i.e., Edwards Retroflex III delivery system for the Sapien valve and Ensemble for the Medtronic Melody valve) (see Figs. 54-2 and 54-3) as described previously. The delivery system is then introduced into the prepared puncture site and advanced over the exchange wire. The delivery system is maneuvered across the dysfunctional tricuspid prosthesis. The position is confirmed by fluoroscopic and echocardiographic imaging before valve deployment.

Results

In the series of Roberts and colleagues, procedural success with device deployment was achieved in all of the tricuspid patients.[73] The mean tricuspid gradient decreased from 12.9 to 3.9 mm Hg, and the degree of tricuspid regurgitation was reduced to mild or none.

Procedural complications occurred in one patient (i.e., atrioventricular block requiring a pacemaker). Another patient had endocarditis 8 weeks after the procedure. One patient with preexisting multiorgan failure died 17 days after the procedure.

In the series reported by Cullen and coworkers, all patients underwent successful implantation of a 22-mm Melody valve into the existing dysfunctional bioprosthetic valve.[4] Among the tricuspid patients, there was no periprocedural death, myocardial infarction, stroke, or device dislodgment. The mean diastolic inflow gradient decreased from 10 ± 4.3 mm Hg to 5.6 ± 2.5 mm Hg. The degree of valve regurgitation improved after valve-in-valve implantation to at least mild in all but one case.

Follow-Up and Outcomes

Mean follow-up was 9 months in the series reported by Roberts and coworkers NYHA functional class improved in 12 of the treated patients. Nine of the patients sustained the good interventional result 9 months after implantation, and one percutaneous valve-in-valve had to be replaced.[73]

A substantially shorter average follow-up of 41 days (range, 11 to 209) was reported by Cullen and associates.[4] The 30-day readmission rate for the tricuspid patients was 30% (3 of 10). One of these patients suffered a Melody valve failure due to occlusive valve thrombosis 18 days after his procedure and needed surgical valve replacement. An underlying heparin-induced thrombocytopenia was later discovered. NYHA functional class improved for 9 of the 10 treated patients with tricuspid dysfunction.

Extended Indications and Future Directions

In addition to the previously described series of valve-in-valve implantations, several research groups selected patients with comparable morbidity profiles to demonstrate the feasibility of percutaneous deployment of the stent-mounted Sapien, Sapien XT, and Melody valves into the venous system (i.e., inferior or superior vena cava, or both). The focus was not on the tricuspid regurgitation itself, but rather on its hemodynamic disturbance. The procedures are therefore called caval-valve implantations.[78-81]

Several animal experimental studies examined the feasibility of percutaneous valve implantation into a native tricuspid valve.[82,83] Like the early, promising results of percutaneous valve replacement in the mitral position,[84] Kefer and colleagues demonstrated the feasibility of Sapien valve implantation into a native tricuspid annulus after failed repair without a bioprosthesis and mixed tricuspid disease.[77] However, the group reported that the procedure had technical challenges due to the lack of a rigid landing zone and fluoroscopic markers compared with implantation in a bioprosthesis.

SUMMARY

The aim of percutaneous pulmonary valve implantation is to prolong the life span of RV-PA conduits that were surgically placed. The increased conduit life span and postponed surgery should reduce the

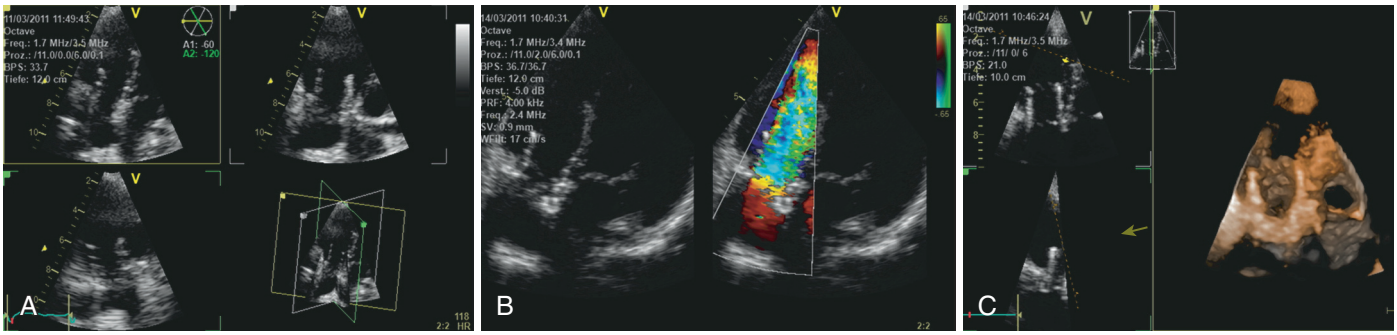

FIGURE 54-9 Periprocedural echocardiographic imaging of Melody valve implantations in the tricuspid position. The Melody valve tricuspid valve implantation procedure is guided triplane (**A**), color Doppler (**B**), and three-dimensional echocardiography (**C**).

number of open heart operations needed over the life spans of children and adults with congenital heart disease or acquired heart disease that required implantation of pulmonic conduits. This sophisticated strategy improves life expectancy.

Pulmonary valve replacement with stent-mounted bovine- or porcine-derived valves is the noninvasive treatment of choice for patients with RVOT dysfunction. It is considered superior to insertion of bare-metal stents. Indications continue to be extended, even to patients with native but dysfunctional outflow tracts, but limitations still exist for percutaneous valve implantation. Although significant improvement has been achieved in the early and late outcomes after percutaneous implantation of pulmonary valves, the risks of stent fractures and graft rupture have not been sufficiently explored. Further research is necessary to avoid these complications.

The percutaneous approach to tricuspid valve replacement has moved beyond its early experimental stage and extended the application of pulmonary valve implantation. Although it has been shown to be feasible, it is currently reserved for high-risk patients with conditions that preclude surgery. Evolution of the interventional treatment of dysfunctional valves and RVOTs can be achieved only by creative thinking and close cooperation of cardiologists, surgeons, imaging specialists, and biomedical engineers.

REFERENCES

1. Shimazaki Y, Blackstone EH, Kirklin JW: The natural history of isolated congenital pulmonary valve incompetence: surgical implications. *Thorac Cardiovasc Surg* 32(4):257–259, 1984.
2. Warnes CA: The adult with congenital heart disease: born to be bad? *J Am Coll Cardiol* 46(1):1–8, 2005.
3. Bonhoeffer P, Boudjemline Y, Saliba Z, et al: Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. *Lancet* 356(9239):1403–1405, 2000.
4. Cullen MW, Cabalka AK, Alli OO, et al: Transvenous, antegrade Melody valve-in-valve implantation for bioprosthetic mitral and tricuspid valve dysfunction: a case series in children and adults. *JACC Cardiovasc Interv* 6(6):598–605, 2013.
5. Warnes CA, Liberthson R, Danielson GK, et al: Task force 1: the changing profile of congenital heart disease in adult life. *J Am Coll Cardiol* 37(5):1170–1175, 2001.
6. Marelli AJ, Mackie AS, Ionescu-Ittu R, et al: Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation* 115(2):163–172, 2007.
7. Tweddell JS, Hoffman GM, Fedderly RT, et al: Patients at risk for low systemic oxygen delivery after the Norwood procedure. *Ann Thorac Surg* 69(6):1893–1899, 2000.
8. Powell AJ, Lock JE, Keane JF, Perry SB: Prolongation of RV-PA conduit life span by percutaneous stent implantation. intermediate-term results. *Circulation* 92(11):3282–3288, 1995.
9. Oosterhof T, Meijboom FJ, Vliegen HW, et al: Long-term follow-up of homograft function after pulmonary valve replacement in patients with tetralogy of Fallot. *Eur Heart J* 27(12):1478–1484, 2006.
10. Corno AF: Valved conduits right ventricle to pulmonary artery for complex congenital heart defects. In Cagini L, editor: *Current Concepts in General Thoracic Surgery*, 2012, InTech. Available at: <http://www.intechopen.com/books/current-concepts-in-general-thoracic-surgery/valved-conduits-right-ventricle-to-pulmonary-artery-for-complex-congenital-heart-defects>.
11. Gatzoulis MA, Balaji S, Webber SA, et al: Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet* 356(9234):975–981, 2000.
12. Frigiola A, Redington AN, Cullen S, Vogel M: Pulmonary regurgitation is an important determinant of right ventricular contractile dysfunction in patients with surgically repaired tetralogy of Fallot. *Circulation* 110(11 Suppl 1):II153–II157, 2004.
13. Carvalho JS, Shinebourne EA, Busst C, et al: Exercise capacity after complete repair of tetralogy of Fallot: deleterious effects of residual pulmonary regurgitation. *Br Heart J* 67(6):470–473, 1992.
14. Oosterhof T, van Straten A, Vliegen HW, et al: Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. *Circulation* 116(5):545–551, 2007.
15. Buechel ER, Dave HH, Kellenberger CJ, et al: Remodelling of the right ventricle after early pulmonary valve replacement in children with repaired tetralogy of Fallot: assessment by cardiovascular magnetic resonance. *Eur Heart J* 26(24):2721–2727, 2005.
16. Therrien J, Provost Y, Merchant N, et al: Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. *Am J Cardiol* 95(6):779–782, 2005.
17. Aggarwal S, Garekar S, Forbes TJ, Turner DR: Is stent placement effective for palliation of right ventricle to pulmonary artery conduit stenosis? *J Am Coll Cardiol* 49(4):480–484, 2007.
18. Peng LF, McElhinney DB, Nugent AW, et al: Endovascular stenting of obstructed right ventricle-to-pulmonary artery conduits: a 15-year experience. *Circulation* 113(22):2598–2605, 2006.
19. Sugiyama H, Williams W, Benson LN: Implantation of endovascular stents for the obstructive right ventricular outflow tract. *Heart* 91(8):1058–1063, 2005.
20. Gillespie MJ, Rome JJ, Levi DS, et al: Melody valve implant within failed bioprosthetic valves in the pulmonary position: a multicenter experience. *Circ Cardiovasc Interv* 5(6):862–870, 2012.
21. Lurz P, Coats L, Khambadkone S, et al: Percutaneous pulmonary valve implantation: impact of evolving technology and learning curve on clinical outcome. *Circulation* 117(15):1964–1972, 2008.
22. Lurz P, Bonhoeffer P, Taylor AM: Percutaneous pulmonary valve implantation: an update. *Expert Rev Cardiovasc Ther* 7(7):823–833, 2009.
23. Lurz P, Giardini A, Taylor AM, et al: Effect of altering pathologic right ventricular loading conditions by percutaneous pulmonary valve implantation on exercise capacity. *Am J Cardiol* 105(5):721–726, 2010.
24. Eicken A, Ewert P, Hager A, et al: Percutaneous pulmonary valve implantation: two-centre experience with more than 100 patients. *Eur Heart J* 32(10):1260–1265, 2011.
25. Boudjemline Y, Brugada G, Van-Aerschot I, et al: Outcomes and safety of transcatheter pulmonary valve replacement in patients with large patched right ventricular outflow tracts. *Arch Cardiovasc Dis* 105(8–9):404–413, 2012.
26. Demkow M, Biernacka EK, Spiewak M, et al: Percutaneous pulmonary valve implantation preceded by routine prestenting with a bare metal stent. *Catheter Cardiovasc Interv* 77(3):381–389, 2011.
27. Gillespie MJ, McElhinney DB: Transcatheter pulmonary valve replacement: a current review. *Curr Pediatr Rep* 1(2):83–91, 2013.
28. Butera G, Milanesi O, Spadoni I, et al: Melody transcatheter pulmonary valve implantation: results from the registry of the Italian Society of Pediatric Cardiology. *Catheter Cardiovasc Interv* 81(2):310–316, 2013.
29. Kreutzer J: Percutaneous pulmonary valve implantation. *Rev Argent Cardioangiol Interv* 4(2):84–91, 2013.
30. Baumgartner H, Bonhoeffer P, De Groot NM, et al: ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 31(23):2915–2957, 2010.
31. Feltes TF, Bacha E, Beekman RH, 3rd, et al: Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. *Circulation* 123(22):2607–2652, 2011.
32. Boone RH, Webb JG, Horlick E, et al: Transcatheter pulmonary valve implantation using the Edwards SAPIEN transcatheter heart valve. *Catheter Cardiovasc Interv* 75(2):286–294, 2010.
33. Garay F, Webb J, Hijazi ZM: Percutaneous replacement of pulmonary valve using the Edwards-Cribier percutaneous heart valve: first report in a human patient. *Catheter Cardiovasc Interv* 67(5):659–662, 2006.
34. Kenny D, Hijazi ZM, Kar S, et al: Percutaneous implantation of the Edwards SAPIEN transcatheter heart valve for conduit failure in the pulmonary position: early phase 1 results from an international multicenter clinical trial. *J Am Coll Cardiol* 58(21):2248–2256, 2011.
35. Sridharan S, Coats L, Khambadkone S, et al: Images in cardiovascular medicine. Transcatheter right ventricular outflow tract intervention: the risk to the coronary circulation. *Circulation* 113(25):e934–e935, 2006.
36. Witsenburg M: The Melody TPV implantation step-by-step: a proctor's guide, 2013, Available at <http://www.aepc.org/@Bin/141218/Melody+Implantation+Step+by+Step_+A+Proctors+Guide_+Rev+1_+May+10_2013.pdf>, (accessed January 29 2015).
37. Nordmeyer J, Lurz P, Khambadkone S, et al: Pre-stenting with a bare metal stent before percutaneous pulmonary valve implantation: acute and 1-year outcomes. *Heart* 97(2):118–123, 2011.
38. Haas NA, Moysich A, Neudorf U, et al: Percutaneous implantation of the Edwards SAPIEN pulmonic valve: initial results in the first 22 patients. *Clin Res Cardiol* 102(2):119–128, 2014.
39. McElhinney DB, Hellenbrand WE, Zahn EM, et al: Short- and medium-term outcomes after transcatheter pulmonary valve placement in the expanded multicenter US Melody valve trial. *Circulation* 122(5):507–516, 2010.
40. Nordmeyer J, Ewert P, Gewillig M, et al: Current results of the Melody Registry: an international multicenter registry of transcatheter pulmonary valve implantation. *J Am Coll Cardiol* 63(12S):2014. doi:10.1016/S0735-1097(14)60480-0.
41. Biermann D, Schonebeck J, Rebel M, et al: Left coronary artery occlusion after percutaneous pulmonary valve implantation. *Ann Thorac Surg* 94(1):e7–e9, 2012.
42. Mauri L, Frigiola A, Butera G: Emergency surgery for extrinsic coronary compression after percutaneous pulmonary valve implantation. *Cardiol Young* 23(3):463–465, 2013.
43. Buber J, Bergersen L, Lock JE, et al: Bloodstream infections occurring in patients with percutaneously implanted bioprosthetic pulmonary valve: a single-center experience. *Circ Cardiovasc Interv* 6(3):301–310, 2013.
44. McElhinney DB, Benson LN, Eicken A, et al: Infective endocarditis after transcatheter pulmonary valve replacement using the Melody valve: combined results of 3 prospective North American and European studies. *Circ Cardiovasc Interv* 6(3):292–300, 2013.
45. Cheung G, Vejlstrup N, Ihlemann N, et al: Infective endocarditis following percutaneous pulmonary valve replacement: diagnostic challenges and application of intra-cardiac echocardiography. *Int J Cardiol* 169(6):425–429, 2013.
46. Villafañe J, Baker GH, Austin EH, 3rd, et al: Melody pulmonary valve bacterial endocarditis: experience in four pediatric patients and a review of the literature. *Catheter Cardiovasc Interv* 84(2):212–218, 2014.
47. Lurz P, Nordmeyer J, Coats L, et al: Immediate clinical and haemodynamic benefits of restoration of pulmonary valvar competence in patients with pulmonary hypertension. *Heart* 95(8):646–650, 2009.
48. Kenny D, Hijazi ZM: The evolution of transcatheter pulmonary valve replacement. *Expert Rev Cardiovasc Ther* 11(7):795–797, 2013.
49. Demkow M, Ruzyllo W, Biernacka EK, et al: Percutaneous Edwards SAPIEN valve implantation for significant pulmonary regurgitation after previous surgical repair with a right ventricular outflow patch. *Catheter Cardiovasc Interv* 83(3):474–481, 2014.
50. McElhinney DB, Cheatham JP, Jones TK, et al: Stent fracture, valve dysfunction, and right ventricular outflow tract reintervention after transcatheter pulmonary valve implantation: patient-related and procedural risk factors in the US Melody Valve Trial. *Circ Cardiovasc Interv* 4(6):602–614, 2011.
51. Nordmeyer J, Khambadkone S, Coats L, et al: Risk stratification, systematic classification, and anticipatory management strategies for stent fracture after percutaneous pulmonary valve implantation. *Circulation* 115(11):1392–1397, 2007.
52. Nordmeyer J, Coats L, Lurz P, et al: Percutaneous pulmonary valve-in-valve implantation: a successful treatment concept for early device failure. *Eur Heart J* 29(6):810–815, 2008.
53. Nordmeyer J, Gaudin R, Tann OR, et al: MRI may be sufficient for noninvasive assessment of great vessel stents: an in vitro comparison of MRI, CT, and conventional angiography. *AJR Am J Roentgenol* 195(4):865–871, 2010.
54. Wilson W, Taubert KA, Gewitz M, et al: Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 116(15):1736–1754, 2007.
55. Coats L, Khambadkone S, Derrick G, et al: Physiological and clinical consequences of relief of right ventricular outflow tract obstruction late after repair of congenital heart defects. *Circulation* 113(17):2037–2044, 2006.
56. Coats L, Khambadkone S, Derrick G, et al: Physiological consequences of percutaneous pulmonary valve implantation: the different behaviour of volume- and pressure-overloaded ventricles. *Eur Heart J* 28(15):1886–1893, 2007.
57. Lurz P, Nordmeyer J, Giardini A, et al: Early versus late functional outcome after successful percutaneous pulmonary valve implantation: are the acute effects of altered right ventricular loading all we can expect? *J Am Coll Cardiol* 57(6):724–731, 2011.
58. Cheatham SL, Holzer RJ, Chisolm JL, Cheatham JP: The Medtronic Melody(R) transcatheter pulmonary valve implanted at 24-mm diameter—it works. *Catheter Cardiovasc Interv* 82(5):816–823, 2013.
59. Robb JD, Harris MA, Minakawa M, et al: Melody valve implantation into the branch pulmonary arteries for treatment of pulmonary insufficiency in an ovine model of right ventricular outflow tract dysfunction following tetralogy of Fallot repair. *Circ Cardiovasc Interv* 4(1):80–87, 2011.
60. Gillespie MJ, Dori Y, Harris MA, et al: Bilateral branch pulmonary artery melody valve implantation for treatment of complex right ventricular outflow tract dysfunction in a high-risk patient. *Circ Cardiovasc Interv* 4(4):e21–e23, 2011.
61. Boudjemline Y, Legendre A, Ladouceur M, et al: Branch pulmonary artery jailing with a bare metal stent to anchor a transcatheter

pulmonary valve in patients with patched large right ventricular outflow tract. *Circ Cardiovasc Interv* 5(2):e22–e25, 2012.
62. Bacha EA, Marshall AC, McElhinney DB, del Nido PJ: Expanding the hybrid concept in congenital heart surgery. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* (10):146–150, 2007.
63. Cubeddu RJ, Hijazi ZM: Bailout perventricular pulmonary valve implantation following failed percutaneous attempt using the Edwards Sapien transcatheter heart valve. *Catheter Cardiovasc Interv* 77(2):276–280, 2011.
64. Schievano S, Taylor AM, Capelli C, et al: First-in-man implantation of a novel percutaneous valve: a new approach to medical device development. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. *EuroIntervention* 5(6):745–750, 2010.
65. Boudjemline Y, Agnoletti G, Bonnet D, et al: Percutaneous pulmonary valve replacement in a large right ventricular outflow tract: an experimental study. *J Am Coll Cardiol* 43(6):1082–1087, 2004.
66. Kilic A, Saha-Chaudhuri P, Rankin JS, Conte JV: Trends and outcomes of tricuspid valve surgery in North America: an analysis of more than 50,000 patients from the Society of Thoracic Surgeons database. *Ann Thorac Surg* 96(5):1546–1552, discussion 1552, 2013.
67. Rogers JH, Bolling SF: Surgical approach to functional tricuspid regurgitation: should we be more aggressive? *Curr Opin Cardiol* 29(2):133–139, 2014.
68. Nishimura RA, Otto CM, Bonow RO, et al: 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 129(23):2440–2492, 2014.
69. Vahanian A, Iung B: The new ESC/EACTS guidelines on the management of valvular heart disease. *Arch Cardiovasc Dis* 105(10):465–467, 2012.
70. Whitlow PL, Feldman T, Pedersen WR, et al: Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. *J Am Coll Cardiol* 59(2):130–139, 2012.
71. Van Garsse LA, ter Bekke RM, van Ommen VG: Percutaneous transcatheter valve-in-valve implantation in stenosed tricuspid valve bioprosthesis. *Circulation* 123(5):e219–e221, 2011.
72. Tanous D, Nadeem SN, Mason X, et al: Creation of a functional tricuspid valve: novel use of percutaneously implanted valve in right atrial to right ventricular conduit in a patient with tricuspid atresia. *Int J Cardiol* 144(1):e8–e10, 2010.
73. Roberts PA, Boudjemline Y, Cheatham JP, et al: Percutaneous tricuspid valve replacement in congenital and acquired heart disease. *J Am Coll Cardiol* 58(2):117–122, 2011.
74. Riede F, Dähnert I: Implantation of a Melody® valve in tricuspid position. *Catheter Cardiovasc Interv* 80(3):474–476, 2012.
75. Petit CJ, Justino H, Frank F: Melody valve implantation in the pulmonary and tricuspid position. *Catheter Cardiovasc Interv* 82(7):E944–E946, 2013.
76. Milburn K, Bapat V, Thomas M: Valve-in-valve implantations: is this the new standard for degenerated bioprostheses? Review of the literature. *Clin Res Cardiol* 103(6):417–429, 2014.
77. Kefer J, Sluysmans T, Vanoverschelde JL: Transcatheter Sapien valve implantation in a native tricuspid valve after failed surgical repair. *Catheter Cardiovasc Interv* 83(5):841–845, 2014.
78. Laule M, Stangl V, Sanad W, et al: Percutaneous transfemoral management of severe secondary tricuspid regurgitation with Edwards Sapien XT bioprosthesis: first-in-man experience. *J Am Coll Cardiol* 61(18):1929–1931, 2013.
79. Lauten A, Hamadanchi A, Doenst T, Figulla HR: Caval valve implantation for treatment of tricuspid regurgitation: post-mortem evaluation after mid-term follow-up. *Eur Heart J* 35(25):1651, 2014.
80. Lauten A, Laube A, Schubert H, et al: Transcatheter treatment of tricuspid regurgitation by caval valve implantation-experimental evaluation of decellularized tissue valves in central venous position. *Catheter Cardiovasc Interv* 85(1):150–160, 2015.
81. Lauten A, Doenst T, Hamadanchi A, et al: Percutaneous bicaval valve implantation for transcatheter treatment of tricuspid regurgitation: clinical observations and 12-month follow-up. *Circ Cardiovasc Interv* 7(2):268–272, 2014.
82. Boudjemline Y, Agnoletti G, Bonnet D, et al: Steps toward the percutaneous replacement of atrioventricular valves: an experimental study. *J Am Coll Cardiol* 46(2):360–365, 2005.
83. Bai Y, Zong GJ, Wang H-R, et al: An integrated pericardial valved stent special for percutaneous tricuspid implantation: an animal feasibility study. *J Surg Res* 160(2):215–221, 2010.
84. Søndergaard L, Reddy V, Kaye D, et al: Transcatheter treatment of heart failure with preserved or mildly reduced ejection fraction using a novel interatrial implant to lower left atrial pressure. *Eur J Heart Fail* 16(7):796–801, 2014.

Hypertrophic Cardiomyopathy

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KEY POINTS

- Hypertrophic cardiomyopathy is a disease process that varies broadly in its clinical presentation and has been associated with many different genetic mutations.
- Obstructive disease is present in a small proportion of patients, where the severity of obstruction varies depending on loading conditions and adrenergic state in the individual patient.
- Imaging with echocardiography and magnetic resonance imaging are primarily used to make the diagnosis.
- Medical management is indicated in symptomatic patients as an initial intervention. Patients at high risk for sudden cardiac death should be considered for an implantable cardioverter-defibrillator.
- If an experienced surgical team is available, myectomy is considered to be the treatment of choice in good surgical candidates when symptoms persist despite optimal medical therapy.
- Alcohol septal ablation provides an excellent treatment option when surgical myectomy is not thought to be optimal for an individual patient. Careful attention to anatomic details and appropriate selection of patients are requisites for procedural success.

By virtue of the broad variability in its phenotypic expression, hypertrophic cardiomyopathy (HCM) is a unique cardiovascular condition with a potential for the development of clinical symptoms during any phase of life.[1-7] The genetic foundation of HCM has been directly related to abnormalities of the genes encoding the cardiac sarcomere unit and may result in a complex disease phenotype that encompasses a spectrum of clinical and pathologic presentations. In the past, the nomenclature regarding HCM was often misleading. *Idiopathic hypertrophic subaortic stenosis* or *hypertrophic obstructive cardiomyopathy* (HOCM) typically described only a subset of patients with this disorder. With improved understanding of the clinical heterogeneity of this process, *hypertrophic cardiomyopathy* appears to be a more appropriate descriptive term.

The rapid demystification of the genetic underpinnings of HCM has greatly expanded understanding of this entity. HCM is inherited in an autosomal dominant fashion, with more than 12 genes identified as being involved in the phenotypic manifestation.[1,7-10] Three of those genes account for more than 50% of the known cases of HCM.[1,9,11] Traditionally, the diagnosis of HCM has been primarily clinical, involving the use of echocardiography to evaluate for certain characteristic features such as asymmetric septal hypertrophy or systolic anterior motion of the mitral valve (SAM) with left ventricular outflow tract (LVOT) obstruction. Although there have been dramatic advances in understanding of the genetic predisposition for this disease state, the utility of genetic study for the absolute diagnosis remains preliminary. However, the future holds promise that genetics will become a more reliable tool for establishing and confirming this diagnosis. The use of genotyping in risk stratification is also evolving.

Given the heterogeneity of the disease process even within the same family, its clinical course and long-term outcomes differ significantly. Therefore management strategies span the range from close outpatient follow-up to surgical remodeling of the myocardium. HCM appears to be an evolving process in some patients, and the phenotype changes with age. This presents a challenging dilemma in terms of grasping the clinical course of this disorder. Consequently, therapeutic strategies need to be individualized for each patient.

EPIDEMIOLOGY

The prevalence of this genetic disorder is on the order of 1 : 500 in the general adult population, and it is one of the more common cardiac genetic disorders known.[1,6,9] Although it is not routinely accounted for in general practice, it is not uncommon to see patients with HCM in tertiary referral centers. The clinical heterogeneity of this disorder plays into the difficulty in establishing a diagnosis. Often, the presentation lacks the classic features on echocardiography. HCM is a disease process that is known to evolve with age, and the development of left ventricular hypertrophy (LVH) has been observed to occur in children after full growth is attained.[12-14] This can make diagnosis of HCM challenging and suggests that repeat evaluation at periodic intervals may be required to establish a diagnosis.

NATURAL HISTORY OF THE DISEASE

The heterogeneity of HCM lies not only in its varied presentations but also in its natural history in the patient population. Attempts to understand the links between genotype, phenotype, and natural history have yielded only limited clinical associations. Selection bias played a significant role in the initial attempts to characterize patient outcomes. Earlier studies from tertiary referral centers implied ominously high annual mortality rates of 3% to 6%; however, this work was limited by a significant referral bias.[1] More recent data from regional and community-based centers suggest an annual mortality rate of approximately 1%.[3,4] However, in selected populations, the annual mortality rate may be as high as 5% to 6%, particularly in those symptomatic patients who are eventually referred to larger centers.[1,15,16]

The clinical course of the HCM population is often difficult to predict and poses a challenge to clinicians. However, the options in terms of disease progression remain limited. The most feared and least predictable of the entities is sudden cardiac death (SCD), particularly in the younger population. More commonly, patients develop symptoms such as angina, syncope, or exertional dyspnea. These symptoms can become progressively worse over time, and such patients can progress toward end-stage heart failure with failure of the left ventricle (LV). HCM patients also develop atrial fibrillation (AF) and are at risk for embolic strokes. A certain percentage of HCM patients remain asymptomatic and have a comparably normal life expectancy. However, at some point even they are at risk for the development of SCD or AF. The challenge for clinicians is to closely monitor those who eventually develop symptoms and to offer timely therapy when it is indicated.

CLINICAL PRESENTATION

Although the spectrum of clinical presentation in HCM is large, most patients are actually asymptomatic and are diagnosed as the result of a murmur on examination, an abnormal electrocardiogram (ECG),

TABLE 55-1 Risk Factors for Sudden Cardiac Death

Spontaneous sustained VT
Nonsustained VT (>3 beats at rate of >120 beats/minute) on ambulatory monitoring
Family history of cardiac arrest or SCD
Prior personal history of cardiac arrest
Unexplained syncope (especially if exertional)
Abnormal response to exercise stress testing (especially hypotension)
LV thickness greater than 30 mm
Early onset of disease
Nuclear stress testing demonstrating ischemia (even if related to microvascular disease)
High-risk genetic mutation (see Table 55-2)
Concomitant CHF or severe aortic stenosis
Other comorbidities, such as pulmonary embolus and malignancy
LVOT gradient >30 mm Hg
Atrial fibrillation*
Near syncope*

CHF, Congestive heart failure; *LV,* left ventricle; *LVOT,* left ventricular outflow tract; *SCD,* sudden cardiac death; *VT,* ventricular tachycardia.
*Direct relationship with SCD less well established.

or unexplained LVH discovered by echocardiography. The complex pathophysiologic interplay among LVOT obstruction, diastolic dysfunction, myocardial ischemia, and mitral regurgitation typically results in the presenting complaints of exertional dyspnea, chest discomfort, syncope or near syncope, and SCD. Symptomatic patients who will have an adverse clinical course typically follow one of several pathways: (1) those at high risk for SCD; (2) progressive symptoms of exertional dyspnea and chest pain associated with presyncope or syncope in the setting of preserved LV function; (3) development of progressive congestive heart failure due to severe LV remodeling, which results in systolic dysfunction; and (4) consequences of supraventricular or ventricular arrhythmias such as AF or ventricular tachycardia (VT).[1,7,17-19]

SCD is the most common presentation and source of mortality in HCM.[1,7,18,20,21] In addition, SCD is the single leading cause of cardiovascular death among young people as well as the most common cause of mortality in competitive athletes.[1,22] It is most commonly observed in asymptomatic children and young adults, and it appears that there is no advanced age at which the risk of SCD becomes negligible.[23] Whereas SCD is obviously the most fearsome and most dramatic complication of HCM, those at high risk for SCD actually constitute only a small fraction of the disease spectrum,[1,6,7,24,25] and much effort has been devoted to the premorbid identification of this subset of patients. Currently identified risk factors for SCD include prior cardiac arrest, family history of SCD, unexplained syncope or near-syncope, LV thickness greater than 30 mm, a high-risk genetic mutation (e.g., β-myosin heavy chain mutations Arg403Gln and Arg719Gln), hypotensive response during exercise stress testing, and nonsustained VT on Holter monitoring (Table 55-1).[1,7,18,24,26-31] In addition, an LVOT gradient greater than 30 mm Hg has been associated with an increased risk of SCD, progression to heart failure, and morbidity related to arrhythmia, including stroke.[32,33] However, an incremental increase in the subaortic gradient above 30 mm Hg has not been demonstrated to impart any additional risk. It is uncommon for HCM patients to suffer SCD without at least one of the aforementioned risk factors (<3%).[24]

It has been suggested that the etiology of SCD in this population is related to the development of complex ventricular tachyarrhythmia,[7,34,35] often during mild to moderate physical exertion and with a circadian predilection for the early morning hours.[36] Chest pain, both typical and atypical in character, is a common feature in HCM and has been reported in up to 80% of patients in this population.[37] In many cases, angiography reveals normal coronary arteries. Despite this finding, numerous studies incorporating nuclear single-photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance imaging (MRI) technologies have demonstrated significant reversible and nonreversible myocardial perfusion defects in this subset of patients, including autopsy findings of myocardial infarction in up to 15% of such patients.[1,7,37-41]

Collectively, these data have led to a mounting body of evidence suggesting that microvascular dysfunction may have a pivotal role in the development of myocardial ischemia and infarction in this group. The etiology of microvascular dysfunction is probably multifactorial and due in part to arteriolar medial hypertrophy, which results in reduced luminal diameter, impaired coronary vasodilatory response, and a supply-demand mismatch due to an abnormally thickened ventricle.[1,7,38,42] In addition, early work has suggested that evidence of microvascular dysfunction, as demonstrated by PET, is an independent predictor of increased mortality and may portend a worse prognosis years before the development of clinical deterioration.[43]

Syncope in patients with HCM is not an uncommon phenomenon and has a diverse array of possible etiologies, making the exact determination of mechanism challenging. Whereas it is regarded as an ominous prognostic sign and a known risk factor for SCD in the younger population, syncope in the adult population has not been independently associated with premature death, and recurrent episodes are rarely reported in patients who have suffered SCD.[44-46] Arrhythmic sources of syncope may be supraventricular (e.g., AF or flutter) or ventricular (e.g., VT or fibrillation). Hemodynamic mechanisms of syncope all result in a sudden and severe reduction in cardiac output that may involve ischemia, outflow tract obstruction, or severe diastolic dysfunction. Additionally, it has been suggested that activation of LV baroreceptors due to elevated intracavitary pressures may induce reflex hypotension and a consequent syncopal episode in a selected subgroup of patients.[47]

Heart failure—as manifested by a symptom complex of exertional dyspnea, orthopnea, and progressive fatigue—is most commonly encountered in adult patients with HCM, but it has been described in the juvenile population as well.[1] Usually, in the setting of preserved systolic function, symptoms are most commonly the consequence of diastolic dysfunction due to an abnormally thickened and noncompliant ventricle.[7] The combined influence of other variables such as ischemia, AF, and mitral regurgitation may also play a significant role in the development of hemodynamic decompensation in this population. A smaller number of patients with HCM and heart failure may have significantly reduced LV systolic function and chamber enlargement. It is important to recognize this subset of patients, given the potential alteration in therapeutic strategy.[45]

AF complicates the course of approximately 20% of patients with HCM and is associated with an increased risk of heart failure–related death.[21,28] The risk seems to be substantially greater in the subset of patients with outflow tract obstruction or an earlier onset of arrhythmia (<50 years of age). Advanced age, left atrial enlargement, and congestive symptoms are independently linked with the development of AF. Although it is strongly associated with an increased risk of fatal and nonfatal stroke, AF does not appear to be a risk factor for the development of SCD, and approximately one third of patients have no long-term sequelae from this arrhythmia.[28]

Severe functional deterioration due to dyspnea, chest pain, palpitations, or pulmonary edema may complicate the course of the chronically affected. This is most likely caused by the loss of atrial contraction, reduction in diastolic filling time, and exacerbation of underlying ischemia.[7,28]

The nature of the clinical presentation may also be affected by a particular patient's age or gender. In contrast to their younger counterparts, older adult patients with HCM often develop marked symptomatology at an advanced age (>55 years), have lesser degrees of LVH usually confined to the septum, and have a dynamic subaortic gradient due to restricted excursion of the often anteriorly displaced mitral leaflets and posteriorly directed septal motion.[48] Whereas HCM seems to have a male predominance, female patients often are diagnosed at a later age, are more symptomatic, and are at a greater risk of death due to heart failure or stroke.[49]

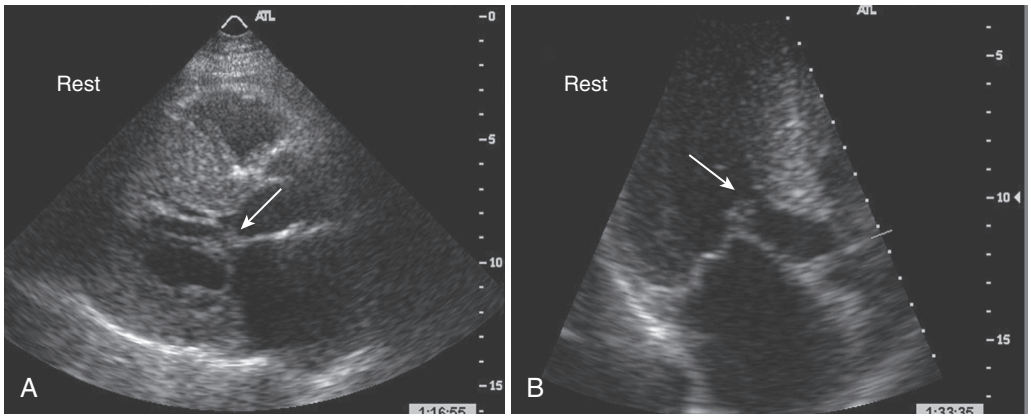

FIGURE 55-1 Echocardiographic parasternal long (**A**) and apical three-chamber (**B**) views demonstrate systolic anterior motion (SAM) *(arrow)* at rest, which results in severe left ventricular outflow tract obstruction in a patient with severe symptomatic hypertrophic obstructive cardiomyopathy.

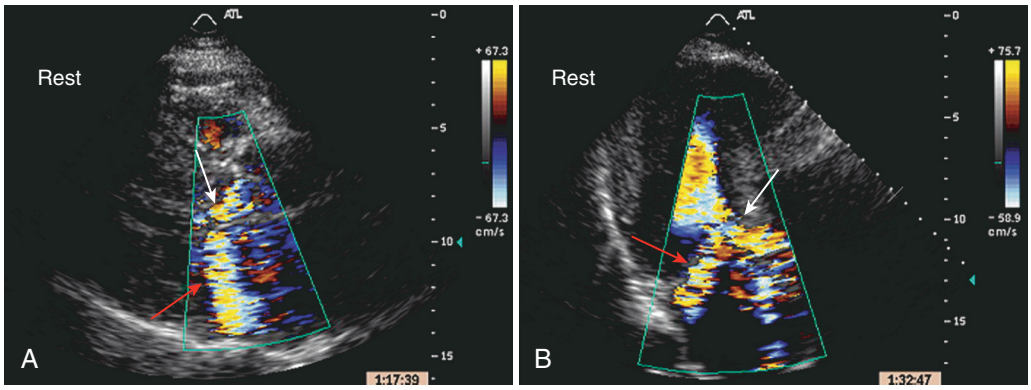

FIGURE 55-2 Color Doppler images display flow acceleration in the left ventricular outflow tract *(white arrow),* which results in posteriorly directed mitral regurgitation *(red arrow)* in the parasternal long (**A**) and apical three-chamber (**B**) views.

DIAGNOSIS

Echocardiography

Given its safety and ubiquity, two-dimensional echocardiography is the most common method for establishing the clinical diagnosis of HCM via identification of a thickened, nondilated LV in the absence of comorbidities known to cause such a degree of LVH (i.e., hypertension or aortic stenosis).[1,7,50] Although LVH was classically thought to involve primarily the ventricular septum, its morphologic expression is extremely heterogeneous, and virtually any pattern of thickening may be observed.[1,7,51] In addition, there are significant differences in the pattern of hypertrophy between young and elderly patients. Elderly patients are often found to have an *elliptical* ventricular cavity with hypertrophy predominantly of the basal septum. In contrast, younger patients (<55 years) often have a crescent-shaped ventricular cavity associated with diffuse hypertrophy of the interventricular septum.[52]

Whereas a maximal wall thickness greater than 15 mm is the traditional echocardiographic benchmark for HCM, the degree of hypertrophy exhibits considerable variability (with a mean thickness of approximately 22 mm).[51] It is important to realize, however, that a paucity of characteristic LVH (>15 mm) on echocardiographic examination *does not* exclude the presence of an HCM gene mutation.[7,9,53,55] Therefore serial echocardiographic assessment may be necessary for adequate identification of suspected carriers, especially in the younger population, in whom the development of LVH may be delayed until after puberty.[1,18,55]

LVOT is observed in approximately 20% of patients with HCM and is usually dynamic in nature.[21,32] Subaortic obstruction is due to SAM of the anterior mitral leaflet, which results in mitral-septal contact during midsystole[7] (Fig. 55-1). Obstruction may not be present under resting conditions but can be provoked by pharmacologic (i.e., amyl nitrite) or physiologic (i.e., Valsalva) maneuvers. Significant mitral regurgitation frequently accompanies SAM owing to distortion of the valvular apparatus and malcoaptation of the anterior and posterior leaflets (Fig. 55-2).

Mitral regurgitation is also observed in up to 30% of patients who do not demonstrate obstructive physiology; it is primarily caused by leaflet prolapse, chordal rupture, or trauma resulting in calcification or fibrosis.[12] Less commonly, a midcavitary gradient is formed because of the anomalous insertion of the anterolateral papillary muscle directly onto the anterior mitral leaflet or an exaggerated proliferation of mid-ventricular papillary musculature coming into apposition with the ventricular septum.[7,13,56]

Whereas the threshold for therapeutic intervention has traditionally been a gradient of greater than 50 mm Hg, it has been demonstrated that the presence of a resting LVOT obstruction of 30 mm Hg or greater is an independent predictor of death from heart failure or stroke, progression of heart failure symptoms, and reduced functional capacity as well as SCD.[32] It is important not to misinterpret the Doppler spectral display of mitral regurgitation as an LVOT gradient, given its frequent presence in the setting of obstruction and its close spatial orientation to the LVOT. In the setting of SAM, mitral regurgitation is usually posteriorly directed into the left atrium and is often difficult to distinguish from LVOT flow. It is most useful to sweep anterior to posterior with continuous Doppler imaging to distinguish these two flows.

Given the magnitude of LVH consummate with HCM, it is not surprising that more than 80% of patients have evidence of diastolic

dysfunction by echocardiogram. This is manifested by reduced maximal flow velocity in early diastole, an increase in isovolumic relaxation time, and an increased atrial contribution to ventricular filling.[50,57] These findings are similar in patients with and without an LVOT gradient or cardiac symptoms, suggesting that diastolic dysfunction may be an earlier clinical manifestation in the spectrum of this disease process. Several studies have suggested that the presence of significant diastolic dysfunction by transthoracic or tissue Doppler echocardiography implies an increased risk of cardiac arrest, VT, or progression to significant cardiac symptoms.[58]

Electrocardiography

ECG findings in HCM are extremely heterogeneous, and most patients (>90%) have demonstrable abnormalities.[1,7,11,59] However, no pattern is highly specific for the condition, and the presence of a normal tracing does not imply absence of the disease state.[11,60] Increased voltages consistent with LVH and early repolarization abnormalities are most commonly encountered; left axis deviation, left atrial enlargement, T-wave inversion, and nonspecific ST-segment abnormalities are also frequently observed. The degree of LVH by ECG does not appear to correlate with the magnitude of hypertrophy when assessed by echocardiography.[14]

In a subset of Japanese patients with hypertrophy primarily limited to the ventricular apex, giant T-wave inversions were frequently seen in the anterior leads; these are often termed Yamaguchi disease.[61] Pathologic Q waves, often in the inferolateral leads, may be observed in up to 50% of patients with known HCM. Although it is not apparent on the surface ECG, approximately one third of patients have delayed His-Purkinje conduction on formal electrophysiologic studies, possibly owing to strain on the anterior fasciculus, which overlies the hypertrophied ventricle.[59]

Magnetic Resonance Imaging

In comparison with traditional echocardiography, cardiac magnetic resonance imaging (CMRI) offers the advantages of superior resolution with precise morphologic characterization, enhanced tissue contrast capability, and production of three-dimensional images.[62] As a result, CMRI can better detect areas of hypertrophy that are not well visualized or are missed by traditional echocardiography. Particularly in patients with atypical hypertrophy of the anterolateral free wall, CMRI is a powerful adjunctive tool in the diagnosis of HCM.[62]

Through delayed hyperenhancement techniques, CMRI has demonstrated that asymptomatic patients with HCM frequently have patchy foci of myocardial scarring at the junction of the interventricular septum and the right ventricular free wall. Furthermore, scarring is limited to the areas of abnormal hypertrophy, and the degree of scarring is proportional to the magnitude of hypertrophy, whereas wall thickening was inversely related.[39] In addition, a greater extent of hyperenhancement has been positively associated with high risk for SCD and with progressive disease.[63]

CMRI also allows for better characterization of papillary muscle insertion and orientation. It is not uncommon to see hypertrophic, displaced, or distorted papillary muscles contributing to the obstruction or to mitral valve dysfunction. Assessment of mitral valve anatomy may be critical before the modality for relief of obstruction is chosen, because patients with mitral valve anomalies are best treated with the use of myectomy rather than ablation. Considering all these facts, CMRI is a valuable adjunctive imaging modality for the diagnosis of HCM.

Catheterization and Hemodynamics

Given the wealth of hemodynamic and anatomic data that can be derived noninvasively by echocardiography, cardiac catheterization is not required for the diagnosis of HCM. Catheterization is often used, however, if noninvasive imaging is of insufficient quality to quantify the degree or location of obstruction, to evaluate for coronary disease before a planned surgical therapy (i.e., myectomy or pacemaker implantation), or if anginal symptoms that may be attributable to ischemia are present in older patients.

The coronary arteries in patients with HCM are usually normal and typically of large caliber. Quite different from intramyocardial "bridging," compression of the left anterior descending (LAD) coronary artery may be observed during systole due to contraction of the hypertrophied ventricle, which results in a "sawfish" appearance.[64] Ventriculography may demonstrate systolic cavity obliteration, varying degrees of mitral regurgitation, and occasionally the hypertrophied septum prolapsing into the LVOT. Direct measurement and localization of the gradient is easily obtained by passing a multipurpose catheter into the apical portion of the LV and slowly withdrawing it while continuously monitoring the pressure waveform. Use of a wire via a guide catheter often results in increased control during the pullback and a more accurate determination of the level of obstruction. Contrary to what is observed in aortic stenosis, the gradient is reduced before the aortic valve is crossed. This same technique can be performed using simultaneous aortic and LV pressure waveforms to allow side-by-side comparison.

The gradient in HCM is characteristically labile and various pharmacological and physiologic maneuvers similar to echocardiography may be employed to accentuate the obstruction in the catheterization laboratory. The term *postextrasystolic potentiation*,[65] or *Brockenbrough-Braunwald-Morrow sign*, refers to the augmentation of LV pressure with a concomitant decrement in aortic systolic and pulse pressures as a result of increased LVOT obstruction in the cardiac cycle that follows a premature ventricular contraction. Postextrasystolic increase in the gradient between LV and aorta is seen even with aortic stenosis, but, unlike the case in HCM, the pulse pressure (stroke volume) does not decrease. This is because in aortic stenosis, the larger stroke volume of the postextrasystolic beat leads to a higher gradient with no change in the severity of obstruction (Fig. 55-3).

Genetic Overview

HCM is the result of mutations in genes primarily encoding sarcomeric proteins that regulate contractile, regulatory, and structural functions;

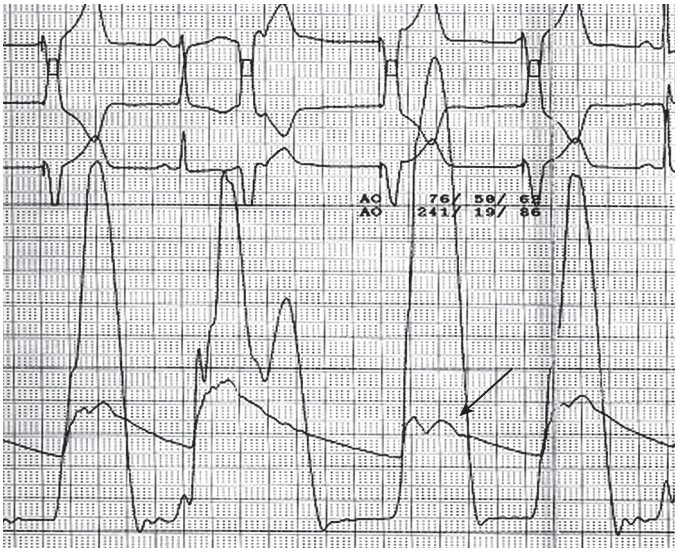

FIGURE 55-3 Brockenbrough-Braunwald-Morrow sign (postextrasystolic potentiation): simultaneous left ventricular and aortic pressure tracing demonstrates the augmentation in left ventricular pressure with concomitant decrement in aortic systolic and pulse pressures as a result of increased left ventricular outflow tract obstruction after a premature ventricular contraction *(arrow)*.

they are inherited in an autosomal dominant manner.[1,7-10] More than 400 mutations involving 12 genes have been described, the most common of which include the cardiac troponins T, C, and I; cardiac myosin-binding protein C; cardiac β- and α-myosin heavy chains; myosin ventricular essential and regulatory light chains; cardiac α-actin; and titin.[8,10] Whereas most of these mutations are missense, resulting from substitution of an incorrect amino acid, deletions, insertions, and splice-site mutations are also well described.[66]

Several nonsarcomeric mutations that produce phenotypes similar to HCM have been identified. *PRKAG2* affects the regulatory subunit of the adenosine monophosphate (AMP)-activated protein kinase and may result in preexcitation, progressive conduction system abnormalities, and mild ventricular hypertrophy due to aberrant accumulation of glycogen within the myocyte.[66,68] Mutations of 2α-galactosidase or acid-α1, 4-glucosidase (both of which are lysosome-associated membrane proteins) frequently result in multisystem glycogen storage disease and may also cause extreme LVH associated with ventricular preexcitation and mental retardation.[66,67,69]

There is great phenotypic heterogeneity among carriers of the same mutations, in part because of the effect of modifier genes and environmental factors.[7,70] Whereas it has long been known that many young carriers do not demonstrate the morphologic characteristics of the disease state until after adolescence, it has now been demonstrated that phenotypic expression of LVH can be delayed into late adulthood owing to incomplete penetrance of mutations involving cardiac myosin-binding protein C or troponin T.[7,53,54,60,71] The majority of studied HCM cases have involved familial mutations, but sporadic cases are also well described and may constitute a significant proportion of the population. Recent work involving the systematic molecular screening of known HCM cases has demonstrated that two mutations (*MYBPC3* and *MYH7*) may account for 82% of familial cases. Mutations were detected in up to 60% of sporadic cases.[10] These data imply that a relatively limited screening process may be sufficient to identify the culprit gene in most familial cases and that identifiable mutations are responsible for most sporadic cases.

Given the fact that a number of studies have identified specific genetic mutations (Table 55-2) seemingly associated with a worse clinical prognosis and higher rates of SCD, there was initial enthusiasm that genetic testing could prospectively identify patients at higher risk for premature death.[1,9,18,31,53,54,72] However, significant limitations, including selection bias, the small number of included familial cohorts, low frequency of specific gene mutations, and variability of the phenotypic product, have hindered most genotype-phenotype correlation studies.[72,73] Therefore, because of the numerous genetic and environmental influences affecting the phenotypic product, there remains a great deal of clinical heterogeneity associated with specific mutations, making accurate risk stratification based on genetic analysis alone impractical at this time.

TABLE 55-2 Sarcomeric Gene Mutations of Hypertrophic Cardiomyopathy

β-Myosin heavy chain	14q12 *MYH7* 30-40
Myosin binding protein C	11q1 MYBPC3 30-40
Cardiac troponin T	1q32 *TNNT2* 15-20
Cardiac troponin I	19q13.4 *TNNI3* 1-5
α-Tropomyosin	15q22.1 *TPM1* 1-5
Myosin essential light chain	3p21 *MYL3* <1
Myosin regulatory light chain	12q24.3 *MYL2* <1
Cardiac troponin C	3p *TNNC1* rare
α-Myosin heavy chain	14q12 *MYHH6* rare
Actin	15q14 *ACTC* rare
Titin	2q24.3 *TTN* rare

Modified from Tsoutsman T, Lam L, Semsarian C: Genes, calcium and modifying factors in hypertrophic cardiomyopathy. *Clin Exp Pharmacol Physiol* 33(1-2):139-145, 2006, and Ho CY, Seidman CE: A contemporary approach to hypertrophic cardiomyopathy. *Circulation* 113(24):e858-e862, 2006.

TREATMENT

Medical Therapy

Medical therapy should be considered the initial therapeutic approach for the treatment of symptoms arising from the numerous pathophysiologic processes constituting HCM. Because of the relatively small number of cases, pharmacologic therapy for HCM is largely based on expert opinion, clinical experience, and retrospective observational analyses. Although patients with LVOT obstruction make up the greatest proportion of the symptomatic population, a significant number of patients without obstruction may also suffer the consequences of diastolic dysfunction, such as heart failure, angina, and AF.[1,7,18] Given the increasing use of early genetic and echocardiographic screening of athletes and affected families, it has become apparent that a significant percentage of phenotypically affected patients are entirely asymptomatic for an extended time. The available data also suggest that this population does not warrant empirical therapy until and unless symptoms develop, although this conclusion is somewhat controversial.[1,5,7,21] Historically, the pharmacologic treatment of HCM has been limited to beta-blockers, verapamil, and disopyramide.

Pharmacotherapy

β-Adrenergic Receptor Blocking Agents

Beta-blockers have traditionally been the drugs of choice for the treatment of HCM. This may stem from the fact that the physiologic effects of these agents are well suited to address much of the problematic pathophysiology encountered in this population. Their negative chronotropic effect results in increased diastolic filling time, which reduces left atrial pressure and may improve congestive symptoms related to diastolic dysfunction. This is especially true in cases complicated by supraventricular arrhythmias such as AF. The negative inotropic effect of these agents results in reduced myocardial oxygen consumption with a resultant decrease in anginal symptoms.

Although there is no convincing evidence that beta-blockers effectively reduce *resting* LVOT gradients, prior work and a large amount of clinical experience suggest that these agents reduce provocable gradients as well as substantially improving disabling symptoms related to exertion.[1,2,7,75] This is supported by data demonstrating an inverse relationship between peak oxygen consumption (VO_2) and degree of LVOT obstruction during cardiopulmonary exercise testing.[7,76] As a result, beta-blockers as a class are the favored agents for patients with *latent* outflow tract obstruction.

The first agent initially used for the treatment of HCM, propranolol, has largely been replaced by newer-generation, longer-acting, nonselective beta-blocking agents including atenolol and metoprolol.[7,16,75] Given the significant heterogeneity in clinical symptomatology, even within the same patient at different times in the disease course, it is important to individualize the titration of therapy based on current symptoms, resting heart rate (goal of 55 to 60 beats/minute), exertional capacity, and the presence of untoward side effects.

Verapamil

Functioning both as a negative inotrope and a negative chronotrope by blocking the intracellular migration of calcium ions, the nondihydropyridine calcium channel blocking agent verapamil produces symptomatic improvement in patients with HCM through increased diastolic filling time and enhanced diastolic ventricular relaxation without negatively affecting systolic function and while ensuring reduced myocardial oxygen consumption.[7,77,78] In addition, verapamil has been shown to increase absolute myocardial blood flow during pharmacologic stress testing while also reducing ischemic burden and improving exercise tolerance in the asymptomatic patient population.[79,80] These effects may result from verapamil's enhanced vasodilatory properties, which are more pronounced than those seen with beta-blockade and may well explain this agent's superior efficacy in patients with chest pain.

Whereas verapamil has classically been used in both obstructing and nonobstructing disease, caution should be exercised in initiating

this agent in symptomatic patients with large resting gradients owing to well-documented reports of severe hemodynamic decompensation resulting in cardiogenic shock and pulmonary edema.[7] In addition, verapamil should not be used in infants with HCM because of a well-established increased risk of SCD when it is administered in the intravenous formulation.[7]

Approximately 5% of patients with HCM will progress to an end stage characterized by impaired systolic function and symptoms of heart failure. Standard therapy for congestive heart failure—including diuretics, cautious use of vasodilators, beta-blockers, avoidance of calcium channel blockers, and possibly digoxin—should constitute the pharmacologic regimen in these patients.[1] In symptomatic patients, it is common clinical practice to initiate therapy with beta-blockers rather than verapamil. Should the patient be intolerant of side effects (i.e., fatigue, depression, or impotence), or if symptoms persist despite adequate titration of the medication, consideration should be given to changing (or adding) therapy to verapamil.[1,7,45] At present, no data suggest that combination therapy is more effective than either a beta-blocker or verapamil alone.

Disopyramide

Disopyramide, a class IA antiarrhythmic agent, has a side-effect profile that includes a negative inotropic effect with reduced contractility and a reflexive increase in systemic vascular resistance, both of which have made it an attractive agent for the treatment of HCM for more than 30 years. Although it appears to have little or no effect on diastolic function, disopyramide has been shown to effectively reduce the outflow obstruction resulting from SAM, with improved symptomatic control in patients with resting gradients for whom other forms of therapy have failed.[7,81,83] Because of the possible potentiation of supraventricular arrhythmias such as AF and case reports of QT prolongation leading to torsades de pointes, close supervision and monitoring are essential during the initiation of this therapy.[84] Other side effects of disopyramide are primarily related to its anticholinergic properties; they include dry mouth (32%), urinary retention (14%), constipation (11%), and, rarely, hypoglycemia.

Amiodarone

Although current data are somewhat conflicting and conclusive evidence is lacking, it has been suggested that amiodarone may reduce the risk of SCD and improve survival in selected high-risk patients who have nonsustained VT on Holter monitoring.[85] However, some reports suggest that amiodarone may improve a patient's symptom score and functional status but may also be proarrhythmic and thus lead to an *increased* risk of SCD due to ventricular arrhythmia.[86,87] In contrast, more recent data indicate that lower-dose amiodarone (200 mg/day) in high-risk patients with recurrent nonsustained VT is not associated with any increase in cardiovascular mortality.[29] Amiodarone has been demonstrated to be effective for the treatment and prevention of ventricular arrhythmias in patients with HCM.[88] Selection of which patients are appropriate for chronic, long-term empirical therapy with this agent, especially considering its attendant side-effect profile, may be impossible to specify until more definitive trial data become available.

Dual-Chamber Pacing

Dual-chamber pacing, as a less invasive alternative to surgical septal myectomy, was met with initial enthusiasm in the early 1990s, when several observational and uncontrolled studies demonstrated a significant decrease in outflow gradient, reduced symptomatology with improved quality of life, and homogenous redistribution of myocardial perfusion reserve.[89,90] Although the exact mechanism is unclear, it has been proposed that activation of the right ventricular apex results in a dyssynchronous contraction of the septum with a reduction in outflow tract obstruction in the short term and a positive ventricular remodeling effect in the long term.[89,91] However, subsequent randomized controlled crossover trials comparing DDD-mode with AAI-mode pacing demonstrated a significant placebo effect in regard to sustained symptomatic relief and quality-of-life assessment, little improvement in functional capacity, and a more modest reduction in outflow gradient in most patients compared with the earlier uncontrolled trials.[1,7,91,93]

Of importance, a subpopulation of older adult patients (age >65 years) was objectively measured to have both symptomatic and clinical benefit as a result of DDD pacing.[92] However, during the same period, a randomized trial did demonstrate a significant improvement in exercise tolerance, symptom score, and LVOT gradient in patients with symptoms refractory to drug therapy and with resting gradients greater than 30 mm Hg.[93] Therefore there may be subsets of patients in whom dual-chamber pacing is of some symptomatic or clinical benefit. However, no data suggest that dual-chamber pacing effectively reduces the risk of SCD in this patient population.[7,89,92]

Further work suggests that the reduction in LVOT gradient depends on optimal timing of the atrioventricular interval, with too short an interval interfering with diastolic filling and left atrial emptying and too long an interval resulting in ineffective reduction of outflow obstruction.[94] Taking this into account, recent nonrandomized, observational data have demonstrated a significant reduction in symptoms, improved functional capacity, and consistent reduction in LVOT gradient when serial echocardiographic assessment was used to optimize the atrioventricular interval, pacing rate, and mode settings in patients using DDD pacemakers.[95] This may constitute the foundation for further randomized trials in this area.

Whereas data comparing dual-chamber pacing with surgical septal myectomy have demonstrated improvement in both groups in regard to functional status, a significantly greater reduction in LVOT gradient, improved subjective symptom status, and increased overall exercise duration was reported in patients who underwent myectomy.[96] Therefore, although it is not considered a primary therapeutic modality for most patients with symptomatic HCM, it has been suggested that the use of dual-chamber pacemakers may be reasonable in certain subsets of patients, including older adult patients averse to more invasive therapies and patients in whom pharmacotherapy is limited owing to bradycardia.[7]

Implantation of an Implantable Cardiac Defibrillator

Ventricular fibrillation or tachycardia is the primary mode of SCD in patients with HOCM. Given the success of implantable cardiac defibrillators (ICDs) in reducing arrhythmic mortality in patients with coronary artery disease and a reduced ejection fraction, there has been an increasing interest in using the ICD for prevention and treatment of HOCM-related arrhythmic death.[97] Although randomized data are lacking, a multicenter, retrospective trial demonstrated that implantation of an ICD in patients classically considered to be at high risk for SCD resulted in appropriate device intervention and aborted SCD in almost 25% of the enrolled patients over a 3-year period.[35] Patients in whom the device was implanted for primary prevention purposes experienced appropriate intervention at a rate of 5% annually, compared with patients who received the device after cardiac arrest or sustained VT, in whom appropriate intervention was noted at a rate of 11% annually.[1,7,35,98] Based on these results, it has been suggested that ICD implantation is reasonable, should be considered in patients with one or more risk factors for SCD, and is warranted in patients with a prior history of cardiac arrest or sustained VT.[1,7]

Device selection should be based primarily on individual patient preference and characteristics. Dual-chamber devices have the advantage of atrial sensing and pacing functions and the ability to discriminate supraventricular from ventricular arrhythmias, resulting in a reduction in the number of inappropriate interventions. However, the dual-chamber devices have a higher potential for complications (usually related to the transvenous lead systems) than do single-chamber devices.[98]

According to the most recent guidelines from the American College of Cardiology and American Heart Association (ACC/AHA), ICD implantation is recommended for patients with prior documented cardiac arrest, ventricular fibrillation, or hemodynamically significant

VT (class I). In addition, it may be reasonable to consider an ICD in patients with HCM under the following circumstances[99]:

- Sudden death presumably caused by HCM in one or more first-degree relatives (class IIa)
- Maximal LV wall thickness 30 mm or greater (class IIa)
- One or more recent, unexplained syncopal episodes (class IIa)
- Nonsustained VT (particularly before 30 years of age), in the presence of other SCD risk factors (class IIa)
- Abnormal blood pressure response to exercise, in the presence of other SCD risk factors (class IIa)

It may be reasonable to consider ICD implantation in high-risk children with HCM, based on unexplained syncope, massive LV hypertrophy, or a family history of SCD, after taking into account the relatively high rate of complications of long-term ICD implantation (class IIa).[99]

The usefulness of ICD is uncertain in specific scenarios, especially when only one risk factor is present. The usefulness of ICD implantation is considered uncertain in patients with HCM who have isolated bursts of nonsustained VT in the absence of other SCD risk factors (class IIb). Likewise, the usefulness of ICD implantation is uncertain in patients with an abnormal blood pressure response to exercise in the absence of other risk factors (class IIb).[99] ICD implantation is not recommended as a routine strategy in patients who have no indication of increased risk for SCD (class III). In addition, ICD implantation in patients with HCM in the absence of clinical manifestations of HCM is potentially harmful and should not be performed (class III). Furthermore, ICD placement as a strategy to permit patients with HCM to participate in intense competitive athletics is not recommended (class III).[99]

Among those who meet indications for ICD placement, single-chamber devices are reasonable in younger patients who do not need atrial or ventricular pacing (class IIa).[49] Dual-chamber ICD implantation should be considered for patients with sinus bradycardia or paroxysmal AF (class IIa). Among patients with HCM who meet indications for ICD implantation, dual-chamber ICD may be reasonable in those with an LVOT gradient greater than 50 mm Hg and significant heart failure symptoms who may benefit from right ventricular pacing (most commonly patients older than 65 years of age) (class IIa). In addition, ICD implantation should be considered in all patients with New York Heart Association (NYHA) class III-IV symptoms on maximal medical therapy and an ejection fraction of 50% or less who do not have any other indication for an ICD (class IIb).[49]

Surgery

Patients with resting or provocable gradients greater than 50 mm Hg who continue to experience significant functional limitation (i.e., NYHA class III-IV) due to limiting symptoms of exertional dyspnea, chest pain, or recurrent syncope despite maximal medical therapy may be considered candidates for surgical therapy.[1,7,18] Surgical therapy is not currently recommended for patients who are without significant outflow tract obstruction, for those who have relatively mild symptoms with obstruction, or to treat associated complications of this condition (e.g., AF, syncope) alone.[7]

There has been a significant evolution in the spectrum of surgical therapy for HOCM designed to effectively reduce outflow tract obstruction, from the original isolated septal myotomy performed by Cleland[100] in the 1960s to the more modern and widely employed Morrow myectomy[101] in combination with mitral valve repair or even replacement in selected patients.[102,103] The "gold standard" septal myectomy, described by Morrow, is performed via an aortotomy so that the proximal septum is approachable via the aortic valve. Between 5 to 15 g of myocardial tissue is resected, from the base of the aortic valve to a region distal to the mitral leaflets, such that the area of mitral-septal contact that results in SAM is removed and the LVOT is enlarged.[7,101,102] Because it is of critical importance to correctly identify the involved portion of the ventricular septum and to resect enough myocardium to relieve the outflow tract gradient, most experienced centers employ transesophageal echocardiography (TEE) to assist in localizing the desired region for resection and to monitor the effect of resection on the gradient intraoperatively.[102]

Despite its more aggressive nature, an alteration in the classic Morrow procedure has been described in which an extended myectomy is combined with partial excision and mobilization of the papillary muscles, which results in amelioration of the outflow tract obstruction, reduced tethering of the subvalvular mitral structures, and a more individualized surgical resection depending on the extent and location of the patient's LVH.[102,104] In patients with specific comorbidities, such as AF or coronary artery disease, myectomy may be combined with adjunctive surgical procedures such as the maze procedure to treat AF or coronary bypass grafting in a single, efficient procedure.

Mitral valvular abnormalities, such as elongated and flexible leaflets, substantially contribute to the degree of outflow tract obstruction in an important minority of patients. These patients often benefit from mitral valve plication at the time of myectomy to more effectively reduce the degree of outflow tract obstruction that results from SAM and to reduce the associated mitral regurgitation.[52,102,105,106] Mitral valve replacement is typically reserved for patients with significant primary valvular abnormalities such as myxomatous degeneration leading to mitral valve prolapse or regurgitation.[7,107]

The modern-day septal myectomy procedure carries a relatively low operative risk due to continued technical refinement, with a cumulative operative mortality rate of approximately 1% to 3% overall, and there are more recent reports of less than 1% mortality in very experienced centers.[1,7,41,108,109] Left bundle branch block (LBBB) after myectomy is understandably very common because of the location of the procedure. Complete heart block requiring implantation of a permanent pacemaker is more recently a rare complication, as is iatrogenic formation of a ventricular septal defect.[7,107,110]

A conclusive reduction in long-term mortality after myectomy has yet to be demonstrated in a randomized controlled fashion. However, nonrandomized multicenter observational data (as well as a wealth of clinical experience) suggest that this procedure results in significant improvement in a patient's functional capacity, heart failure symptoms, quality of life, and possibly even life expectancy.[1,7,14,102] In addition, reduction of the outflow tract gradient usually results in amelioration of SAM of the mitral apparatus and the resultant mitral regurgitation.[7,102,111,112] One clinical surgical series suggested that patients treated with surgical myectomy have an excellent prognosis, with a life expectancy similar to that of the general population, which may be partly due to a reduction in the rate of SCD.[113]

Septal Ablation

Percutaneous septal ablation was introduced by Sigwart in 1995 in an effort to provide an alternative treatment strategy to relieve outflow tract obstruction in symptomatic patients who do not wish to undergo the more invasive surgical myectomy, who are suboptimal surgical candidates due to comorbidities, or who are located in areas without sufficient surgical expertise.[114] Through selective infusion of 100% ethanol into either the first or second septal perforator arteries, the septal ablation technique attempts to mimic the effect of the more traditional Morrow myectomy by inducing a controlled infarct in the basal portion of the hypertrophied septum, resulting in scarring, thinning, and akinesis and leading to a significant reduction in the LVOT gradient and SAM of the mitral valvular apparatus.[1,7,45,114,117] Despite the paucity of large-scale randomized controlled trials documenting the long-term outcome of these patients, short-term observational studies have demonstrated a significant reduction in LVOT gradient, often a rapid reduction in limiting symptoms, improved exercise tolerance after ablation, and a mortality rate equal to or less than that of surgery at 1% to 4%.[7,115,120] The short-term success of this procedure combined with its obviously less invasive nature has led to a dramatic increase in its use over the past 10 years, with ablation estimated to be 15 to 20 times more common than surgical myectomy. More than 5000 ablations have been performed worldwide to date.[7,121-123]

It is very important to carefully screen all patients being considered for septal ablation and to select those patients who will realize

TABLE 55-3 Patient Selection Criteria for Alcohol Septal Ablation

Severe heart failure symptoms (i.e., NYHA class III-IV) despite maximal medical therapy
Septal thickness >18 mm
Subaortic gradient >50 mm Hg (resting or with provocation) due to mitral-septal contact
Absence of papillary muscle or mitral valvular anomalies (i.e., anomalous papillary muscle insertion)
Absence of significant coronary arterial disease
Compatible septal perforator branch arterial anatomy
Relative contraindications to surgical myectomy (i.e., age, comorbidity)*

NYHA, New York Heart Association.
*Relative contraindication to surgical myectomy is a controversial selection criteria not uniformly followed.

maximum benefit from the intervention (Table 55-3). As in the case of patients recommended for the traditional myectomy, the updated American College of Cardiology/European Society of Cardiology (ACC/ESC) consensus statement recommends that selection criteria include patients with septal hypertrophy greater than 18 mm, dynamic LVOT obstruction with a gradient greater than 50 mm Hg (either at rest or with provocation), and severely limiting heart failure symptoms (i.e., NYHA functional class III-IV) despite maximal medical therapy.[7,124] A thorough search for abnormalities that are better addressed surgically is essential before proceeding with catheter-based septal ablation. Such abnormalities include anomalous papillary muscle insertion into the mitral valve, an anatomically abnormal mitral valve with a long anteroposterior leaflet, coexistent coronary artery disease, primary valvular disease (aortic or mitral), and subaortic membrane or pannus, none of which would be adequately addressed by septal ablation.[7,124] Abnormally elongated and flexible anterior mitral leaflets resulting in an anterior location of the coaptation line and outflow tract obstruction also are not correctable via catheter-based techniques and require surgical myectomy with plication.[12] In addition, many experienced centers refer patients with a septal thickness greater than 2.5 cm for surgical correction.

Procedural Technique

Given the fact that most cases of HOCM are diagnosed noninvasively with echocardiography and, often, no invasive hemodynamic studies have been performed before ablation, many operators reconfirm the presence of significant LVOT obstruction by positioning an end-hole catheter in the ventricular apex and recording a slow pullback under fluoroscopic guidance. Alternatively, simultaneous measurement of the ascending aortic and intracavitary pressures may be obtained via the placement of an ascending aortic catheter and an end-hole catheter as described earlier. If an LVOT gradient is not confirmed under basal or resting conditions, provocation with amyl nitrate or the Valsalva maneuver may be attempted.[124] Failure to confirm a significant gradient after these maneuvers should prompt the operator to further pursue alternative etiologies for the patient's symptom complex.

Standard diagnostic coronary cineangiography is performed as a first step to clearly define the patient's anatomy and to evaluate for concomitant atherosclerotic disease. Once this is completed, attention is turned to selection of the appropriate septal perforator branch through which to perform the ablation. To best view the anatomy of the septal branches as they course through the basal interventricular septum, the camera should be positioned in the right anterior oblique (RAO) posteroanterior (PA) cranial view or PA cranial view. It is also important to determine the septal vessel's course along the septum (i.e., on the right or left side), using the left anterior oblique (LAO) projection. At times, septal anatomy may vary such that one subdivision runs along the left side of the septum and another runs along the right. Selection of the left-sided subdivision is optimal for the ablation, because there is a reduced likelihood of inducing complete heart block during ethanol infusion. Most septal perforators arise from the LAD, substantial anatomic variation has been described in which the vessels may arise from the left main trunk, the ramus intermedius, the left circumflex artery, diagonal branches, or even a branch of the right coronary artery.[124]

A temporary transvenous pacemaker is placed in advance as a prophylactic measure in case of the development of complete heart block during, or in days after, the ablation. Because heparin will be used for anticoagulation during the procedure, care should be taken to minimize the risk of bleeding during pacemaker insertion. After successful placement of both the temporary pacemaker and the arterial sheath, heparin is administered to achieve an activated clotting time of 250 to 300 seconds to prevent thrombosis in guide catheters and on wires.

After angiographic identification of the septal arteries, close attention must be given to vessel size, angulation, and the distribution of myocardial territories served by the given vessel. Angulation of the septal vessels, either at the origin from the primary vessel (e.g., the LAD) or at the bifurcation of a larger septal artery, is an important consideration in vessel selection. Vessels with angulations greater than 90 degrees are often technically challenging and result in difficulty passing the balloon into the selected vessel, with frequent prolapse of the wire into the mid-LAD.[124] Specialized techniques using catheters that allow control of the distal angle (Venture Catheter, St. Jude Medical, St. Paul, MN) may be useful in these circumstances.

There is substantial variation in the distribution of blood flow supplied by the septal perforators in patients with HOCM compared with the unaffected population. In both autopsy and angiography studies, it has been demonstrated that the first septal artery may provide blood flow to regions other than the targeted basal septum (including the right ventricle); it may supply the basal septum incompletely and share this responsibility with a second septal branch, or it may subtend a substantially larger distribution of myocardium than would be expected.[124,125] Therefore an intimate knowledge of the myocardial distribution of blood flow supplied by the selected septal branch is essential to accurately target the correct area for ablation and to avoid infarction of an unanticipated region or an oversized infarction of the septum itself. This is most commonly accomplished during the procedure by the selective injection of dye under cine guidance and the concomitant use of transthoracic echocardiography (TTE) using injectable contrast material (see later discussion).

After angiographic assessment of the septal anatomy, a guide catheter providing extra support (such as a 6- or 7-Fr XB catheter) is used to engage the left main trunk. Subsequently, a 0.014-inch extra support wire with a soft tip is passed into the selected septal perforator branch, most commonly the first septal perforator (Fig. 55-4). A short angioplasty balloon, usually 1.5 to 2 mm in diameter and 10 mm in length, is passed over the guidewire and into the septal branch. Difficulty in passing the balloon may be resolved by use of a stiffer guidewire to provide greater support for balloon placement.[124] Care must be taken to seat the balloon deeply enough into the septal artery and to fully expand the balloon to ensure that the injected ethanol is not refluxed in to the LAD. Conversely, if the balloon is placed too deeply into the septal vessel, the injected ethanol may spare the basal portion of the septum, resulting in an unsuccessful procedure (Fig. 55-5).

It is essential at this point to verify the distribution of myocardium being supplied by the selected vessel, given the substantial degree of variability in the cardiac anatomy in this patient population. This can be accomplished by traditional angiography or TEE, often with the aid of echocardiographic contrast. After correct positioning, as described earlier, the operator inflates the balloon (typically to 10 to 12 atmospheres) to occlude the perforator, and 1 to 2 mL of contrast material is injected to assess the full extent of myocardium supplied by the chosen vessel. Contrast should be injected slowly so as to mimic the anticipated alcohol infusion. Extreme caution should be taken to verify that the infused contrast material does not reflux into the LAD or into other coronary arteries (e.g., the posterior descending artery), thus possibly exposing a large amount of unintended myocardium to damage when the ethanol is infused. Aggressive contrast infusion may overwhelm collateral vessels and create an inferior LV wall infarction.

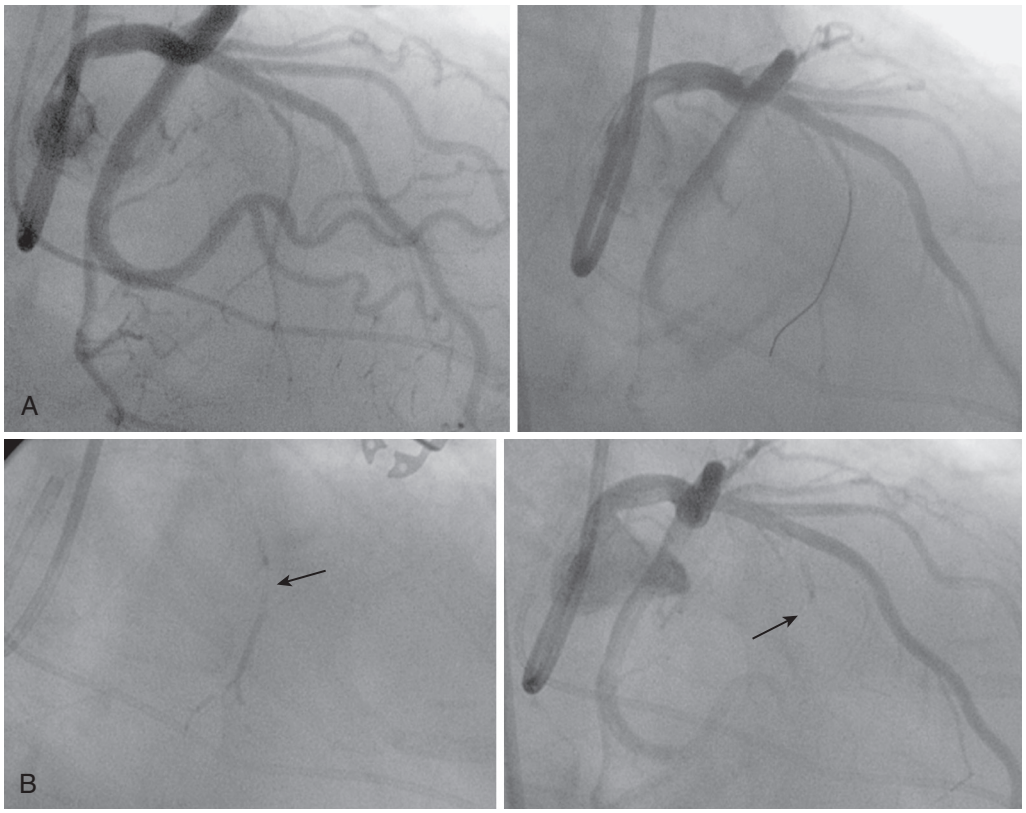

FIGURE 55-4 This figure demonstrates alcohol septal ablation performed in a hypertrophic cardiomyopathy patient with severe obstructive symptoms despite medical therapy. **A,** Coronary angiogram (digital subtraction angiography) demonstrates the introduction of a 0.014-inch guidewire into a septal perforator branch with anatomic characteristics ideal for septal ablation. **B,** Coronary angiogram demonstrates the introduction of a 1.5- by 10-mm balloon *(arrow)* into the selected septal vessel. Injection of contrast into the balloon and the left anterior descending coronary artery subsequently confirmed correct positioning.

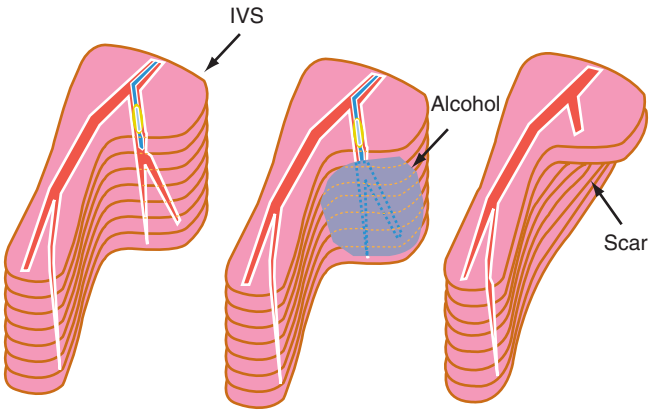

FIGURE 55-5 Schematic overview of the alcohol septal ablation procedure depicts the resultant basal septal scar and enlargement of the left ventricular outflow tract. If the balloon is placed distally, the anterior septum is not ablated, which can result in a suboptimal result. *IVS,* Interventricular septum.

After angiographic confirmation of septal occlusion, further assessment of the septal distribution is obtained via contrast echocardiography (Fig. 55-6). After careful inspection of the septum in the apical long-axis, four-chamber, and parasternal long-axis views, 1 to 2 mL of Albunex contrast is injected into the septal branch through a tuberculin-type syringe. Because Albumex, a first-generation echocardiographic contrast agent, is no longer available in many countries, second- and third-generation agents are currently used. These agents have proved to be suboptimal because they traverse the capillary beds rapidly and produce a large amount of echocardiographic "shadowing" from the opacified ventricles. Therefore, it is important to dilute these agents before injection. In our laboratory, the contrast vials are typically opened 10 to 15 minutes before the time of expected use so as to decrease their potency. The contrast is then further diluted with sterile saline in a 1:5 or 1:10 mixture at the time of injection.

Pulsed-wave Doppler echocardiography is the imaging method of choice in using the diluted contrast material to avoid destruction of the microbubbles with the higher-frequency continuous-wave ultrasound. This procedure allows the operator to verify that the chosen vessel primarily supplies the proximal interventricular septum and not portions of the inferior wall, LV papillary musculature, or right ventricular free wall via the moderator band.[124,126] Ideally, contrast material will appear in the basal portion of septum responsible for the greatest extent of septal-mitral contact. Appearance of contrast in the distal septum or other regions of myocardium is a contraindication to ethanol infusion, because it can result in infarction of an undesired territory or an infarction of unanticipated size.

As a final method of ensuring that the desired area of myocardium has been selected, it is recommended that the operator document a greater than 30% reduction in the LVOT gradient during balloon inflation. A rather rapid reduction in gradient can be observed with prolonged balloon occlusion of a septal perforator branch. Such an observation suggests that the correct septal distribution has been targeted for ablation.[124,127] Before proceeding with ethanol injection, it is essential to confirm that the balloon has not migrated during this process and that the previously placed temporary pacemaker continues

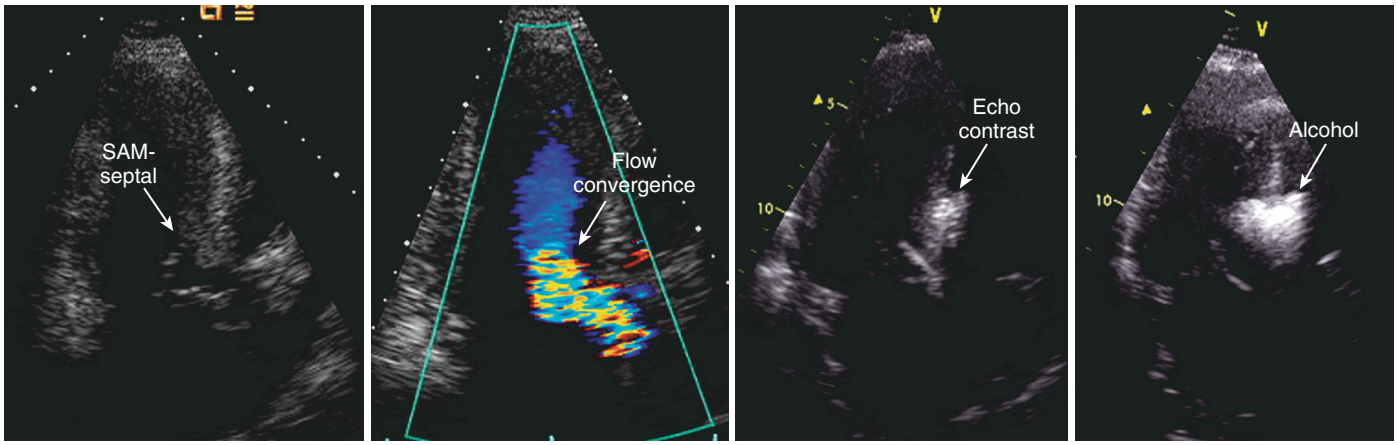

FIGURE 55-6 Contrast echocardiography (apical three-chamber views) confirm the desired distribution of myocardial blood flow on injection of an appropriately selected septal perforator artery before ethanol infusion. *SAM,* Systolic anterior motion of the mitral valve.

to have a suitable pacing threshold. This is easily done by fluoroscopic verification and injection of another 1 to 2 mL of contrast agent through the guide catheter.

After confirmation of proper balloon positioning, the operator may proceed with ethanol injection. Whereas most experienced centers use between 1 to 3 mL of desiccated ethanol, this volume may be adjusted based on the appearance of the septal anatomy and the degree of contrast washout.[7,116,124,128-130] Research has documented similar midterm hemodynamic outcomes with reduced complication rates, especially the requirement for a permanent pacemaker, when smaller amounts of ethanol (1 to 2 mL) are used.[131] If there is rapid contrast washout due to collateralization of the septal branch, the rate and volume of ethanol infusion should be reduced to prevent the alcohol from escaping to undesirable areas of myocardium via the collaterals.[115,116,124]

The ethanol is injected into the vessel over a 1- to 5-minute period with the balloon remaining inflated. During the initial infusion, continued monitoring of the resting gradient is essential to judge the efficacy of the procedure. In general, a reduction in the LVOT gradient to less than 30 mm Hg in the setting of a resting gradient greater than 50 mm Hg, or a greater than 50% reduction of a provocable gradient, is considered indicative of a successful procedure in the catheterization laboratory[116,124] (Fig. 55-7).

Before the balloon is disengaged from the septal vessel, it is recommended that the guidewire be placed again into the septal branch for smooth removal of the balloon and maintenance of access across the left main trunk and the LAD. As a final step, angiography of the LAD and septal vessels is performed to verify the integrity of the coronary circulation. Phasic flow may be observed in the injected septal branch immediately after the ablation, although total occlusion is frequently observed. Postprocedural care should take place in a coronary intensive care unit for 48 hours after ablation to allow for the rapid identification and treatment of possible complications. The amount of induced myocardial tissue destruction often results in elevation of the enzyme creatinine phosphokinase (CPK) to levels between 800 and 1200 U/L, although this is variable depending on the amount of alcohol injected, vessel size, and the method of enzyme measurement.[7,115,122,130,131] The transvenous pacing wire may be discontinued 48 hours after the procedure if there is an absence of bradyarrhythmia or heart block that would require continued observation or a permanent pacemaker. In most centers, the patient is transferred to a regular nursing floor for another 48 to 72 hours to observe for postprocedural complications before discharge.

The complication rate after septal ablation is relatively low and is comparable to that of septal myectomy. As opposed to the LBBB so commonly observed after septal myectomy, a right bundle branch block (RBBB) is observed in up to 80% of patients who have undergone ablation.[7,116,124] The incidence of complete heart block has decreased in recent years and now ranges from 5% to 40%, with an average value of 12% to 15% at experienced centers.[7,109,116,117,124,132] The presence of a preexisting LBBB and a rapid bolus injection of ethanol during ablation have both been positively correlated with an increased incidence of high-degree atrioventricular block requiring permanent pacemaker implantation.[132] Extravasation of alcohol into the LAD during infusion is a rare but catastrophic complication that often results in a large infarction of the middle to distal anterior wall and is clearly associated with increased mortality. Coronary dissection caused by the extra support guidewire or the catheter has been reported in rare instances. Tamponade due to perforation of the right ventricular apex during insertion of a transvenous pacing wire or during interatrial septal puncture for periprocedural hemodynamic monitoring has also been reported. Overly extensive infarction of the interventricular septum as a result of too generous a quantity of infused alcohol or too rapid an infusion rate during ablation can result in a ventricular septal rupture.[124]

Ventricular arrhythmias can be seen both during and up to 48 hours after the procedure, but this complication is rare and usually does not require prolonged therapy. Unlike myectomy, septal ablation results in the formation of a large intramyocardial scar that may serve as substrate for future malignant ventricular arrhythmias. There has been some conjecture that this could result in an increased risk of late arrhythmic mortality, especially in younger patients undergoing ablation.[7,35,116,129] However, this hypothesis has yet to garner substantial evidentiary support. Patients should be observed closely for recurrence of symptoms or any arrhythmia. ICD implantation should be considered if there is evidence of nonsustained VT, but this is extremely rare. Objective assessment of functional capacity using exercise testing is appropriate for monitoring these patients. Repeat alcohol ablation may be considered if symptoms recur and an appropriate septal perforator is available for injection. If repeat ablation is not feasible, surgical myectomy may need to be considered in this group[133] (Fig. 55-8).

Despite the increased number of septal ablation procedures performed worldwide, there remains a paucity of randomized controlled trials. Existing data suggest that septal ablation and surgical myectomy have similar success rates in both short and longer terms.[134] In the immediate postprocedural period (3 to 72 hours), both modalities of septal reduction result in similar degrees of LVOT gradient reduction, and this improvement appears to be maintained for up to 1 year after either procedure.[1,7,109,116,120,130,133-136] A meta-analysis demonstrated that, after adjusting for preprocedural gradient, the reduction in gradient after the procedure is similar in the two modalities[137] (Fig. 55-9). In addition to improvements in NYHA functional class and in the

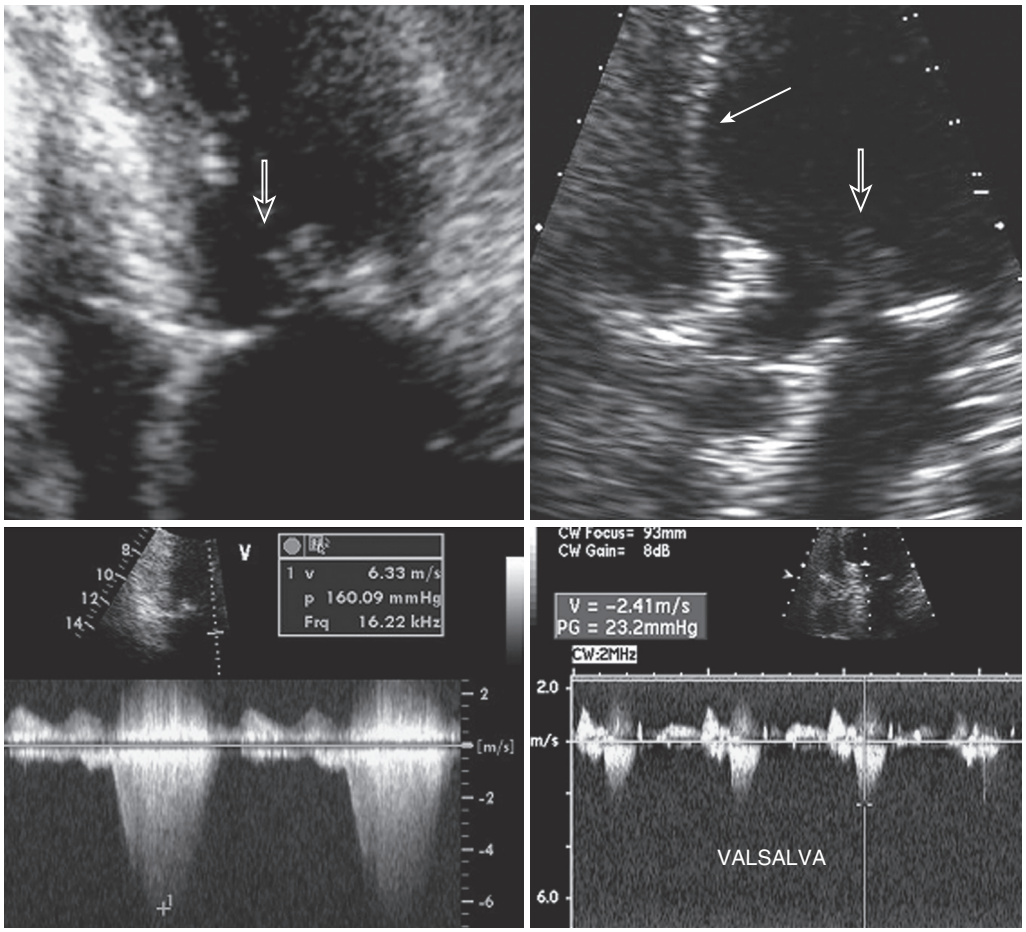

FIGURE 55-7 Contrast echocardiography. The images on the left were taken before alcohol ablation. The images on the right were acquired from the same patient 6 months after successful ablation and clearly demonstrate scarring *(white arrow)* in the basal septum with a resultant increase in the left ventricular outflow tract area and decrease in the outflow tract obstruction. Systolic anterior motion *(open arrow)* is present at baseline and absent on follow-up.

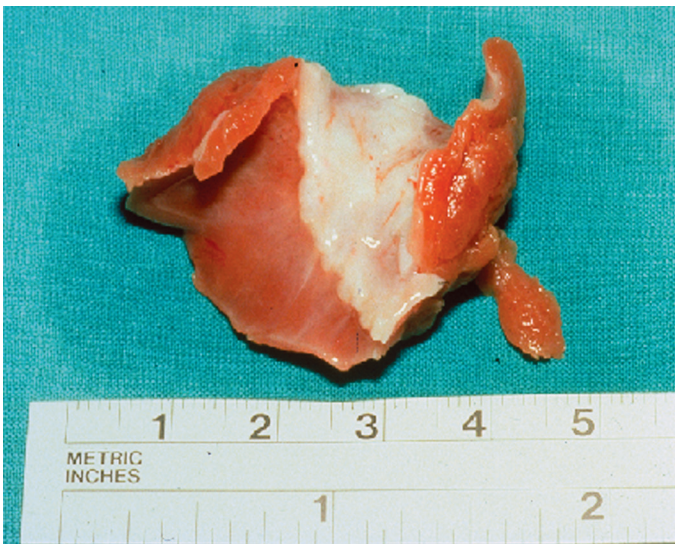

FIGURE 55-8 Pathology specimen of the basal interventricular septum in a patient with hypertrophic cardiomyopathy several years after an ethanol ablation demonstrates fibrosis and scarring.

Canadian Cardiovascular Society (CCS) angina class, the number of syncopal and presyncopal events was reduced to a similar significant degree in both groups at 6- and 12-month follow-up.[109,120,135]

Both procedures have advantages and associated complications, underscoring the importance of careful patient selection and consideration of comorbidities before an intervention is chosen. Complete heart block requiring permanent pacemaker has been reported in up to 25% of patients undergoing alcohol ablation, compared with only 5% to 10% after myectomy.[109,135] Given that ablation commonly produces a pattern of RBBB, patients with a preexisting LBBB are at very high risk of complete heart block after the procedure.[137] In addition, it has been suggested that female gender, first-degree atrioventricular block, and an increased volume of injected alcohol are additional risk factors for postprocedural complete heart block.[138] In contrast, myectomy produces a LBBB and less commonly requires permanent pacing. Myectomy can result in mild to moderate aortic insufficiency in up to 10% to 20% of patients but rarely leads to an adverse outcome.[135] By the nature of the procedure, ablation results in a permanent scar in the interventricular septum, and there remains some concern that this may serve as substrate for future ventricular arrhythmias, although this has not as yet been objectively documented.

As would be expected, ablation results in a reduced length of stay compared with myectomy and substantially contributes to an overall reduction in cost. Mortality is relatively low with both interventions

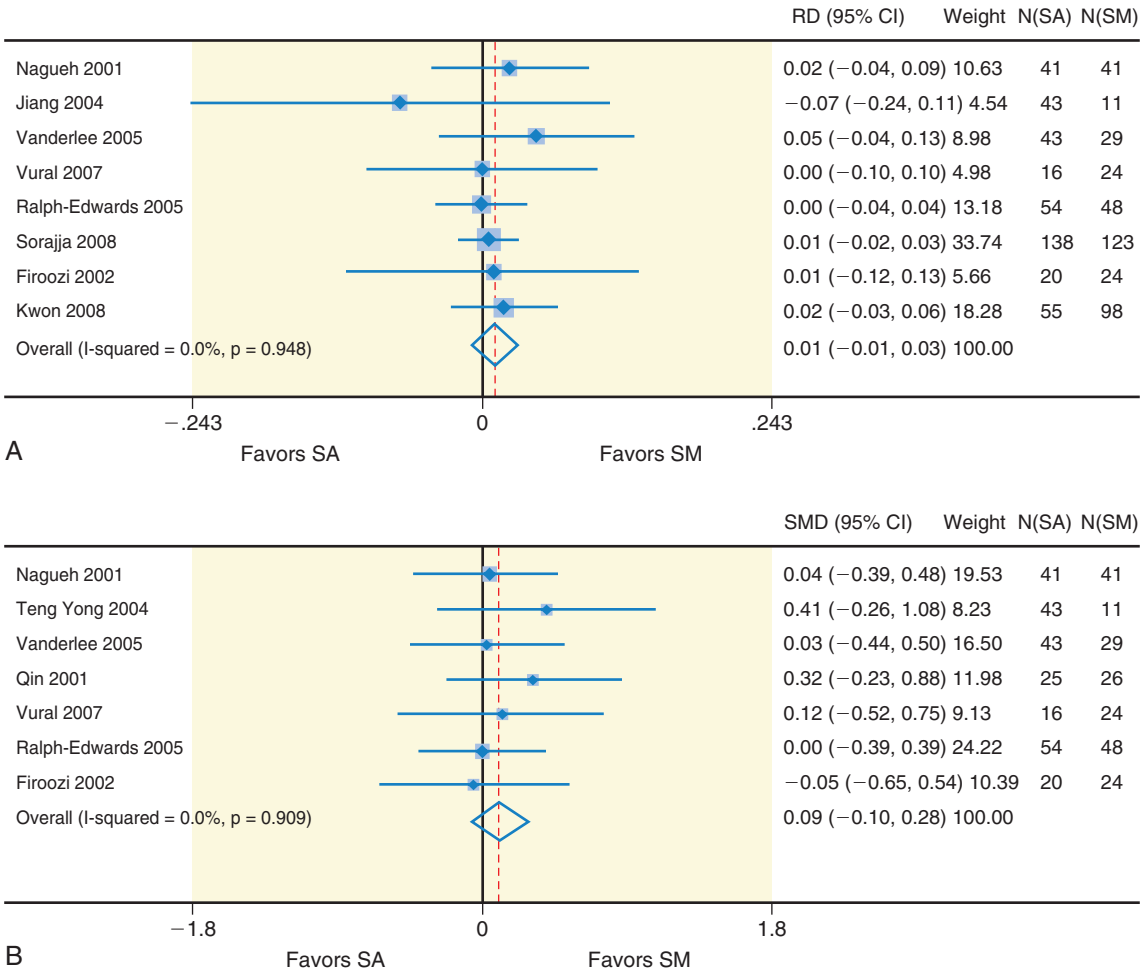

FIGURE 55-9 **A,** Short-term mortality risk difference (RD) estimates for septal ablation (SA) and septal myectomy (SM) groups. **B,** Postprocedure reduction in left ventricular outflow tract gradient from preprocedure value; standardized mean difference (SMD) between the SA and SM groups. *CI,* Confidence interval.

and approaches 1% in experienced centers.[7,45,109,135] Several meta-analyses have also shown similar postprocedural outcomes, with no difference in long-term mortality between ablation and myectomy.[137,139,140] In summary, either surgical myectomy or alcohol ablation may be selected as a viable treatment option in symptomatic patients with LVOT obstruction. Which therapy should be selected is a complex decision that must be made only after taking into consideration the patient's clinical situation.

CONCLUSIONS

HCM is a complex genetic disease with multiple heterogeneous phenotypes and clinical manifestations. Because of the considerable heterogeneity of the disease and the lack of randomized controlled trials in this arena, HCM is variably managed across the world. The management in any patient with HCM should ideally focus on the following aspects:

- Control of heart failure symptoms
- Assessment of the risk of sudden death and appropriate risk management
- Treatment of AF
- Management of LVOT obstruction using invasive techniques, when indicated
- Screening of family members

Although the current guidelines provide an important framework that helps in evaluation and treatment of HCM, the unique characteristics and preferences of each patient should play a vital role in the decision-making and management strategies.

Despite significant improvement in the understanding of disease pathophysiology in the last few decades, there are considerable gaps in that need to be addressed to improve care in this patient population. Long-term data on alcohol septal ablation will define its precise role in relation to myectomy in the management of medically refractory HCM. In addition, establishment of referral systems that facilitate the treatment of HCM at centers of excellence would be critical in optimal management. Improvements in risk stratification for SCD will more accurately identify patients with HCM at risk for SCD. Development of subcutaneous and leadless ICD systems will likely reduce complications and lower the threshold for device implantation in young patients. The role of genetic testing will also become clearer as genotyping becomes cheaper and more accessible. Further research is needed for a more thorough understanding of the genetic basis of this disease and to develop greater and more widespread clinical utility of genotyping in HCM.

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REFERENCES

1. Maron BJ: Hypertrophic cardiomyopathy: a systematic review. *JAMA* 287(10):1308–1320, 2002.
2. Braunwald E, Lambrew CT, Rockoff SD, et al: Idiopathic hypertrophic subaortic stenosis: I. A description of the disease based upon an analysis of 64 patients. *Circulation* 30(Suppl 4):3–119, 1964.
3. Maron BJ, Spirito P: Impact of patient selection biases on the perception of hypertrophic cardiomyopathy and its natural history. *Am J Cardiol* 72(12):970–972, 1993.
4. Maron BJ, Casey SA, Poliac LC, et al: Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. *JAMA* 281(7):650–655, 1999.
5. Spirito P, Chiarella F, Carratino L, et al: Clinical course and prognosis of hypertrophic cardiomyopathy in an outpatient population. *N Engl J Med* 320(12):749–755, 1989.
6. Elliott P: Relation between the severity of left ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. *Lancet* 357:420–424, 2001.
7. Maron BJ, McKenna WJ, Danielson GK, et al: ACC/ESC Expert Consensus Document on Hypertrophic Cardiomyopathy. *J Am Coll Cardiol* 42(9):1687–1713, 2003.
8. Ho CY, Seidman CE: A contemporary approach to hypertrophic cardiomyopathy. *Circulation* 113(24):e858–e862, 2006.
9. Maron BJ, Moller JH, Seidman CE, et al: Impact of laboratory molecular diagnosis on contemporary diagnostic criteria for genetically transmitted cardiovascular diseases: hypertrophic cardiomyopathy, long-QT syndrome, and Marfan syndrome. A statement for healthcare professionals from the Councils on Clinical Cardiology, Cardiovascular Disease in the Young, and Basic Science, American Heart Association. *Circulation* 98(14): 1460–1471, 1998.
10. Richard P, Charron P, Carrier L, et al: Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. *Circulation* 107(17):2227–2232, 2003.
11. Maron BJ: The electrocardiogram as a diagnostic tool for hypertrophic cardiomyopathy: revisited. *Ann Noninvasive Electrocardiol* 6(4):277–279, 2001.
12. Klues HG, Maron BJ, Dollar AL, et al: Diversity of structural mitral valve alterations in hypertrophic cardiomyopathy. *Circulation* 85(5):1651–1660, 1992.
13. Wigle ED, Sasson Z, Henderson MA, et al: Hypertrophic cardiomyopathy: the importance of the site and the extent of hypertrophy—a review. *Prog Cardiovasc Dis* 28(1):1–83, 1985.
14. Maron BJ, Wolfson JK, Ciro E, et al: Relation of electrocardiographic abnormalities and patterns of left ventricular hypertrophy identified by 2-dimensional echocardiography in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 51(1):189–194, 1983.
15. McKenna WJ, Deanfield JE: Hypertrophic cardiomyopathy: an important cause of sudden death. *Arch Dis Child* 59(10):971–975, 1984.
16. Shah PM, Adelman AG, Wigle ED, et al: The natural (and unnatural) history of hypertrophic obstructive cardiomyopathy. *Circ Res* 35(Suppl 2):II179–II195, 1974.
17. Maron BJ: Hypertrophic cardiomyopathy. *Lancet* 350:127–133, 1997.
18. Spirito P: The management of hypertrophic cardiomyopathy. *N Engl J Med* 336:775–785, 1997.
19. Maron BJ: Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 39:301–307, 2002.
20. Elliott P, McKenna WJ: Hypertrophic cardiomyopathy. *Lancet* 363(9424):1881–1891, 2004.
21. Spirito P, Autore C: Management of hypertrophic cardiomyopathy. *BMJ* 332(7552):1251–1255, 2006.
22. Maron BJ, Shirani J, Poliac LC, et al: Sudden death in young competitive athletes: clinical, demographic, and pathological profiles. *JAMA* 276(3):199–204, 1996.
23. Maron BJ, Olivotto I, Spirito P, et al: Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. *Circulation* 102(8):858–864, 2000.
24. Elliott PM, Poloniecki J, Dickie S, et al: Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. *J Am Coll Cardiol* 36(7):2212–2218, 2000.
25. Spirito P, Bellone P, Harris KM, et al: Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. *N Engl J Med* 342(24):1778–1785, 2000.
26. Monserrat L, Elliott PM, Gimeno JR, et al: Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. *J Am Coll Cardiol* 42(5):873–879, 2003.
27. Yoshida N, Ikeda H, Wada T, et al: Exercise-induced abnormal blood pressure responses are related to subendocardial ischemia in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 32(7):1938–1942, 1998.
28. Olivotto I, Cecchi F, Casey SA, et al: Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation* 104(21):2517–2524, 2001.
29. Cecchi F, Olivotto I, Montereggi A, et al: Prognostic value of non-sustained ventricular tachycardia and the potential role of amiodarone treatment in hypertrophic cardiomyopathy: assessment in an unselected non-referral based patient population. *Heart* 79(4):331–336, 1998.
30. Moolman JC, Corfield VA, Posen B, et al: Sudden death due to troponin T mutations. *J Am Coll Cardiol* 29(3):549–555, 1997.
31. Watkins H: Sudden death in hypertrophic cardiomyopathy. *N Engl J Med* 342(6):422–424, 2000.
32. Maron MS, Olivotto I, Betocchi S, et al: Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 348(4):295–303, 2003.
33. Kofflard MJ, Ten Cate FJ, van der Lee C, et al: Hypertrophic cardiomyopathy in a large community-based population: clinical outcome and identification of risk factors for sudden cardiac death and clinical deterioration. *J Am Coll Cardiol* 41(6):987–993, 2003.
34. Elliott PM, Sharma S, Varnava A, et al: Survival after cardiac arrest or sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 33(6):1596–1601, 1999.
35. Maron BJ, Shen WK, Link MS, et al: Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med* 342(6):365–373, 2000.
36. Maron BJ, Kogan J, Proschan MA, et al: Circadian variability in the occurrence of sudden cardiac death in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 23(6):1405–1409, 1994.
37. Maron BJ, Epstein SE, Roberts WC: Hypertrophic cardiomyopathy and transmural myocardial infarction without significant atherosclerosis of the extramural coronary arteries. *Am J Cardiol* 43(6):1086–1102, 1979.
38. Dilsizian V, Bonow RO, Epstein SE, et al: Myocardial ischemia detected by thallium scintigraphy is frequently related to cardiac arrest and syncope in young patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 22(3):796–804, 1993.
39. Choudhury L, Mahrholdt H, Wagner A, et al: Myocardial scarring in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 40(12):2156–2164, 2002.
40. Basso C, Thiene G, Corrado D, et al: Hypertrophic cardiomyopathy and sudden death in the young: pathologic evidence of myocardial ischemia. *Hum Pathol* 31(8):988–998, 2000.
41. Schwartzkopff B, Mundhenke M, Strauer BE: Alterations of the architecture of subendocardial arterioles in patients with hypertrophic cardiomyopathy and impaired coronary vasodilator reserve: a possible cause for myocardial ischemia. *J Am Coll Cardiol* 31(5):1089–1096, 1998.
42. Schwartzkopff B, Mundhenke M, Strauer BE: Remodelling of intramyocardial arterioles and extracellular matrix in patients with arterial hypertension and impaired coronary reserve. *Eur Heart J* 16(Suppl I):82–86, 1995.
43. Cecchi F, Olivotto I, Gistri R, et al: Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. *N Engl J Med* 349(11):1027–1035, 2003.
44. Maron BJ, Roberts WC, Epstein SE: Sudden death in hypertrophic cardiomyopathy: a profile of 78 patients. *Circulation* 65(7): 1388–1394, 1982.
45. Spirito P, Seidman CE, McKenna WJ, et al: The management of hypertrophic cardiomyopathy. *N Engl J Med* 336(11):775–785, 1997.
46. Nienaber CA, Hiller S, Spielmann RP, et al: [Risk of syncope in hypertrophic cardiomyopathy: a multivariate analysis of prognostic variables]. *Z Kardiol* 79(4):286–296, 1990.
47. Gilligan D: Investigation of a hemodynamic basis for syncope in hypertrophic cardiomyopathy: use of a head-up tilt test. *Circulation* 85:2140–2148, 1992.
48. Lewis JF, Maron BJ: Clinical and morphologic expression of hypertrophic cardiomyopathy in patients > or = 65 years of age. *Am J Cardiol* 73(15):1105–1111, 1994.
49. Olivotto I, Maron MS, Adabag AS, et al: Gender-related differences in the clinical presentation and outcome of hypertrophic cardiomyopathy. *J Am Coll Cardiol* 46(3):480–487, 2005.
50. Poliac LC, Barron ME, Maron BJ: Hypertrophic cardiomyopathy. *Anesthesiology* 104(1):183–192, 2006.
51. Klues HG, Schiffers A, Maron BJ: Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. *J Am Coll Cardiol* 26(7):1699–1708, 1995.
52. Lever HM, Karam RF, Currie PJ, et al: Hypertrophic cardiomyopathy in the elderly: distinctions from the young based on cardiac shape. *Circulation* 79(3):580–589, 1989.
53. Watkins H, McKenna WJ, Thierfelder L, et al: Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. *N Engl J Med* 332(16):1058–1064, 1995.
54. Niimura H, Bachinski LL, Sangwatanaroj S, et al: Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy. *N Engl J Med* 338(18): 1248–1257, 1998.
55. Spirito P, Maron BJ: Absence of progression of left ventricular hypertrophy in adult patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 9(5):1013–1017, 1987.
56. Klues HG, Roberts WC, Maron BJ: Anomalous insertion of papillary muscle directly into anterior mitral leaflet in hypertrophic cardiomyopathy: significance in producing left ventricular outflow obstruction. *Circulation* 84(3):1188–1197, 1991.
57. Maron BJ, Spirito P, Green KJ, et al: Noninvasive assessment of left ventricular diastolic function by pulsed Doppler echocardiography in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 10(4):733–742, 1987.
58. Chikamori T, Dickie S, Poloniecki JD, et al: Prognostic significance of radionuclide-assessed diastolic function in hypertrophic cardiomyopathy. *Am J Cardiol* 65(7):478–482, 1990.
59. Fananapazir L, Tracy CM, Leon MB, et al: Electrophysiologic abnormalities in patients with hypertrophic cardiomyopathy: a consecutive analysis in 155 patients. *Circulation* 80(5):1259–1268, 1989.
60. Maron BJ, Niimura H, Casey SA, et al: Development of left ventricular hypertrophy in adults in hypertrophic cardiomyopathy caused by cardiac myosin-binding protein C gene mutations. *J Am Coll Cardiol* 38(2):315–321, 2001.
61. Yamaguchi H, Ishimura T, Nishiyama S, et al: Hypertrophic nonobstructive cardiomyopathy with giant negative T waves (apical hypertrophy): ventriculographic and echocardiographic features in 30 patients. *Am J Cardiol* 44(3):401–412, 1979.
62. Rickers C, Wilke NM, Jerosch-Herold M, et al: Utility of cardiac magnetic resonance imaging in the diagnosis of hypertrophic cardiomyopathy. *Circulation* 112(6):855–861, 2005.
63. Moon JC, McKenna WJ, McCrohon JA, et al: Toward clinical risk assessment in hypertrophic cardiomyopathy with gadolinium cardiovascular magnetic resonance. *J Am Coll Cardiol* 41(9):1561–1567, 2003.
64. Brugada P, Bar FW, de Zwaan C, et al: "Sawfish" systolic narrowing of the left anterior descending artery: an angiographic sign of hypertrophic cardiomyopathy. *Circulation* 66:800–803, 1982.
65. Brockenbrough EC, Braunwald E, Morrow AG: A hemodynamic technic for the detection of hypertrophic subaortic stenosis. *Circulation* 23:189–194, 1961.
66. Maron BJ, Seidman JG, Seidman CE: Proposal for contemporary screening strategies in families with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 44(11):2125–2132, 2004.
67. Arad M, Benson DW, Perez-Atayde AR, et al: Constitutively active AMP kinase mutations cause glycogen storage disease mimicking hypertrophic cardiomyopathy. *J Clin Invest* 109(3): 357–362, 2002.
68. Gollob MH, Green MS, Tang AS, et al: Identification of a gene responsible for familial Wolff-Parkinson-White syndrome. *N Engl J Med* 344(24):1823–1831, 2001.
69. Arad M, Maron BJ, Gorham JM, et al: Glycogen storage diseases presenting as hypertrophic cardiomyopathy. *N Engl J Med* 352(4):362–372, 2005.
70. Osterop AP, Kofflard MJ, Sandkuijl LA, et al: AT1 receptor A/C1166 polymorphism contributes to cardiac hypertrophy in subjects with hypertrophic cardiomyopathy. *Hypertension* 32(5): 825–830, 1998.
71. Erdmann J, Raible J, Maki-Abadi J, et al: Spectrum of clinical phenotypes and gene variants in cardiac myosin-binding protein C mutation carriers with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 38(2):322–330, 2001.
72. Anan R, Shono H, Kisanuki A, et al: Patients with familial hypertrophic cardiomyopathy caused by a Phe110Ile missense mutation in the cardiac troponin T gene have variable cardiac morphologies and a favorable prognosis. *Circulation* 98(5):391–397, 1998.
73. Marian AJ: On genetic and phenotypic variability of hypertrophic cardiomyopathy: nature versus nurture. *J Am Coll Cardiol* 38(2):331–334, 2001.
74. Reference deleted in review.
75. Flamm MD, Harrison DC, Hancock EW: Muscular subaortic stenosis: prevention of outflow obstruction with propranolol. *Circulation* 38(5):846–858, 1968.
76. Sharma S, Elliott P, Whyte G, et al: Utility of cardiopulmonary exercise in the assessment of clinical determinants of functional capacity in hypertrophic cardiomyopathy. *Am J Cardiol* 86(2): 162–168, 2000.
77. Bonow RO, Dilsizian V, Rosing DR, et al: Verapamil-induced improvement in left ventricular diastolic filling and increased exercise tolerance in patients with hypertrophic cardiomyopathy: short- and long-term effects. *Circulation* 72(4):853–864, 1985.
78. Bonow RO, Rosing DR, Bacharach SL, et al: Effects of verapamil on left ventricular systolic function and diastolic filling in patients with hypertrophic cardiomyopathy. *Circulation* 64(4): 787–796, 1981.
79. Gistri R, Cecchi F, Choudhury L, et al: Effect of verapamil on absolute myocardial blood flow in hypertrophic cardiomyopathy. *Am J Cardiol* 74(4):363–368, 1994.
80. Udelson JE, Bonow RO, O'Gara PT, et al: Verapamil prevents silent myocardial perfusion abnormalities during exercise in asymptomatic patients with hypertrophic cardiomyopathy. *Circulation* 79(5):1052–1060, 1989.
81. Pollick C: Muscular subaortic stenosis: hemodynamic and clinical improvement after disopyramide. *N Engl J Med* 307(16):997–999, 1982.
82. Reference deleted in review.
83. Sherrid M, Delia E, Dwyer E: Oral disopyramide therapy for obstructive hypertrophic cardiomyopathy. *Am J Cardiol* 62(16): 1085–1088, 1988.
84. Podrid PJ, Lampert S, Graboys TB, et al: Aggravation of arrhythmia by antiarrhythmic drugs—incidence and predictors. *Am J Cardiol* 59(11):38E–44E, 1987.

85. McKenna WJ, Oakley CM, Krikler DM, et al: Improved survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia. *Br Heart J* 53(4):412–416, 1985.
86. Fananapazir L, Leon MB, Bonow RO, et al: Sudden death during empiric amiodarone therapy in symptomatic hypertrophic cardiomyopathy. *Am J Cardiol* 67(2):169–174, 1991.
87. Prasad K, Frenneaux MP: Hypertrophic cardiomyopathy: is there a role for amiodarone? *Heart* 79(4):317–318, 1998.
88. Almendral JM, Ormaetxe J, Martinez-Alday JD, et al: Treatment of ventricular arrhythmias in patients with hypertrophic cardiomyopathy. *Eur Heart J* 14(Suppl):J71–J72, 1993.
89. Fananapazir L, Epstein ND, Curiel RV, et al: Long-term results of dual-chamber (DDD) pacing in obstructive hypertrophic cardiomyopathy: evidence for progressive symptomatic and hemodynamic improvement and reduction of left ventricular hypertrophy. *Circulation* 90(6):2731–2742, 1994.
90. Posma JL, Blanksma PK, Van Der Wall EE, et al: Effects of permanent dual chamber pacing on myocardial perfusion in symptomatic hypertrophic cardiomyopathy. *Heart* 76(4):358–362, 1996.
91. Nishimura RA, Trusty JM, Hayes DL, et al: Dual-chamber pacing for hypertrophic cardiomyopathy: a randomized, double-blind, crossover trial. *J Am Coll Cardiol* 29(2):435–441, 1997.
92. Maron BJ, Nishimura RA, McKenna WJ, et al: Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic patients with obstructive hypertrophic cardiomyopathy: a randomized, double-blind, crossover study (M-PATHY). *Circulation* 99(22):2927–2933, 1999.
93. Kappenberger L, Linde C, Daubert C, et al: Pacing in hypertrophic obstructive cardiomyopathy: a randomized crossover study. PIC Study Group. *Eur Heart J* 18(8):1249–1256, 1997.
94. Betocchi S, Elliott PM, Briguori C, et al: Dual chamber pacing in hypertrophic cardiomyopathy: long-term effects on diastolic function. *Pacing Clin Electrophysiol* 25(10):1433–1440, 2002.
95. Topilski I, Sherez J, Keren G, et al: Long-term effects of dual-chamber pacing with periodic echocardiographic evaluation of optimal atrioventricular delay in patients with hypertrophic cardiomyopathy >50 years of age. *Am J Cardiol* 97(12):1769–1775, 2006.
96. Ommen SR, Nishimura RA, Squires RW, et al: Comparison of dual-chamber pacing versus septal myectomy for the treatment of patients with hypertropic obstructive cardiomyopathy: a comparison of objective hemodynamic and exercise end points. *J Am Coll Cardiol* 34(1):191–196, 1999.
97. Moss AJ, Zareba W, Hall WJ, et al: Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 346(12):877–883, 2002.
98. Boriani G, Maron BJ, Shen WK, et al: Prevention of sudden death in hypertrophic cardiomyopathy: but which defibrillator for which patient? *Circulation* 110(15):e438–e442, 2004.
99. Gersh BJ, Maron BJ, Bonow RO, et al: ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 58(25):e212–e260, 2011.
100. Goodwin JF, Hollman A, Cleland WP, et al: Obstructive cardiomyopathy simulating aortic stenosis. *Br Heart J* 22:403–414, 1960.
101. Morrow AG: Hypertrophic subaortic stenosis: operative methods utilized to relieve left ventricular outflow obstruction. *J Thorac Cardiovasc Surg* 76(4):423–430, 1978.
102. Maron BJ, Dearani JA, Ommen SR, et al: The case for surgery in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 44(10):2044–2053, 2004.
103. Schoendube FA, Klues HG, Reith S, et al: Long-term clinical and echocardiographic follow-up after surgical correction of hypertrophic obstructive cardiomyopathy with extended myectomy and reconstruction of the subvalvular mitral apparatus. *Circulation* 92(9 Suppl):II122–II127, 1995.
104. Maron BJ, Nishimura RA, Danielson GK: Pitfalls in clinical recognition and a novel operative approach for hypertrophic cardiomyopathy with severe outflow obstruction due to anomalous papillary muscle. *Circulation* 98(23):2505–2508, 1998.
105. McIntosh CL, Maron BJ, Cannon RO, III, et al: Initial results of combined anterior mitral leaflet plication and ventricular septal myotomy-myectomy for relief of left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy. *Circulation* 86(5 Suppl):II60–II67, 1992.
106. van der Lee C, Kofflard MJ, van Herwerden LA, et al: Sustained improvement after combined anterior mitral leaflet extension and myectomy in hypertrophic obstructive cardiomyopathy. *Circulation* 108(17):2088–2092, 2003.
107. Krajcer Z, Leachman RD, Cooley DA, et al: Mitral valve replacement and septal myomectomy in hypertrophic cardiomyopathy: ten-year follow-up in 80 patients. *Circulation* 78(3 Pt 2):I35–I143, 1988.
108. Merrill WH, Friesinger GC, Graham TP, Jr, et al: Long-lasting improvement after septal myectomy for hypertrophic obstructive cardiomyopathyc. *Ann Thorac Surg* 69(6):1732–1735, discussion 1735–1736, 2000.
109. Qin JX, Shiota T, Lever HM, et al: Outcome of patients with hypertrophic obstructive cardiomyopathy after percutaneous transluminal septal myocardial ablation and septal myectomy surgery. *J Am Coll Cardiol* 38(7):1994–2000, 2001.
110. McCully RB, Nishimura RA, Tajik AJ, et al: Extent of clinical improvement after surgical treatment of hypertrophic obstructive cardiomyopathy. *Circulation* 94(3):467–471, 1996.
111. Sherrid MV, Chaudhry FA, Swistel DG: Obstructive hypertrophic cardiomyopathy: echocardiography, pathophysiology, and the continuing evolution of surgery for obstruction. *Ann Thorac Surg* 75(2):620–632, 2003.
112. Nishimura RA, Holmes DR, Jr: Clinical practice: hypertrophic obstructive cardiomyopathy. *N Engl J Med* 350(13):1320–1327, 2004.
113. Ommen SR, Olivotto I, Betocchi S, et al: The effect of surgical myectomy on survival in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 43(Suppl A):215A, 2004.
114. Sigwart U: Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. *Lancet* 346(8969):211–214, 1995.
115. Faber L, Meissner A, Ziemssen P, et al: Percutaneous transluminal septal myocardial ablation for hypertrophic obstructive cardiomyopathy: long term follow up of the first series of 25 patients. *Heart* 83(3):326–331, 2000.
116. Gietzen FH, Leuner CJ, Raute-Kreinsen U, et al: Acute and long-term results after transcoronary ablation of septal hypertrophy (TASH): catheter interventional treatment for hypertrophic obstructive cardiomyopathy. *Eur Heart J* 20(18):1342–1354, 1999.
117. Lakkis NM, Nagueh SF, Dunn JK, et al: Nonsurgical septal reduction therapy for hypertrophic obstructive cardiomyopathy: one-year follow-up. *J Am Coll Cardiol* 36(3):852–855, 2000.
118. Reference deleted in review.
119. Reference deleted in review.
120. Firoozi S, Elliott PM, Sharma S, et al: Septal myotomy-myectomy and transcoronary septal alcohol ablation in hypertrophic obstructive cardiomyopathy: a comparison of clinical, haemodynamic and exercise outcomes. *Eur Heart J* 23(20):1617–1624, 2002.
121. Maron BJ: Role of alcohol septal ablation in treatment of obstructive hypertrophic cardiomyopathy. *Lancet* 355(9202):425–426, 2000.
122. Roberts R, Sigwart U: Current concepts of the pathogenesis and treatment of hypertrophic cardiomyopathy. *Circulation* 112(2):293–296, 2005.
123. Sigwart U: Catheter treatment for hypertrophic obstructive cardiomyopathy: for seniors only? *Circulation* 118:107–108, 2008.
124. Holmes DR, Jr, Valeti US, Nishimura RA: Alcohol septal ablation for hypertrophic cardiomyopathy: indications and technique. *Catheter Cardiovasc Intervent* 66(3):375–389, 2005.
125. Singh M, Edwards WD, Holmes DR, Jr, et al: Anatomy of the first septal perforating artery: a study with implications for ablation therapy for hypertrophic cardiomyopathy. *Mayo Clin Proc* 76(8):799–802, 2001.
126. Nagueh SF, Lakkis NM, He ZX, et al: Role of myocardial contrast echocardiography during nonsurgical septal reduction therapy for hypertrophic obstructive cardiomyopathy. *J Am Coll Cardiol* 32(1):225–229, 1998.
127. Bhagwandeen R, Woo A, Ross J, et al: Septal ethanol ablation for hypertrophic obstructive cardiomyopathy: early and intermediate results of a Canadian referral centre. *Can J Cardiol* 19(8):912–917, 2003.
128. Faber L, Seggewiss H, Gleichmann U: Percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: results with respect to intraprocedural myocardial contrast echocardiography. *Circulation* 98(22):2415–2421, 1998.
129. Kuhn H, Gietzen FH, Leuner C, et al: Transcoronary Ablation of Septal Hypertrophy (TASH): a new treatment option for hypertrophic obstructive cardiomyopathy. *Z Kardiol* 89(Suppl 4):IV41–IV54, 2000.
130. Boekstegers P, Steinbigler P, Molnar A, et al: Pressure-guided nonsurgical myocardial reduction induced by small septal infarctions in hypertrophic obstructive cardiomyopathy. *J Am Coll Cardiol* 38(3):846–853, 2001.
131. Veselka J, Duchonova R, Prochazkova S, et al: Effects of varying ethanol dosing in percutaneous septal ablation for obstructive hypertrophic cardiomyopathy on early hemodynamic changes. *Am J Cardiol* 95(5):675–678, 2005.
132. Chang SM, Nagueh SF, Spencer WH, III, et al: Complete heart block: determinants and clinical impact in patients with hypertrophic obstructive cardiomyopathy undergoing nonsurgical septal reduction therapy. *J Am Coll Cardiol* 42(2):296–300, 2003.
133. Ralph-Edwards A, Woo A, McCrindle BW, et al: Hypertrophic obstructive cardiomyopathy: comparison of outcomes after myectomy or alcohol ablation adjusted by propensity score. *J Thorac Cardiovasc Surg* 129(2):351–358, 2005.
134. Smedira NG, Lytle BW, Lever HM, et al: Current effectiveness and risks of isolated septal myectomy for hypertrophic obstructive cardiomyopathy. *Ann Thorac Surg* 85:127–133, 2008.
135. Nagueh SF, Ommen SR, Lakkis NM, et al: Comparison of ethanol septal reduction therapy with surgical myectomy for the treatment of hypertrophic obstructive cardiomyopathy. *J Am Coll Cardiol* 38(6):1701–1706, 2001.
136. van Dockum WG, Beek AM, ten Cate FJ, et al: Early onset and progression of left ventricular remodeling after alcohol septal ablation in hypertrophic obstructive cardiomyopathy. *Circulation* 111(19):2503–2508, 2005.
137. Agarwal S, Tuzcu EM, Desai MY, et al: Updated meta-analysis of septal alcohol ablation versus myectomy for hypertrophic cardiomyopathy. *J Am Coll Cardiol* 55:823–834, 2010.
138. Talreja DR, Nishimura RA, Edwards WD, et al: Alcohol septal ablation versus surgical septal myectomy: comparison of effects on atrioventricular conduction tissue. *J Am Coll Cardiol* 44(12):2329–2332, 2004.
139. Alam M, Dokainish H, Lakkis NM: Hypertrophic obstructive cardiomyopathy-alcohol septal ablation vs. myectomy: a meta-analysis. *Eur Heart J* 30:1080–1087, 2009.
140. Leonardi RA, Kransdorf EP, Simel DL, et al: Meta-analyses of septal reduction therapies for obstructive hypertrophic cardiomyopathy: comparative rates of overall mortality and sudden cardiac death after treatment. *Circ Cardiovasc Interv* 3(2):97–104, 2010.

Pericardial Interventions

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KEY POINTS

- Pericardiocentesis is a catheter-based procedure in which fluid is aspirated from the pericardium. It is done to diagnose and treat patients with pericarditis with pericardial effusion, pericardial effusion with pericardial tamponade, and effusive-constrictive pericarditis.
- The pericardial space can be safely entered with a blunt-tipped needle using a subxiphoid approach under fluoroscopic guidance, even in the absence of significant pericardial effusion.
- Percutaneous balloon pericardiotomy (PBP) is an effective therapy for recurrent, free flowing, and hemodynamically significant pericardial effusions, especially if associated with neoplastic disease.
- PBP consists of creating a parietal pericardial window with a balloon catheter under fluoroscopic guidance in the cardiac catheterization laboratory.
- PBP is a less invasive alternative than a surgical pericardial window and avoids its perioperative risks.
- PBP should be avoided in patients with large pleural effusions or marginal pulmonary reserve to avoid further pulmonary compromise.
- Catheter-based diagnostic and interventional techniques in the pericardial space have become increasingly common and include epicardial mapping and ablation, intrapericardial delivery of therapies, intrapericardial echocardiography, pericardioscopy-guided biopsy, and potentially, other advanced techniques.

The clinical presentation of patients with pericardial effusion varies. Some are completely asymptomatic, but others develop pericardial tamponade and cardiovascular collapse. Pericardiocentesis is a catheter-based technique that uses a needle to aspirate the pericardial fluid, usually under fluoroscopic or echocardiographic guidance.

Percutaneous balloon pericardiotomy (PBP) is a relatively novel catheter-based technique that is gradually replacing the more invasive surgical pericardial window procedure. The improved techniques for percutaneous access to the pericardial space and the adjunctive use of pericardioscopy provide additional opportunities for the use of this space in diagnostic and interventional techniques. As a result, novel pericardial interventions, such as epicardial mapping and ablation, percutaneous pericardial biopsy (PPB), and intrapericardial echocardiography, are rapidly evolving.

PERICARDIAL EFFUSION AND TAMPONADE

The normal pericardium is a fibroelastic sac composed of visceral and parietal layers separated by a thin layer (20 to 50 mL) of straw-colored fluid.[1] The normal pericardium has a steep pressure-volume curve; it is distensible when the intrapericardial volume is small but becomes gradually inextensible when the volume increases.[1] The intrapericardial pressure depends on the relationship between the absolute volume of a pericardial effusion, speed of fluid accumulation, and pericardial elasticity. The clinical presentation is related to the size of the effusion and the rapidity of fluid accumulation.

Pericardial effusion may result from a variety of clinical conditions (Table 56-1). Among medical patients, malignant disease is the most common cause of pericardial effusion with tamponade.[1,2] Pericardial tamponade is a clinical syndrome with defined hemodynamic and echocardiographic abnormalities that result from the accumulation of intrapericardial fluid and impairment of ventricular diastolic filling.[1,3] The ultimate mechanism of hemodynamic compromise is the compression of cardiac chambers due to increased intrapericardial pressure.

In all cases of cardiac tamponade, initial treatment consists of removing pericardial fluid by prompt pericardiocentesis and drainage. Reaccumulation of fluid with recurrence of cardiac tamponade may be an indication for a surgical intervention.[1]

Autopsy and surgical studies have shown that myocardial or pericardial metastases are found in approximately 50% of patients who have cardiac tamponade due to malignancy.[3-7] Although the short-term survival of patients with cardiac tamponade depends primarily on its early diagnosis and relief, long-term survival depends on the prognosis of the primary illness regardless of the intervention performed.[4,5,8]

PERICARDIOCENTESIS

Indications

Pericardiocentesis is the technique of catheter-based aspiration of pericardial fluid.[1,3] It is used to diagnose and treat patients with pericarditis with pericardial effusion, pericardial effusion with pericardial tamponade, and effusive-constrictive pericarditis.

Many asymptomatic patients with large effusions do not require pericardiocentesis if they have no hemodynamic compromise, unless there is a diagnostic need for fluid analysis. In a prospective study with long-term follow-up of patients with large, idiopathic, chronic pericardial effusions, Sagrista-Sauleda and colleagues[9] concluded that the pericardial effusions were usually well tolerated for long periods by most patients with severe tamponade; however, they could develop unexpectedly at any time. Although pericardiocentesis was effective in resolving these effusions, recurrences were common, prompting the study authors to recommend referral of patients with recurrences for pericardiectomy.[10]

When cardiac tamponade occurs, the emergency drainage of pericardial fluid by pericardiocentesis is lifesaving therapy for a patient who would otherwise develop pulseless electrical activity and cardiac arrest. Pericardiocentesis can relieve tamponade, obtain fluid for appropriate analysis, and assess hemodynamics before and after pericardial fluid evacuation to exclude effusive-constrictive pericardial effusion. Elective pericardiocentesis is contraindicated for patients receiving anticoagulation, those with bleeding disorders or thrombocytopenia with platelet counts less than 50,000/μL, and those with hemorrhagic pericardial tamponade complicating aortic dissection. Pericardiocentesis is also ill advised when the effusion is very small or loculated.[1,3]

Technique

Pericardiocentesis is most commonly performed using a subxiphoid approach under electrocardiographic (ECG) and fluoroscopic guidance (Fig. 56-1, *A*).[3] Traditionally, pericardiocentesis has been performed in the cardiac catheterization laboratory with arterial and right

TABLE 56-1 Causes of Pericardial Effusion and Tamponade

Idiopathic Cases
Infections
Viral
Bacterial
Fungal
Others
Metabolic disorders
Uremia
Myxedema
Collagen and Other Autoimmune Disorders
Systemic lupus erythematosus
Rheumatoid arthritis
Rheumatic fever
Dressler syndrome
Others
Neoplastic Disorders
Primary
Pericardial metastasis
Local invasion
Volume overload
Chronic heart failure
Miscellaneous Disorders
Chest wall irradiation
Cardiotomy or thoracic surgery
Adverse drug reaction
Aortic dissection
After myocardial infarction
Trauma

From Jneid H, Maree AO, Palacios IF: Pericardial tamponade: clinical presentation, diagnosis and catheter-based therapies. In Parillo J, Dellinger PR, editors: *Critical care medicine,* ed 3, St. Louis, 2008, Mosby.

heart pressure monitoring.[3] The procedure is now also performed in the noninvasive laboratory, intensive care unit, or at bedside under echocardiographic guidance. With all modalities, it is a safe procedure when performed by appropriately trained personnel.

Pericardiocentesis is a procedure based on the Seldinger technique of percutaneous catheter insertion. After administration of local anesthesia to the skin and deeper tissues of the left xiphocostal area, the pericardial needle is connected to an ECG lead. The needle is advanced from the left of the subxiphoid area while aiming toward the left shoulder. This is usually done under fluoroscopic or echocardiographic guidance, but blinded procedures can be undertaken during emergency procedures. Often, a discrete pop is felt as the needle enters the pericardial space. When ST-segment elevation is observed on the ECG lead tracing, it signifies that the needle has touched the epicardium and should be withdrawn slightly until the ST-segment elevation disappears (see Fig. 56-1, *B*).

After the pericardial space is entered, a stiff guidewire is introduced into the pericardial space through the needle, which is then. A catheter is then inserted into the pericardial sac over the guidewire (Fig. 56-1, *C*). The drainage catheter typically has an end hole and multiple side holes. Intrapericardial pressure is measured by connecting a pressure transducer system to the intrapericardial catheter. Pericardial fluid is then removed, and samples of pericardial fluid are sent for appropriate biochemical, cytologic, bacteriologic, and immunologic analyses for diagnostic purposes; the first sample is usually reserved for microbiologic studies.

In cases of pericardial tamponade, aspiration of fluid should be continued until clinical and hemodynamic improvement occurs. The catheter is frequently left in place for continuous drainage and as a route to instill sclerosing or chemotherapeutic agents when needed. The catheter is secured to the skin using sterile sutures and covered with a sterile dressing. The success rate of pericardiocentesis is greater and the incidence of complications improves with increasing size of the effusion.

With increasing need to access the pericardial space (discussed later), especially in patients with no pericardial effusion ("dry taps"), variations in the technique have been developed. For example, a microneedle or a 17-gauge Tuohy needle (Pajunk Medical Systems, Norcross, GA) containing a curved tip can be introduced using the subxiyphoid approach while observing its track fluoroscopically in the lateral projection. This reduces the risk of inadvertent right ventricular puncture.

Complications

Potential complications of pericardiocentesis include a heart or coronary vessel laceration, sometimes causing fatal consequences. Puncture of the right atrium or ventricle with hemopericardial fluid accumulation, arrhythmias, air embolism, pneumothorax, and puncture of the peritoneal cavity or abdominal viscera has been reported. Acute pulmonary edema may infrequently occur when the pericardial tamponade is decompressed too rapidly.

The right xiphocostal, apical, right-sided, and parasternal approaches also are used for pericardiocentesis. Although they may be useful under certain circumstances, they are associated with a greater incidence of complications. The right xiphocostal approach is associated with a higher incidence of right atrial and inferior vena cava injury. Puncture of the left pleura and the lingula occurs more frequently with the apical approach, and puncture of the left anterior descending artery and the internal mammary artery is more common with the parasternal approach.

Echocardiographically guided pericardiocentesis is a safe and effective technique. In a cohort of 1127 therapeutic echocardiography-guided pericardiocenteses performed in 977 patients at the Mayo Clinic (1979 through 1998), the procedural success rate was 97% overall with a total complication rate of 4.7%.[10] Echocardiography may be especially useful for patients with loculated effusions, and unlike pericardiocenteses performed in the cardiac catheterization laboratory, the left chest wall is often used with echocardiographically guided pericardiocenteses.

Postprocedural Management

Pericardiocentesis may not completely evacuate the effusion in most cases because active secretion and bleeding may continue into the pericardial space.[1,3] The pericardial catheter should be left in place for 24 to 72 hours after the initial fluid evacuation until total daily drainage is 75 to 100 mL or less.

The patient is admitted for continuous ECG monitoring and assessment of the rate of pericardial drainage. The pericardial space should be drained every 8 hours and the catheter flushed with heparinized saline. Systemic antibiotics—usually first-generation cephalosporin for empirical coverage of gram-positive bacteria—are administered for the duration of the catheter stay. Based on the cause of the effusion, the patient's clinical and hemodynamic condition, and the amount of fluid drained, the pericardial catheter is usually removed within 72 hours, or decisions for additional therapy are contemplated.

Echocardiography can be used to monitor resolution of the pericardial effusion and signs of cardiac compression before catheter removal. Patients who continue to drain more than 75 to 100 mL/24 hours after 3 days of standard catheter drainage should be considered for more aggressive therapy. Reaccumulation of the pericardial fluid is particularly common in patients with malignant pericardial effusions. Additional therapeutic approaches to prevent pericardial fluid reaccumulation include intrapericardial instillation of sclerosing agents and use of chemotherapy, radiotherapy, PBP, and surgical pericardial

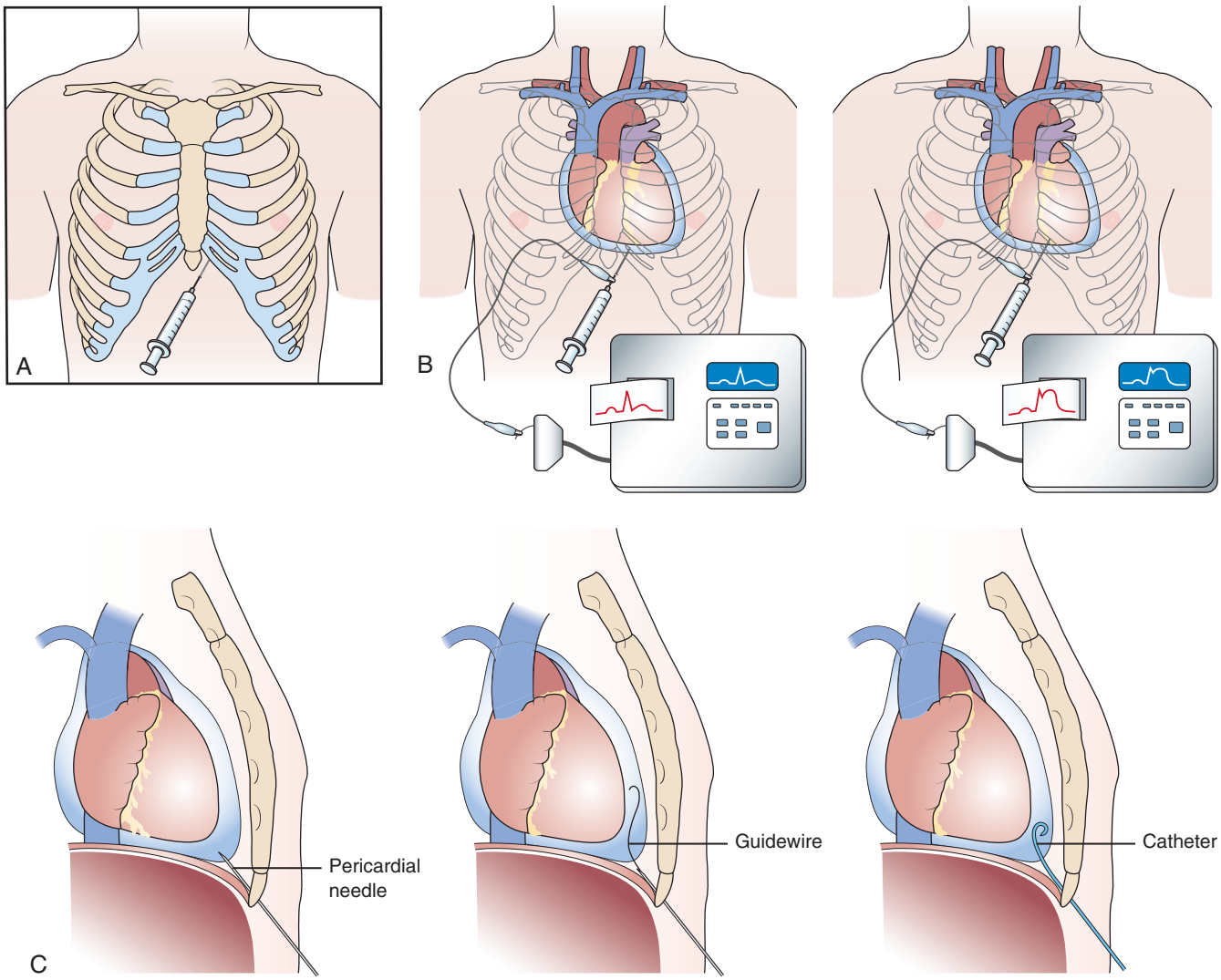

FIGURE 56-1 **A,** Diagrammatic representation of a pericardiocentesis procedure using the subxiphoid approach. **B,** The pericardial needle is connected to an electrocardiographic (ECG) lead. The needle is advanced from the left of the subxiphoid area, aiming toward the left shoulder. ST-segment elevation is seen on the ECG lead tracing when the needle touches the epicardium. The needle should be retracted slightly until the ST-segment elevation disappears. **C,** After the pericardial space is entered with the pericardial needle, a guidewire is introduced in the pericardial space through the needle. The needle is removed, and a catheter is inserted in the pericardial sac over the guidewire anteriorly or inferiorly in the pericardial sac. (Modified from Jneid H, Maree AO, Palacios IF: Pericardial tamponade: clinical presentation, diagnosis and catheter-based therapies. In Parillo J, Dellinger PR, editors: *Critical care medicine,* ed 3, St. Louis, 2008, Mosby.)

window. Reaccumulation of fluid with recurrence of cardiac tamponade is considered an absolute indication for a pericardial window.

PERCUTANEOUS BALLOON PERICARDIOTOMY

Management of cardiac tamponade or large pericardial effusions at risk for progression to tamponade remains controversial and is dictated to a large extent by local institutional practices. Life-threatening cardiac tamponade requires immediate removal of pericardial fluid to relieve the hemodynamic compromise and to prevent recurrence.

For many patients with a pericardial effusion and tamponade, standard percutaneous pericardial drainage with an indwelling pericardial catheter is sufficient to avoid recurrence. Recurrences after catheter drainage have been reported for 14% to 50% of patients with pericardial effusion and tamponade.[5,11-13] Patients who continue to drain more than 75 to 100 mL/24 hours after 3 days of standard catheter drainage have been considered for more aggressive therapy. Several approaches are available to prevent reaccumulation of pericardial fluid, including intrapericardial instillation of sclerosing agents, chemotherapy, and radiation therapy.[14,15] A surgically created pericardial window may provide an alternative for the treatment of pericardial effusions,[16,17] but morbidity and late recurrences are common.[8,18,19]

The use of a subxiphoid surgical pericardial window has been advocated as primary therapy for malignant pericardial tamponade based on the high initial success in relieving tamponade[18-23] and an acceptable recurrence rate.[19] However, it is associated with high morbidity rates.[8,16-23] Patients with advanced malignancy and cardiac tamponade are often poor candidates for surgical therapy. Because life expectancy is already limited, the increased length of hospital stay associated with a surgical procedure may compromise the quality of their remaining lives. The malnutrition and chemotherapy associated with advanced

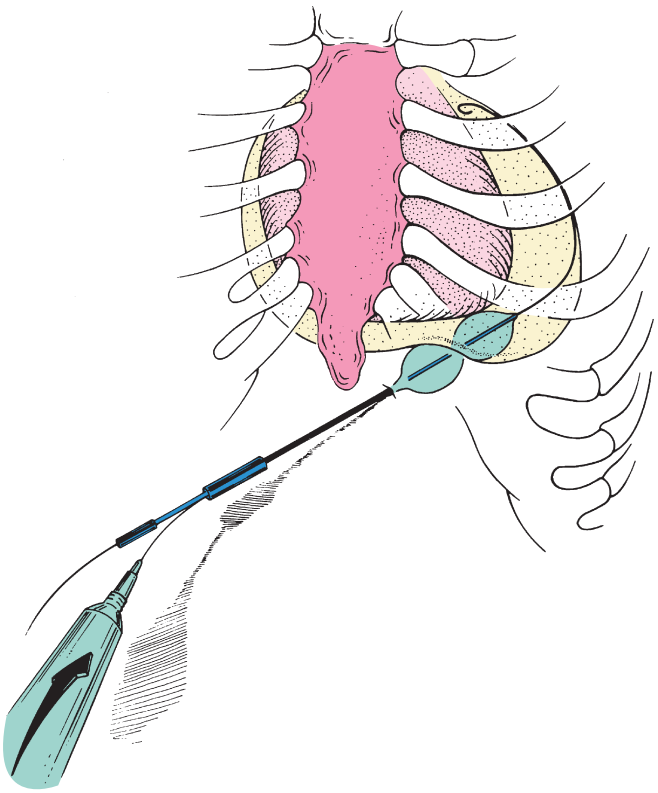

FIGURE 56-2 Percutaneous balloon pericardiotomy technique. (From Ziskind AA, Pearce AC, Lemmon CC, et al: Percutaneous balloon pericardiotomy for the treatment of cardiac tamponade and large pericardial effusions: description of technique and report of the first fifty cases. *J Am Coll Cardiol* 21:1-5, 1993.)

malignancy increase the risk of infection and other perioperative complications. It is preferable to offer a less invasive alternative.

Palacios and colleagues[24] proposed PBP as a less invasive alternative to the surgical pericardial window procedure. With this technique, a pericardial window and adequate drainage of pericardial effusion can be done percutaneously with a balloon catheter (Fig. 56-2). Since their initial report of 8 patients, the multicenter PBP registry investigators have reported data on more than 130 patients.[25]

Technique

The PBP technique is relatively simple and safe. It is performed in the catheterization laboratory with the patient under local anesthesia and mild sedation with intravenous narcotics and a short-acting benzodiazepine. There is minimal discomfort. Patients may be candidates for PBP if they have undergone prior pericardiocentesis and have persistent catheter drainage. PBP also may be done as a primary therapy at the time of initial pericardiocentesis. For those who have previously undergone standard pericardiocentesis using the subxiphoid approach, a pigtail catheter has typically been left in the pericardial space for drainage. For patients who continue to drain more than 75 to 100 mL/24 hours after 3 days, PBP is offered as an alternative to a surgical procedure.

The subxiphoid area around the indwelling pigtail pericardial catheter is infiltrated with 1% lidocaine. A 0.038-inch guidewire with a preshaped curve at the tip is advanced through the pigtail catheter into the pericardial space (Fig. 56-3, *A*). The catheter is then removed, leaving the guidewire in the pericardial space. The location of the wire should be confirmed by its looping within the pericardium.

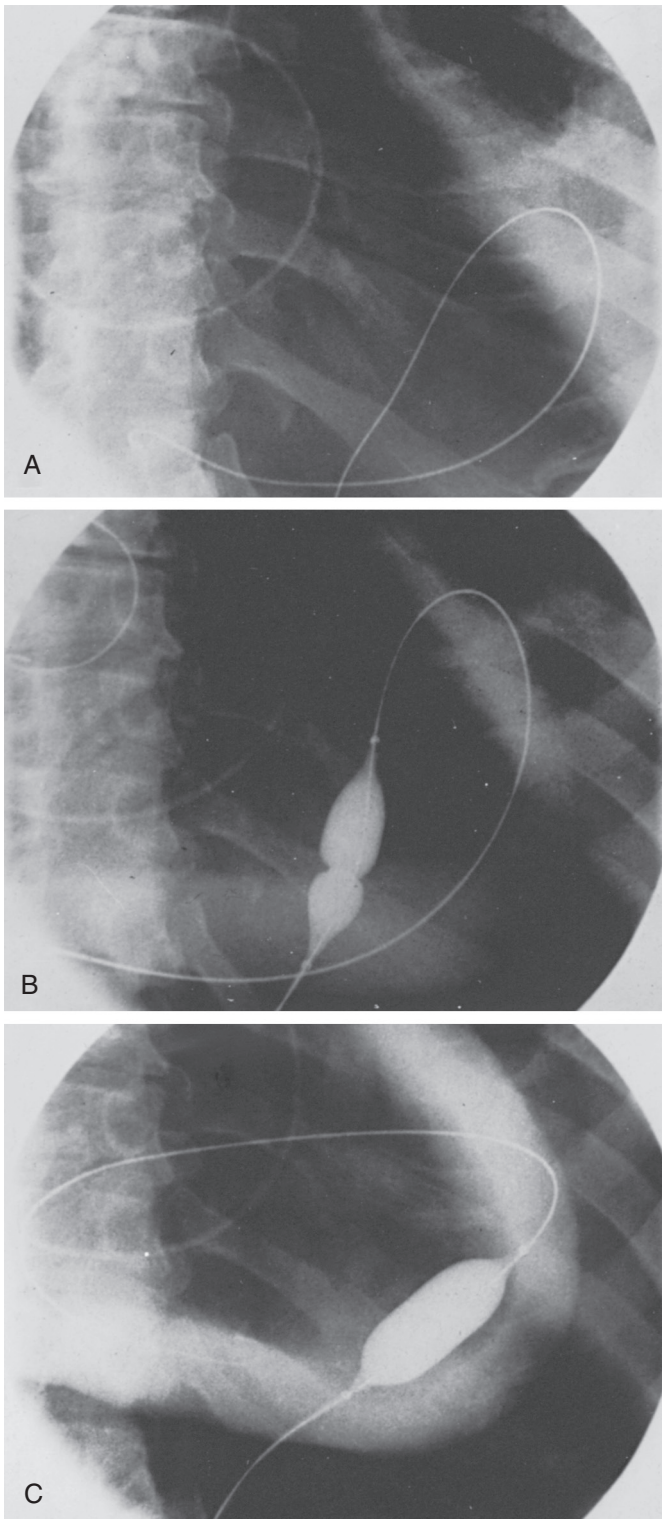

FIGURE 56-3 Anteroposterior fluoroscopic images. **A,** The 0.038-inch guidewire has been advanced through the pigtail catheter and can be seen looping freely in the pericardial space. **B,** As the balloon is inflated manually, a waist is seen at the pericardial margin. **C,** The waist disappears with full inflation of the balloon as the pericardial window is created.

After predilation along the track of the wire with a 10-Fr dilator, a 20-mm-diameter, 3-cm-long balloon dilation catheter (Boston Scientific, Natick, MA) is advanced over the guidewire and positioned to straddle the parietal pericardium. Care should be taken to advance the proximal end of the balloon beyond the skin and subcutaneous tissue. Precise localization of the balloon is accomplished by gentle inflation to identify the waist at the pericardial margin. The balloon is inflated manually until the waist produced by the parietal pericardium disappears (see Fig. 56-3, *B* and *C*). If the pericardium is apposed to the chest wall, as indicated by failure of the proximal portion of the balloon to expand, a countertraction technique should be used in which the catheter is withdrawn slightly and then gently advanced while the skin and soft tissues are pulled manually in the opposite direction. This maneuver isolates the pericardium for dilation (Fig. 56-4).

Fluoroscopic imaging using multiple views (preferably biplane fluoroscopy) helps to ensure correct positioning of the balloon, which should be straddling the parietal pericardium (Fig. 56-5). At the operator's discretion, 5 to 10 mL of radiographic contrast material may be instilled into the pericardial space to help identify the pericardial margin. Two or three balloon inflations are then performed to ensure the creation of an adequate opening in the pericardium. Although transthoracic and transesophageal echocardiography may provide additional guidance to some aspects of the procedure, it is our experience that the balloon cannot be imaged adequately with echocardiography to identify the waist at the site of the pericardial margin.[26]

The balloon dilation catheter is then removed, leaving the 0.038-inch guidewire in the pericardial space. A new pigtail catheter is then advanced over this guidewire and placed in the pericardial space. If PBP is being performed at the time of primary pericardiocentesis, the pericardium is entered using a standard subxiphoid approach, and a drainage catheter is inserted into the pericardial space. After the pericardial pressure has been measured, most of the pericardial fluid should be withdrawn, which reduces the volume remaining to pass into the pleural space.

Technical variations of the subxiphoid technique have included dilation of two adjacent pericardial sites, use of the apical approach,[27] use of an Inoue balloon catheter,[27-29] use of double balloons,[30] use of a combination of one long and one short balloon,[31] and use of an 18-mm dilating balloon to facilitate introduction of a 16-Fr chest tube into the pericardial space.[32] Other investigators have attempted laparoscopic pericardial fenestration,[33,34] used a cutting pericardiotome,[35] or implanted a pericardioperitoneal shunt.[36] Thoracoscopic techniques have been developed to create a larger pericardial window with low morbidity rates compared with those for open surgical techniques.[37] With this technique, adequate long-term drainage may be provided and specimens for pathologic study obtained.[33,38]

Postprocedural Management

After the PBP procedure, the patient is returned to a telemetry floor. The pericardial catheter should be aspirated every 6 hours and flushed with heparinized saline (5 mL of 100 U/mL). Pericardial drainage volumes should be recorded, and the catheter should be removed after there is no significant pericardial drainage (75 to 100 mL) for 24 hours.

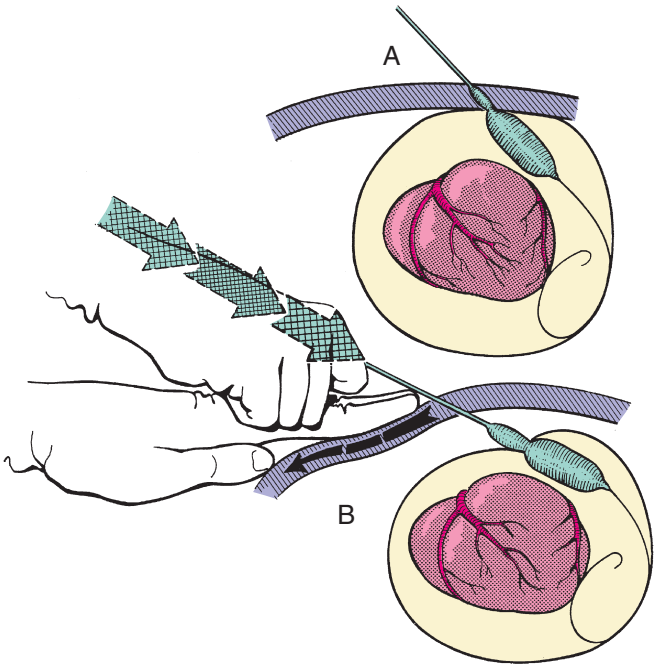

FIGURE 56-4 Countertraction technique to separate the pericardium from the adjacent chest wall is shown in a transverse view from below. **A,** Initial trial inflation of the balloon demonstrates trapping of the proximal portion of the balloon in the chest wall structures. **B,** Simultaneous traction on the skin and pushing of the balloon catheter results in displacement of the pericardium away from the chest wall, allowing proper inflation to occur. (Modified from Ziskind AA, Burstein S: Echocardiography vs. fluoroscopic imaging [letter]. *Cathet Cardiovasc Diagn* 27:86, 1992.)

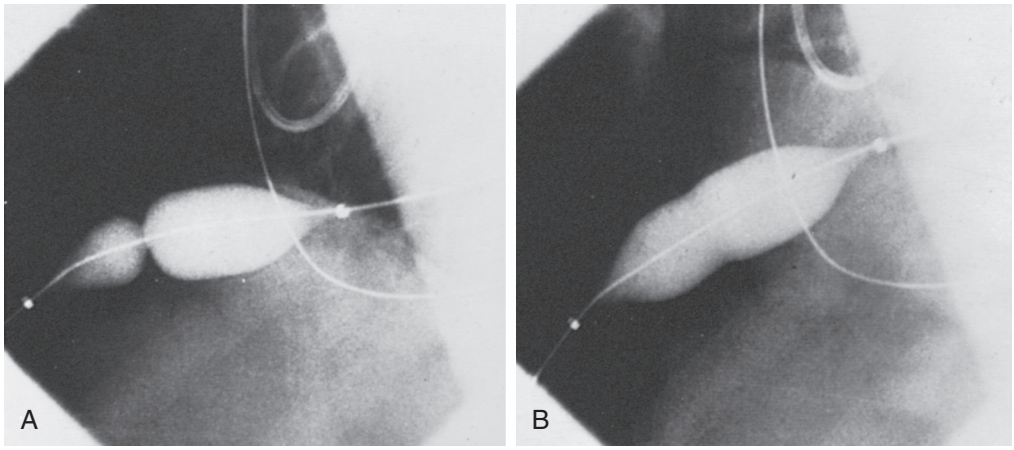

FIGURE 56-5 Lateral fluoroscopic image of balloon inflation. **A,** A waist is seen at the pericardial margin. **B,** It disappears with full inflation.

At the time of the catheter removal, there often is evidence on the chest radiograph of a new or increasing pleural effusion. Follow-up two-dimensional transthoracic echocardiography is performed approximately 48 hours after removal of the pericardial catheter. Data are being collected on immediate removal of the pericardial catheter after PBP to facilitate early discharge. However, leaving the pericardial catheter in place may provide a measure of safety by allowing monitoring to determine whether the window is effective and whether bleeding is occurring. Periodic postprocedural echocardiography can be used to check for reaccumulation of pericardial fluid. Chest radiography should be performed to monitor the possible development of a pleural effusion (usually left) caused by drainage of the pericardial fluid.

Mechanism

The precise mechanism by which PBP works remains unclear. We assume that balloon inflation results in localized tearing of the parietal pericardial tissues, creating a communication of the pericardial space with the pleural space and possibly with the abdominal cavity.[39,40] The use of a flexible fiberoptic pericardioscope introduced over the guidewire after PBP has demonstrated a pericardial window freely communicating with the left pleural space[41] (Fig. 56-6).

Chow and colleagues supported this finding with their postmortem studies of balloon dilation, in which they used an Inoue balloon inflated to a maximum diameter of 23 mm.[42] Balloon dilation produced, without tearing, a smooth, oval pericardial window measuring 18.8 ± 16.4 mm. Histologic analysis revealed fragmentation and breakage of the elastic and collagenous fibers in the connective tissue bordering the pericardial sites.[42]

We have demonstrated passage of pericardial fluid from the pericardial space to the pleural space in some patients after PBP by manually injecting 10 mL of radiographic contrast material through the pericardial catheter. However, the ability to visualize free exit of contrast from the pericardial space does not appear to correlate with procedural success. Based on experience with the subxiphoid surgical pericardial window procedure, it is unlikely that a long-term communication persists between the pericardium and the pleural cavity or subcutaneous tissues.

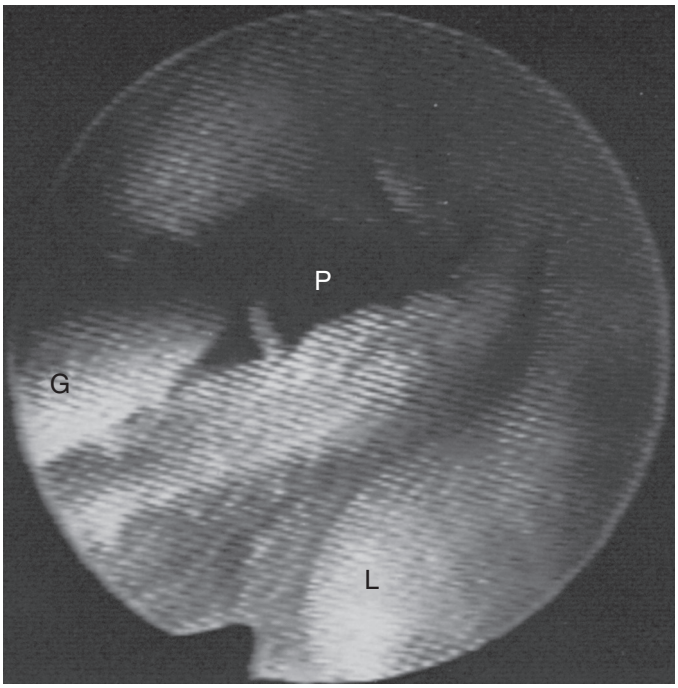

FIGURE 56-6 Pericardioscopic view of the balloon pericardiotomy site. The scope has been withdrawn over a guidewire to visualize the external pericardial surface. This figure demonstrates direct communication of the pericardial window with the left pleural space. *G,* Guidewire; *L,* lung in left pleural space immediately outside the pericardium; *P,* pericardial window created by balloon dilation.

Sugimoto and colleagues studied 28 patients who underwent surgical subxiphoid pericardial window procedures followed by tube decompression; 93% experienced permanent relief.[43] Postoperative echocardiograms demonstrated thickening of the pericardium-epicardium with obliteration of the pericardial space. Autopsy data that confirmed this fusion were available for four patients. The study authors concluded that the success of the subxiphoid pericardial window procedure depended on the inflammatory fusion of the epicardium to the pericardium, not on maintenance of a window.[43] Based on this surgical experience, it is unlikely that the PBP window remains open indefinitely. It is also possible that PBP, by leading to more effective pericardial drainage and maintaining a fluid-free pericardial space for a prolonged time, may permit autosclerosis to occur.

Results

Evidence-Based Literature

Palacios and coworkers reported the initial results of PBP in eight patients with malignant pericardial effusion and tamponade.[24] The technique was successful in all patients. There were no immediate or late complications related to the procedure. The mean time to radiologic development of a new or a significantly increased pleural effusion was 2.9 ± 0.4 days (range, 2 to 5 days). The mean follow-up in this initial report was 6 ± 2 months (range, 1 to 11 months). No patients had recurrence of pericardial tamponade or pericardial effusion. Five patients died at 1, 4, 9, 10, and 11 months after PBP. In all cases, the cause of death was the patient's primary malignant disease. The remaining three patients were alive and free of cardiac symptoms at the time of the report. After this initial favorable experience, the multicenter PBP registry was developed to collect additional data on a larger group of patients.

Multicenter Registry Experience

The PBP technique has been studied in a multicenter registry to evaluate its therapeutic effectiveness and risks systematically. Data on 130 patients undergoing PBP from 1987 to 1994 in 16 centers have been analyzed.[25,41] In this cohort of 130 patients, the mean age was 59 ± 13 years, 52% were men, 69% had cardiac tamponade, and 58% had a prior pericardiocentesis procedure performed. Of these patients, 85% had known malignancy (mostly lung cancer), and only 15% had nonmalignant pericardial effusion (i.e., predominantly idiopathic or related to human immunodeficiency virus infection [HIV]).

PBP was defined as successful if there was no recurrence of pericardial effusion on echocardiographic follow-up and if no complications occurred that required surgical exploration or a surgical pericardial window. PBP was successful in 111 (85%) of 130 patients, with no recurrences of pericardial effusion or tamponade during a mean follow-up of 5.0 ± 5.8 months. Five cases were considered failures because of pericardial bleeding, and those patients underwent surgical windowing. Thirteen patients had recurrence of pericardial effusion (mean time to recurrence, 53 ± 65 days). Of those 13 patients, 12 underwent surgical pericardial procedures, but 6 had a subsequent recurrence. Minor complications occurred in 11 patients (13%); the most common was fever. No patient had documented bacteremia or positive pericardial fluid cultures. After PBP, thoracentesis or chest tube placement was required in 15% of patients with preexisting pleural effusions, compared with 9% of patients without preexisting pleural effusions.

Of the 104 patients with a history of malignancy, 86 died, compared with 2 of 16 patients with nonmalignant disease. The mean survival time for patients with a history of malignancy was 3.8 ± 3.3 months. No procedure-related variables were found to influence survival or freedom from recurrence (e.g., number of sites dilated, visualization of

free fluid exit, duration of catheter placement). There was no significant difference in recurrence rates if PBP was performed as a primary treatment or after failed pericardiocentesis.

Technical Considerations

Echocardiographic and Chest Radiographic Qualifications

Echocardiography should be performed before PBP to rule out loculated pericardial fluid. If pericardial fluid is not free flowing, a surgical approach should be considered. If the chest radiograph reveals evidence of a large pleural effusion before PBP, this issue is less clear.

If a left effusion is moderate or large before PBP, the chance of needing thoracentesis is high, and PBP should be performed only if the cardiac benefits outweigh the risks of thoracentesis or chest tube placement. Patients with marginal pulmonary mechanics, such as those who have undergone pneumonectomy, should be evaluated with caution, because the development of a left pleural effusion may compromise their remaining lung function.

Prophylactic Antibiotic Administration

Febrile episodes were documented six times in the first 37 patients, although no patient had documented bacteremia or positive pericardial drainage cultures. Beginning with the 38th patient, prophylactic antibiotic therapy was initiated and continued until the catheter was removed. No febrile episodes were seen in 49 subsequent patients. It is unclear whether this was related to prophylactic antibiotics, a random effect, or more extensive operator experience, with a concomitant decrease in procedural time and catheter manipulation.

Bleeding Risk

The risk of bleeding from the pericardiotomy site appears to be increased in patients with platelet or coagulation abnormalities. For this reason, we do not recommend performing PBP on patients with uremic pericardial effusions or when coagulation parameters cannot be normalized (i.e., refractory coagulopathy or thrombocytopenia). In patients at high risk for bleeding, a surgical procedure under direct visualization may be safer.

Fluoroscopic Guidance

Attempts to guide balloon placement by transthoracic or transesophageal echocardiography have been disappointing. Although the dilating balloon can be visualized, it is not possible to distinguish proper placement (with a discrete waist) from entrapment of the proximal balloon in the soft tissues and ineffective pericardial dilation. We have found fluoroscopic guidance to be particularly essential to the countertraction technique and think it should be mandatory for PBP.[26]

Risks of Cardiac and Pulmonary Injury

Because PBP is not performed until successful access to the pericardial space is obtained and the guidewire is seen to be freely looping within the pericardium, the risks of cardiac injury are usually small. If the right ventricle is inadvertently entered and the balloon advanced, the results may be catastrophic. For this reason, PBP should be performed only by operators who have extensive experience with pericardiocentesis. In the emergency setting, it may be prudent to stabilize the patient with pericardiocentesis and leave a catheter in place for elective PBP under more controlled conditions.

Pleural Effusion

Development of a large pleural effusion after PBP is a significant concern. A left pleural effusion develops in most patients within 24 to 48 hours of the procedure (Fig. 56-7). In most cases, the pleural effusion resolves, presumably because of the greater resorptive capacity of the pleural surfaces.

Thoracentesis or chest tube placement was required in 15% of patients with preexisting pleural effusions, compared with 9% of those without preexisting pleural effusions in the multicenter PBP registry. It is likely that some patients have a large volume of fluid flow from the pericardial to the pleural space, but in many cases, it is difficult to determine whether the effusion results from drainage of fluid from the pericardial space or from the progression of concomitant pleural disease. For this reason, it is desirable to remove most of the pericardial fluid before creating the PBP window to limit the potential volume of fluid that can immediately move to the pleural space.

Duration of Catheter Placement

Most patients have a drainage catheter left in the pericardial space to monitor fluid output after the procedure. It is typically removed when pericardial drainage is less than 75 to 100 mL/24 hours. It may be possible to perform PBP without leaving a pericardial catheter in place, permitting an even shorter hospital stay and further decreasing the risk of infection.

Management of Balloon Rupture

Balloon rupture at the time of PBP can occur as a result of the combination of a large balloon, excessive inflation pressure, and an inelastic pericardium. Uncommonly, balloon rupture may be accompanied by catheter fracture because excessive resistance limits withdrawal. Our experience suggests that the frequency of balloon rupture can be minimized with proper technique, particularly the use of countertraction to isolate the pericardium, thereby avoiding dilation of the adjacent nonpericardial tissues.[26] Hemiballoon dislodgment sometimes occurs, and Block and Wilson have described a technique to retrieve it by placing a second pericardial catheter, snaring the guidewire, and using a second catheter to pull the balloon fragment back.[44]

Adjunctive Diagnostic Approaches

Although patients with pericardial effusion may have a history of malignancy, in only 50% of them is malignancy the cause of the effusion.[1,4] Although cytologic analysis of the pericardial fluid may aid in the diagnosis, pericardial tissue is not routinely obtained by PBP for pathologic analysis, as is the case during a surgical pericardial window procedure. To address this need, a percutaneously introduced pericardial bioptome has been successful in providing diagnostic quality tissue.[25] With the use of an aggressive serrated-jaw bioptome (Boston Scientific, Natick, MA) (Fig. 56-8, *A*) that is advanced though an 8-Fr vascular introducer, multiple samples can be obtained from the posterolateral aspect of the parietal pericardium (see Fig. 56-8, *B*). This technique remains investigational.

Summary

PBP offers a nonsurgical alternative for the management of pericardial effusion. PBP is particularly useful for critically ill patients with advanced malignancy and limited survival for whom it is desirable to avoid the risks and discomfort of anesthesia and surgery. PBP appears to palliate malignant pericardial disease successfully for the duration of their survival.

The decision to perform PBP rather than pericardiocentesis with or without sclerotherapy may depend on patient and institutional variables. PBP should be considered if pericardial fluid recurs after primary pericardiocentesis. In institutions with an aggressive surgical approach to malignant pericardial disease, this less invasive alternative to a surgical pericardial window may be considered for the primary treatment of malignant cardiac tamponade. In contrast, pericardiocentesis alone, without PBP at that time, is preferred if the cause of the pericardial fluid is unknown.

Samples of pericardial fluid should be sent for cell counts, cytologic analysis, culture, and special stains to assist with the diagnosis. Simple pericardiocentesis is also preferred if uremic platelet dysfunction or other coagulation abnormalities exist or there is the possibility of bacterial or fungal infection that could be spread to the pleural space.

The immediate and late results of PBP for patients with malignant pericardial effusion appear to be similar to those of surgical pericardiotomy. However, the role of PBP in the management of nonmalignant pericardial disease remains unclear. It is possible that PBP could be

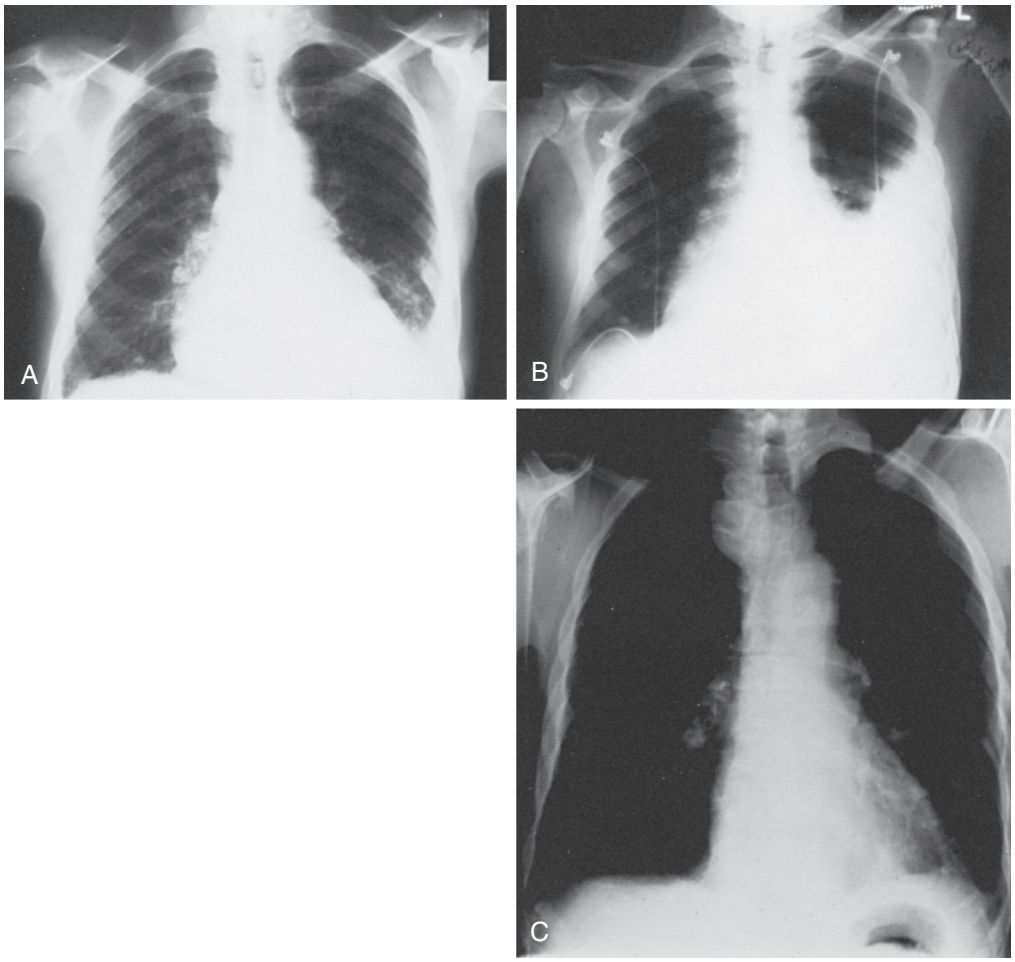

FIGURE 56-7 Posteroanterior chest radiographs. **A,** At admission, the radiograph shows an enlarged cardiac silhouette. **B,** At 24 hours after percutaneous balloon pericardiotomy, a new left pleural effusion is seen. **C,** One month later, complete resolution of the left pleural effusion is apparent. (From Palacios IF, Tuzcu EM, Ziskind AA, et al: Percutaneous balloon pericardial window for patients with malignant pericardial effusion and tamponade. *Cathet Cardiovasc Diagn* 22:244-249, 1991.)

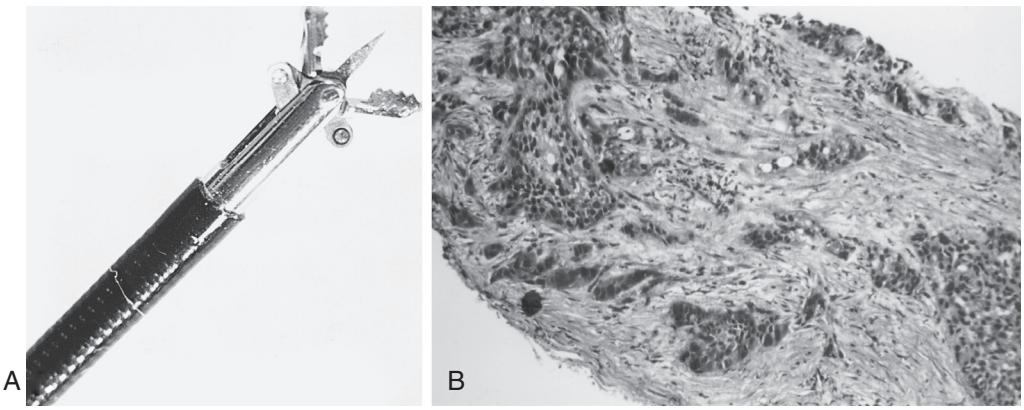

FIGURE 56-8 **A,** Pericardial bioptome with a center needle and aggressive serrated-jaw configuration. **B,** Percutaneous pericardial biopsy specimen from a patient with newly diagnosed lung cancer. It contains sheets of squamous cell carcinoma. Malignant cells are seen trapped in the fibrin of the inflammatory exudate. (From Ziskind AA, Rodriguez S, Lemmon C, Burstein S: Percutaneous pericardial biopsy as an adjunctive technique for the diagnosis of pericardial disease. *Am J Cardiol* 74:288-291, 1994.)

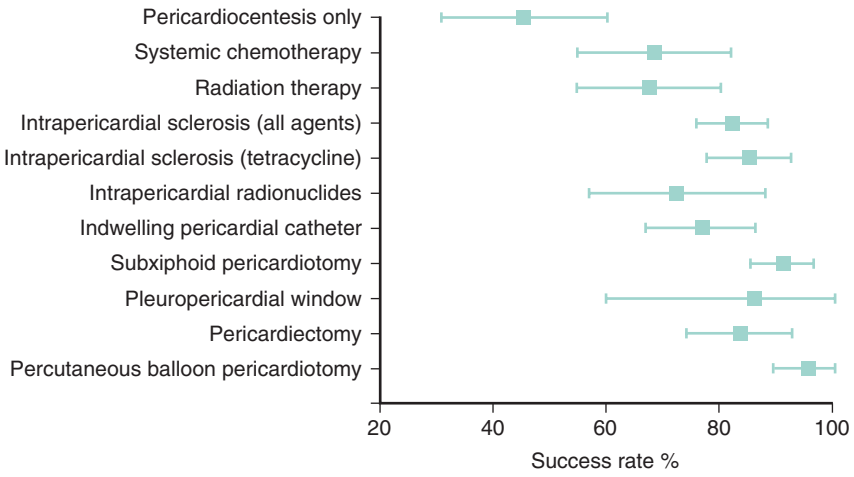

FIGURE 56-9 Success rates with 95% confidence intervals *(bars)* for various treatment modalities for malignant pericardial effusions. (From Vaitkus PT, Herrmann HC, Le Winter MM: Treatment of malignant pericardial effusion. *JAMA* 272:272, 1994.)

used for the treatment of pericardial effusions caused by viral infection, HIV-related disease, hypothyroidism, collagen vascular disease, and idiopathic effusions. PBP was reported with favorable results in a series of pediatric patients with nonmalignant effusions.[45] Additional long-term follow-up is needed on larger numbers of patients to clarify the role of this procedure in nonmalignant pericardial disease.

The application of PBP to patients with malignant pericardial disease is likely to increase in the future. It may expand to the treatment of patients without malignancy,[45] especially those with limited survival time (e.g., advanced HIV infection). PBP procedures need not be limited to tertiary care hospitals, although they should be performed in centers that routinely perform pericardiocentesis procedures. The infrequency of effusive pericardial disease and the larger number of patients required limit the feasibility of randomized studies to compare the effectiveness of various treatment strategies.

Vaitkus and colleagues performed a meta-analysis of prior studies in which treatment of malignant pericardial effusions was defined as successful if the patient survived the procedure, the symptoms did not recur, and no other interventions directed at the pericardium were required regardless of the length of survival.[46] Success rates for the various treatments are shown in Figure 56-9. Because no randomized data are available comparing the efficacy of PBP with that of a surgical or thoracoscopic pericardial window or with catheter drainage and sclerotherapy, the combined use of PBP with sclerotherapy has not been done.

NOVEL CATHETER-BASED INTERVENTIONS IN THE PERICARDIAL SPACE

The use of percutaneous intervention techniques in the pericardial space has been progressively increasing and now encompasses multiple disciplines in cardiology. Many factors contributed to the emergence of these techniques. Epicardial catheter mapping and ablation in the electrophysiology laboratory have opened a new horizon in cardiac electrophysiology, which was previously limited largely to the operating room. The pericardial space has been recognized as a natural drug receptacle that can restrict drug delivery to the heart, with many investigators attempting to exploit it as a reservoir to deliver therapeutic substances.[47] There has been an increasing need to replace the standard pericardiocentesis procedure with a safer technique, particularly in patients with small pericardial effusions who are at high risk for complications.

Epicardial Mapping and Ablation

Epicardial scar-related reentry has been recognized as an important cause of ventricular tachycardia, especially in patients with nonischemic cardiomyopathy. Other infrequent but clinically significant arrhythmias, such as supraventricular tachycardias and idiopathic ventricular tachycardia, also possess epicardial foci that cannot be ablated except from the epicardium.

Catheter-based intervention techniques in the pericardial space gained momentum after invasive cardiologists realized that pericardial fluid is not a prerequisite for a safe percutaneous entry into the pericardial space. Sosa and colleagues[48] were the first to show that the pericardial space can be safely entered with a blunt-tipped needle using a subxiphoid approach under fluoroscopic guidance. In their seminal work in 1996 in patients with Chagas disease,[48] they advanced an epidural needle toward the right ventricular apex until a slight negative pressure was felt, and they confirmed the needle position by small injections of contrast to delineate the cardiac silhouette. They established the feasibility and safety of epicardial mapping in patients with Chagas disease and recurrent ventricular tachycardia, one of whom underwent a successful epicardial circuit ablation.[48]

Epicardial mapping and ablation were subsequently adopted by several interventional electrophysiologists.[49] Sosa and colleagues[50] performed epicardial mapping to guide endocardial and epicardial ablation in a series of 10 consecutive patients with ventricular tachycardia and Chagas disease. Epicardial mapping in that study enabled the detection of an epicardial circuit in 14 of 18 mappable ventricular tachycardias and helped guide endocardial ablation in four patients and epicardial ablation in six. The same approach was also attempted successfully in patients with recurrent ventricular tachycardia after myocardial infarction, demonstrating that postinfarction pericardial adherence does not preclude epicardial mapping and ablation.[51]

It has since become clear that failure of endocardial ablation can reflect an epicardial arrhythmic substrate, which can be safely treated by epicardial mapping and ablation using the percutaneous pericardial technique. In one series of 48 patients with prior unsuccessful endocardial ablation, Schweikert and colleagues[52] showed that epicardial instrumentation and ablation provided a safe and effective alternative strategy.

Laham and colleagues[53] subsequently confirmed the safety of subxiphoid access of the normal pericardium in a large animal model, using fluoroscopic guidance and continuous positive pressure of 20 to 30 mm Hg (achieved by saline infusion using an intraflow system) to push the right ventricle away from the needle's path. Access to the pericardial space was achieved in all 49 Yorkshire pigs with no adverse events, and histologic examination of 15 animals 1 month after the procedure showed no evidence of myocardial damage.[53] Many invasive cardiologists argue that needle advancement under continuous positive pressure by saline infusion may not be necessary for a successful technique.

In addition to the subxiphoid approach for pericardial puncture (i.e., from the epicardial surface of the heart), other investigational approaches have been studied. Mickelsen and colleagues examined

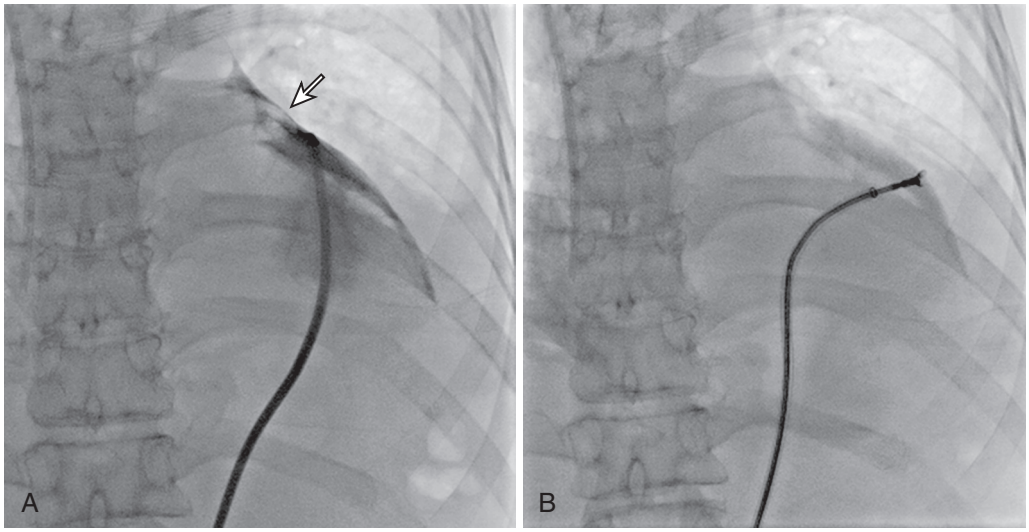

FIGURE 56-10 **A,** Contrast injection through an Arrow braided sheath confirms the intrapericardial location. **B,** A biopsy is obtained through a 7-Fr BiPal catheter passed through the sheath and away from the cardiac shadow into the lateral pericardial wall.

transvenous access to the pericardial space for epicardial lead implantation for cardiac resynchronization therapy.[54] This approach was feasible in eight pigs, which underwent puncture of the terminal anterior superior vena cava or the right atrial appendage to access the pericardial space. However, it resulted in a hemodynamically significant pericardial effusion in four of the eight animals.[54]

Intrapericardial Echocardiography

Intrapericardial echocardiography is being investigated at the Massachusetts General Hospital[55] and is another example of a promising catheter-based technique in the pericardial space. Rodrigues and coworkers[55] introduced phased-array ultrasound transducers into the pericardial space of seven goats with 10-Fr steerable catheters advanced using the transthoracic subxiphoid approach. They obtained detailed imaging of cardiac structures. This promising approach may help establish the relative positions of the ablation catheters and may facilitate epicardial ablation in the electrophysiology laboratory.

Several devices are being studied for safe and effective percutaneous access to the pericardial space. An example is the PerDUCER (Comedicus, Columbia Heights, MN), which provided efficient, safe, and effective pericardial access in the normal or minimally abnormal pericardial space.[56,57]

Percutaneous Pericardial Biopsy

PPB was described in 1988 by Endrys and colleagues,[58] who reported a series of 18 patients undergoing pericardial biopsy using an endomyocardial bioptome inserted through an 8-Fr, 4 0-cm Teflon sheath with a curved tip and multiple side holes.[58] Endrys and colleagues allowed air to enter the pericardium to delineate the visceral and parietal pericardial layers, and they obtained an average of eight samples per patient with no complications. They therefore showed that PPB could be safely performed using conventional invasive cardiology techniques.[58]

Because the floppy nature of the bioptome made it difficult to direct it to the appropriate site in the pericardial cavity, a modified technique using the distal portion of a 9-Fr, right Judkins coronary guiding catheter was adopted to target pericardial biopsy sites.[59] Ziskind and colleagues subsequently used a special pericardial bioptome with a central needle and serrated jaws to perform pericardial biopsy.[25] They also maintained separation of the visceral-pericardial layer by avoiding complete evacuation of pericardial fluid at the beginning of the procedure and therefore avoided instilling air into the pericardial cavity.[25] Selig and colleagues described a modified PPB technique using echocardiographic guidance without fluoroscopy.[60]

Palacios and coworkers reported a case series of seven patients with pericardial effusion undergoing PPB.[61] After complete drainage of the pericardial fluid under fluoroscopic and ECG guidance and using the subxiphoid approach, Palacios and colleagues exchanged the 5-Fr drainage pigtail catheter for an 8-Fr, 23-cm Arrow braided sheath and subsequently passed a 7-Fr BiPal biopsy forceps (Cordis, Johnson and Johnson, Bridgewater, NJ) through the sheath and away from the cardiac shadow to the lateral pericardial wall (Fig. 56-10). They obtained a total of five biopsy specimens per patient with no complications and demonstrated that pericardial biopsy added incremental diagnostic value to the analysis of pericardial fluid alone. In their case series, PPB confirmed the absence of malignant invasion in four patients with neoplastic disease and lymphocytic and organizing effusive pericarditis in one and two patients, respectively.[61]

In summary, the PPB technique is safe and feasible in the cardiac catheterization laboratory. It is less invasive than surgical biopsy, can be easily modified to obtain tissue samples from pericardial masses, and has increased the diagnostic yield of pericardiocentesis and pericardial fluid analysis. One clinical scenario in which PPB may prove to be of particular importance is in the setting of tuberculous pericardial effusion because *Mycobacterium tuberculosis* is rarely cultured and a positive acid-fast stain is infrequently obtained from the pericardial fluid, which makes tuberculosis, unlike malignant pericarditis, a commonly missed diagnosis without the technique of PPB.

Pericardioscopy

Seferovic and associates[62] reported their experience with the use of pericardioscopy to assist pericardial biopsy and demonstrated the diagnostic value of pericardial biopsy to be significantly improved by pericardioscopy-guided extensive sampling. Their study included 49 patients with large pericardial effusions undergoing parietal pericardial biopsy. In 12 patients (group 1), pericardial biopsy was guided by fluoroscopy and obtained three to six samples per patient. In 22 patients (group 2), four to six pericardial biopsies per patient were obtained by pericardioscopic guidance using a 16-Fr flexible endoscope. In group 3, extensive pericardial sampling (18 to 20 samples per patient) was performed, guided by pericardioscopy in 15 patients.

Sampling efficiency was better with pericardioscopy (group 2, 84.9%; group 3, 84.2%) compared with fluoroscopic guidance (group

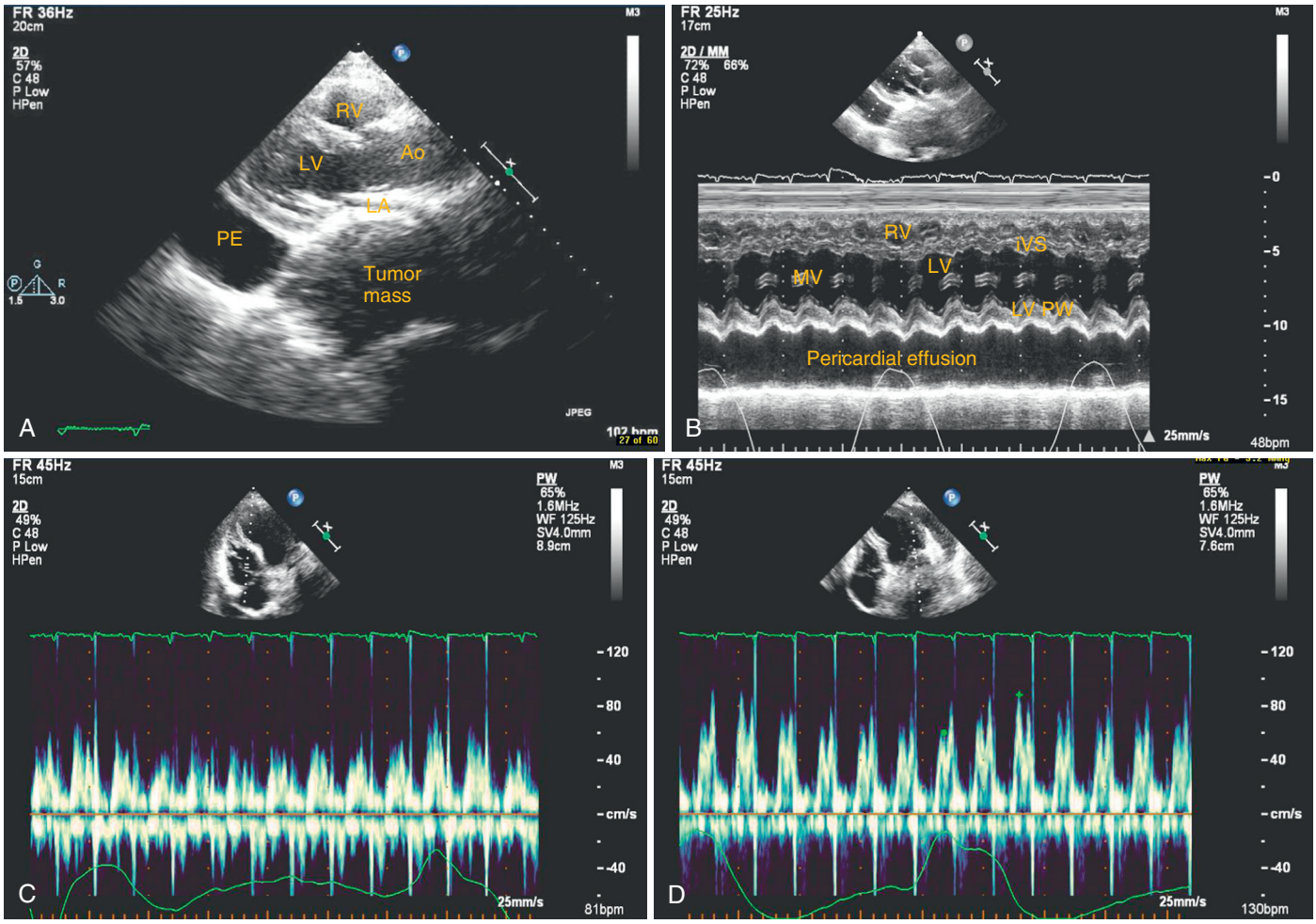

FIGURE 56-11 **A,** Parasternal long-axis view shows a large pericardial effusion located predominantly posteriorly and adjacent to a tumor mass in a patient diagnosed with lung cancer. The left atrium appears very small due to extrinsic compression by the tumor. **B,** M-mode view of the pericardial effusion measuring 4.2 cm in its maximal diameter. **C,** Marked respiratory variation in the inflow velocities across the tricuspid valve suggests increased intrapericardial pressure. **D,** Marked respiratory variation in mitral inflow E velocities (>25%) suggests cardiac tamponade. *IVS,* Interventricular septum; *LA,* left atrium; *LV,* left ventricle; *LVPW,* left ventricular posterior wall; *MV,* mitral valve; *PE,* pericardial effusion; *RV,* right ventricle.

1, 43.7%; $P < .01$). Pericardial biopsy in group 3 had higher diagnostic value than in group 1 for revealing a new diagnosis (40% vs. 8.3%, $P < .05$) or establishing the cause (53.3% vs. 8.3%, $P < .05$). For group 2, pericardial biopsy had a higher yield in establishing the cause than for group 1 (40.9% vs. 8.3%; $P < .05$). No major complications were observed in their study.

Percutaneous Left Atrial Appendage Suture Ligation

Percutaneous left atrial appendage (LAA) suture ligation is an alternative to oral anticoagulation for stroke prevention in patients with atrial fibrillation. The Lariat procedure[63] to percutaneously close the LAA depends on the ability of the operator to safely access and work in the pericardial space in a patient who usually has no pericardial effusion. It is performed in patients who have suitable LAA anatomy amenable to Lariat ligation.

A13.5-Fr soft-tipped sheath is introduced into the pericardial space, and a transseptal puncture is performed by means of the femoral vein by standard techniques. A magnet-tipped, 0.025-inch guidewire is advanced into the anterior aspect of the LAA. A magnet-tipped, 0.035-inch wire is then advanced into the pericardium through the pericardial sheath to form a connection with the magnet-tipped wire in the LAA, over which the Lariat snare is advanced and closed at the mouth of the LAA using transesophageal echocardiography and fluoroscopic guidance. The preloaded suture is released from the snare and tightened with the suture-tensioning device. The snare is removed, and the suture is cut using a suture cutter. The pericardial sheath is exchanged for a drain, which is left in place for at least 4 to 6 hours or more if needed.

Price and colleagues[64] reported the results of the multicenter U.S. registry inclusive of 154 consecutive patients undergoing LAA ligation with the Lariat device at eight sites. Device success was achieved in 94% of patients, with an 86% procedural success rate and 10% major complication rate. Significant pericardial effusion occurred in 16 patients (10.4%) after the procedure.

CONCLUSIONS

Pericardial effusion is caused by myriad conditions and can complicate acute pericarditis and chronic effusive constrictive pericarditis or result in acute cardiac tamponade (Fig. 56-11). Pericardiocentesis (Fig. 56-12) serves as a diagnostic and therapeutic modality in patients with pericardial effusions. PBP is an effective therapy for recurrent,

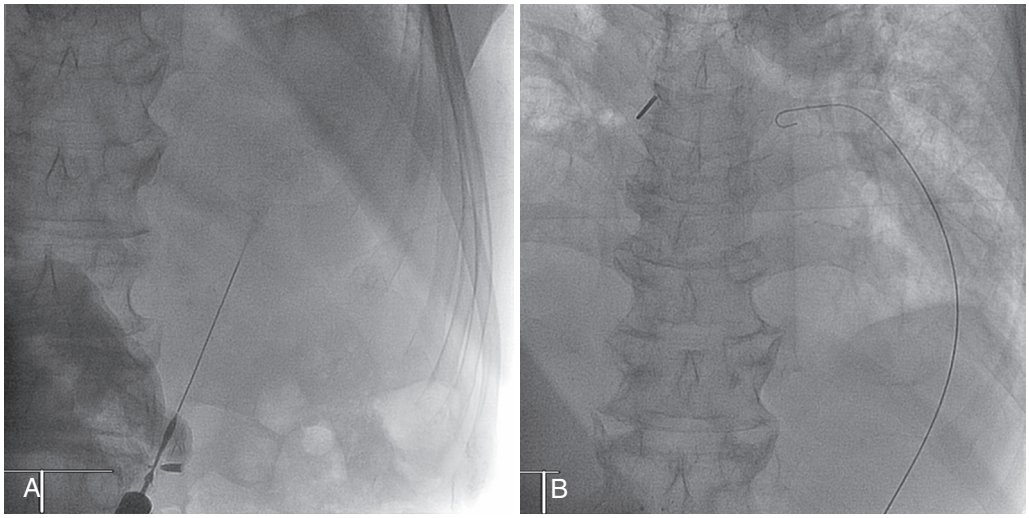

FIGURE 56-12 **A,** The pericardial space is accessed by the subxiphoid approach using a micropuncture kit in a patient with a large pericardial effusion. Injection of iodinated contrast material into the pericardial space confirmed intrapericardial location. Subsequent transthoracic echocardiogram imaging with a bubble study further confirmed pericardial access. **B,** A 0.035-inch guidewire is positioned in the pericardial space, over which a draining catheter is subsequently advanced to evacuate the effusion (Video 56-1).

free-flowing, and hemodynamically significant pericardial effusions, especially those associated with neoplastic disease.

Catheter-based diagnostic and interventional techniques in the pericardial space have become increasingly common and include epicardial mapping and ablation, intrapericardial delivery of therapies, intrapericardial echocardiography, pericardioscopy-guided biopsy, and percutaneous LAA suture ligation.

REFERENCES

1. Jneid H, Maree AO, Palacios IF: Pericardial tamponade: clinical presentation, diagnosis and catheter-based therapies. In Parillo J, Dellinger PR, editors: *Crit Care Med*, ed 3, St. Louis, 2008, Mosby.
2. Guberman BA, Fowler NO, Engel PJ, et al: Cardiac tamponade in medical patients. *Circulation* 64(3):633–640, 1981.
3. Jneid H, Maree AO, Palacios IF: Acute pericardial disease: pericardiocentesis and percutaneous pericardiotomy. In Mebazaa AGM, Zannad FM, Parillo J, editors: *Acute heart failure*, London, 2008, Springer.
4. Mills SA, Julian S, Holliday RH, et al: Subxiphoid pericardial window for pericardial effusive disease. *J Cardiovasc Surg (Torino)* 30(5):768–773, 1989.
5. Markiewicz W, Borovik R, Ecker S: Cardiac tamponade in medical patients: treatment and prognosis in the echocardiographic era. *Am Heart J* 111(6):1138–1142, 1986.
6. Bisel HF, Wroblewski F, Ladue JS: Incidence and clinical manifestations of cardiac metastases. *JAMA* 153(8):712–715, 1953.
7. Goldman BS, Pearson FG: Malignant pericardial effusion: review of hospital experience and report of a case successfully treated by talc poudrage. *Can J Surg* 8:157–161, 1965.
8. Piehler JM, Pluth JR, Schaff HV, et al: Surgical management of effusive pericardial disease. Influence of extent of pericardial resection on clinical course. *J Thorac Cardiovasc Surg* 90(4):506–516, 1985.
9. Sagrista-Sauleda J, Angel J, Permanyer-Miralda G, et al: Long-term follow-up of idiopathic chronic pericardial effusion. *N Engl J Med* 341(27):2054–2059, 1999.
10. Tsang TS, Enriquez-Sarano M, Freeman WK, et al: Consecutive 1127 therapeutic echocardiographically guided pericardiocenteses: clinical profile, practice patterns, and outcomes spanning 21 years. *Mayo Clin Proc* 77(5):429–436, 2002.
11. Flannery EP, Gregoratos G, Corder MP: Pericardial effusions in patients with malignant diseases. *Arch Intern Med* 135(7):976–977, 1975.
12. Kopecky SL, Callahan JA, Tajik AJ, et al: Percutaneous pericardial catheter drainage: report of 42 consecutive cases. *Am J Cardiol* 58(7):633–635, 1986.
13. Patel AK, Kosolcharoen PK, Nallasivan M, et al: Catheter drainage of the pericardium: practical method to maintain long-term patency. *Chest* 92(6):1018–1021, 1987.
14. Shepherd FA, Morgan C, Evans WK, et al: Medical management of malignant pericardial effusion by tetracycline sclerosis. *Am J Cardiol* 60(14):1161–1166, 1987.
15. Davis S, Sharma SM, Blumberg ED, et al: Intrapericardial tetracycline for the management of cardiac tamponade secondary to malignant pericardial effusion. *N Engl J Med* 299(20):1113–1114, 1978.
16. Fontenelle LJ, Cuello L, Dooley BN: Subxiphoid pericardial window: a simple and safe method for diagnosing and treating acute and chronic pericardial effusions. *J Thorac Cardiovasc Surg* 62(1):95–97, 1971.
17. Santos GH, Frater RW: The subxiphoid approach in the treatment of pericardial effusion. *Ann Thorac Surg* 23(5):467–470, 1977.
18. Palatianos GM, Thurer RJ, Kaiser GA: Comparison of effectiveness and safety of operations on the pericardium. *Chest* 88(1):30–33, 1985.
19. Palatianos GM, Thurer RJ, Pompeo MQ, et al: Clinical experience with subxiphoid drainage of pericardial effusions. *Ann Thorac Surg* 48(3):381–385, 1989.
20. Hankins JR, Satterfield JR, Aisner J, et al: Pericardial window for malignant pericardial effusion. *Ann Thorac Surg* 30(5):465–471, 1980.
21. Levin BH, Aaron BL: The subxiphoid pericardial window. *Surg Gynecol Obstet* 155(6):804–806, 1982.
22. Alcan KE, Zabetakis PM, Marino ND, et al: Management of acute cardiac tamponade by subxiphoid pericardiotomy. *JAMA* 247(8):1143–1148, 1982.
23. Little AG, Kremser PC, Wade JL, et al: Operation for diagnosis and treatment of pericardial effusions. *Surgery* 96(4):738–744, 1984.
24. Palacios IF, Tuzcu EM, Ziskind AA, et al: Percutaneous balloon pericardial window for patients with malignant pericardial effusion and tamponade. *Cathet Cardiovasc Diagn* 22(4):244–249, 1991.
25. Ziskind AA, Rodriguez S, Lemmon C, et al: Percutaneous pericardial biopsy as an adjunctive technique for the diagnosis of pericardial disease. *Am J Cardiol* 74(3):288–291, 1994.
26. Ziskind AA, Burstein S: Echocardiography vs. fluoroscopic imaging. *Cathet Cardiovasc Diagn* 27(1):86–87, 1992.
27. Chow WH, Chow TC, Cheung KL: Nonsurgical creation of a pericardial window using the Inoue balloon catheter. *Am Heart J* 124(4):1100–1102, 1992.
28. Chow WH, Chow TC, Yip AS, et al: Inoue balloon pericardiotomy for patients with recurrent pericardial effusion. *Angiology* 47(1):57–60, 1996.
29. Ohke M, Bessho A, Haraoka K, et al: Percutaneous balloon pericardiotomy by the use of Inoue balloon for the management of recurrent cardiac tamponade in a patient with lung cancer. *Intern Med* 39(12):1071–1074, 2000.
30. Iaffaldano RA, Jones P, Lewis BE, et al: Percutaneous balloon pericardiotomy: a double-balloon technique. *Cathet Cardiovasc Diagn* 36(1):79–81, 1995.
31. Hsu KL, Tsai CH, Chiang FT, et al: Percutaneous balloon pericardiotomy for patients with recurrent pericardial effusion: using a novel double-balloon technique with one long and one short balloon. *Am J Cardiol* 80(12):1635–1637, 1997.
32. Hajduczok ZD, Ferguson DW: Percutaneous balloon pericardiostomy for non-surgical management of recurrent pericardial tamponade: a case report. *Intensive Care Med* 17(5):299–301, 1991.
33. Ready A, Black J, Lewis R, et al: Laparoscopic pericardial fenestration for malignant pericardial effusion. *Lancet* 339(8809):1609, 1992.
34. Hartnell GG: Laparoscopic pericardial fenestration. *Lancet* 340(8821):737, 1992.
35. Sochman J, Peregrin J, Pavcnik D: The cutting pericardiotome: another option for pericardiopleural draining in recurrent pericardial effusion: initial experience. *Int J Cardiol* 77(1):69–74, 2001.
36. Wang N, Feikes JR, Mogensen T, et al: Pericardioperitoneal shunt: an alternative treatment for malignant pericardial effusion. *Ann Thorac Surg* 57(2):289–292, 1994.
37. Ozuner G, Davidson PG, Isenberg JS, et al: Creation of a pericardial window using thoracoscopic techniques. *Surg Gynecol Obstet* 175(1):69–71, 1992.
38. Krasna M, Fiocco M: Thoracoscopic pericardiectomy. *Surg Laparosc Endosc* 5(3):202–204, 1995.
39. Bertrand O, Legrand V, Kulbertus H: Percutaneous balloon pericardiotomy: a case report and analysis of mechanism of action. *Cathet Cardiovasc Diagn* 38(2):180–182, 1996.
40. Block PC: Whither pericardial fluid? *Cathet Cardiovasc Diagn* 38(2):183, 1996.
41. Ziskind AA, Pearce AC, Lemmon CC, et al: Percutaneous balloon pericardiotomy for the treatment of cardiac tamponade and large pericardial effusions: description of technique and report of the first 50 cases. *J Am Coll Cardiol* 21(1):1–5, 1993.
42. Chow LT, Chow WH: Mechanism of pericardial window creation by balloon pericardiotomy. *Am J Cardiol* 72(17):1321–1322, 1993.
43. Sugimoto JT, Little AG, Ferguson MK, et al: Pericardial window: mechanisms of efficacy. *Ann Thorac Surg* 50(3):442–445, 1990.
44. Block PC, Wilson MA: Hemi-balloon dislodgement during a percutaneous balloon pericardial window procedure: removal using a second pericardial catheter. *Cathet Cardiovasc Diagn* 29(4):289–291, 1993.
45. Thanopoulos BD, Georgakopoulos D, Tsaousis GS, et al: Percutaneous balloon pericardiotomy for the treatment of large, nonmalignant pericardial effusions in children: immediate and medium-term results. *Cathet Cardiovasc Diagn* 40(1):97–100, 1997.
46. Vaitkus PT, Herrmann HC, LeWinter MM: Treatment of malignant pericardial effusion. *JAMA* 272(1):59–64, 1994.
47. Stoll HP, Carlson K, Keefer LK, et al: Pharmacokinetics and consistency of pericardial delivery directed to coronary arteries: direct comparison with endoluminal delivery. *Clin Cardiol* 22(1 Suppl 1):I10–I16, 1999.

48. Sosa E, Scanavacca M, d'Avila A, et al: A new technique to perform epicardial mapping in the electrophysiology laboratory. *J Cardiovasc Electrophysiol* 7(6):531–536, 1996.
49. Strickberger SA: Pericardial space exploration for ventricular tachycardia mapping: should the countdown begin? *J Cardiovasc Electrophysiol* 7(6):537–538, 1996.
50. Sosa E, Scanavacca M, D'Avila A, et al: Endocardial and epicardial ablation guided by nonsurgical transthoracic epicardial mapping to treat recurrent ventricular tachycardia. *J Cardiovasc Electrophysiol* 9(3):229–239, 1998.
51. Sosa E, Scanavacca M, d'Avila A, et al: Nonsurgical transthoracic epicardial catheter ablation to treat recurrent ventricular tachycardia occurring late after myocardial infarction. *J Am Coll Cardiol* 35(6):1442–1449, 2000.
52. Schweikert RA, Saliba WI, Tomassoni G, et al: Percutaneous pericardial instrumentation for endo-epicardial mapping of previously failed ablations. *Circulation* 108(11):1329–1335, 2003.
53. Laham RJ, Simons M, Hung D: Subxyphoid access of the normal pericardium: a novel drug delivery technique. *Catheter Cardiovasc Interv* 47(1):109–111, 1999.
54. Mickelsen SR, Ashikaga H, DeSilva R, et al: Transvenous access to the pericardial space: an approach to epicardial lead implantation for cardiac resynchronization therapy. *Pacing Clin Electrophysiol* 28(10):1018–1024, 2005.
55. Rodrigues AC, d'Avila A, Houghtaling C, et al: Intrapericardial echocardiography: a novel catheter-based approach to cardiac imaging. *J Am Soc Echocardiogr* 17(3):269–274, 2004.
56. Macris MP, Igo SR: Minimally invasive access of the normal pericardium: initial clinical experience with a novel device. *Clin Cardiol* 22(1 Suppl 1):I36–I39, 1999.
57. Hou D, March KL: A novel percutaneous technique for accessing the normal pericardium: a single-center successful experience of 53 porcine procedures. *J Invasive Cardiol* 15(1):13–17, 2003.
58. Endrys J, Simo M, Shafie MZ, et al: New nonsurgical technique for multiple pericardial biopsies. *Cathet Cardiovasc Diagn* 15(2): 92–94, 1988.
59. Mehan VK, Dalvi BV, Lokhandwala YY, et al: Use of guiding catheters to target pericardial and endomyocardial biopsy sites. *Am Heart J* 122(3 Pt 1):882–883, 1991.
60. Selig MB: Percutaneous pericardial biopsy under echocardiographic guidance. *Am Heart J* 122(3 Pt 1):879–882, 1991.
61. Margey R, Suh W, Witzke C, et al: Percutaneous pericardial biopsy: a novel interventional technique to aid diagnosis and management of pericardial disease. Abstract presented at the Transcatheter Cardiovascular Therapeutics (TCT) meeting, September 2010; Washington, DC.
62. Seferovic PM, Ristic AD, Maksimovic R, et al: Diagnostic value of pericardial biopsy: improvement with extensive sampling enabled by pericardioscopy. *Circulation* 107(7):978–983, 2003.
63. Bartus K, Han FT, Bednarek J, et al: Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. *J Am Coll Cardiol* 62(2):108–118, 2013.
64. Price MJ, Gibson DN, Yakubov SJ, et al: Early safety and efficacy of percutaneous left atrial appendage suture ligation: results from the U.S. Transcatheter LAA Ligation Consortium. *J Am Coll Cardiol* 64(6):565–572, 2014.

57 Transcatheter Therapies for Congenital Heart Disease

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KEY POINTS

- Catheter-based therapies are available for a wide variety of congenital structural cardiovascular defects.
- Balloon dilation provides relief of obstruction for patients with congenital pulmonary or aortic valve stenosis. This therapy may not be adequate if the valve is hypoplastic or calcified.
- Congenital pulmonary artery stenosis can be effectively relieved with balloon-expandable stents; late stent redilation may be necessary in a growing child.
- Coarctation of the aorta can be treated with balloon-expandable stenting; covered stents may provide an important safety advantage for older patients with a fragile aorta.
- Transcatheter occlusion devices are available to safely and effectively treat a secundum-type arterial septal defect or a patent ductus arteriosus.
- Transcatheter pulmonary valve replacement is effective therapy in patients who have a dysfunctional right ventricle–to–pulmonary artery conduit or a bioprosthetic pulmonary valve, as in postoperative tetralogy of Fallot.

This chapter summarizes the current state of the art of transcatheter therapy for structural congenital heart disease (CHD). It discusses catheter-based therapies that are available for some of the more common congenital defects, including semilunar valve stenosis, pulmonary artery (PA) stenosis, coarctation of the aorta, secundum atrial septal defect (ASD), and patent ductus arteriosus (PDA). New developments in transcatheter pulmonary valve replacement (TPVR) are also reviewed.

Percutaneous balloon valvuloplasty provides effective treatment in patients with congenital pulmonary or aortic valve stenosis. Surgical valvotomy for congenital semilunar valve stenosis has been replaced by these interventional catheterization techniques in most pediatric centers. Balloon-expandable stenting is standard therapy for most patients with PA stenosis. These arterial lesions often are elastic in nature—a characteristic that makes balloon angioplasty alone a less successful intervention. Coarctation stenting is an effective therapeutic intervention for selected patients with coarctation of the aorta. Transcatheter occlusion devices provide a safe, highly effective therapy for a secundum ASD or a PDA and constitute the treatment of choice for these defects. Finally, TPVR is now routine therapy for selected patients with a dysfunctional right ventricle–to–pulmonary artery (RV-PA) conduit or bioprosthetic pulmonary valve (BPV); this remarkable new intervention can replace reoperation and is therefore an important therapeutic option for many patients.

PULMONARY BALLOON VALVULOPLASTY

Pulmonary valve stenosis is a common disorder, accounting for approximately 8% of congenital cardiac defects.[1] Except for neonates with critical pulmonary stenosis, patients with untreated pulmonary valve stenosis often survive well into adulthood.[2] However, when more than mild obstruction to right ventricular (RV) outflow is present, pulmonary valve stenosis should be relieved to prevent progression of obstruction,[3] RV hypertrophy, myocardial fibrosis, and dysfunction. Left untreated, significant pulmonary valve stenosis eventually produces clinical symptoms such as fatigue, dyspnea, and exercise intolerance. These long-term sequelae can be avoided if pulmonary valve stenosis is treated in childhood. Nevertheless, treatment is indicated at any age if hemodynamically significant pulmonary stenosis is documented. Since its introduction in 1982 by Kan and associates,[4] percutaneous balloon valvuloplasty has been shown to provide substantial relief of right ventricular outflow tract (RVOT) obstruction in patients with valvular pulmonary stenosis. Balloon pulmonary valvuloplasty can be performed safely and is minimally invasive. It is therefore regarded as the treatment of choice for patients with moderate to severe isolated pulmonary valve stenosis.

In congenital pulmonary valve stenosis, the valve leaflets are thickened and the commissures are fused to varying degrees. The lines of commissural fusion may appear as two or three raphes extending from the valve annulus to a small central orifice.[5] During childhood and young adulthood, the pulmonary valve leaflets are typically supple, doming upward during systole (Fig. 57-1). In older adults, pulmonary valve calcification may occur and may lead to diminished leaflet mobility. A less common form of pulmonary stenosis has been referred to as *pulmonary valve dysplasia* or *dysplastic pulmonary valve* syndrome.[5,6] It often occurs as a familial trait or as part of Noonan syndrome. A dysplastic pulmonary valve is characterized by thick, cartilaginous valve leaflets with poor mobility. The pulmonary valve annulus is often hypoplastic, and there may be little or no commissural fusion.

In isolated pulmonary valve stenosis, balloon dilation reduces the degree of valvular obstruction by separating fused commissures or by tearing the valve leaflets themselves.[7,8] Patients with severe pulmonary valve dysplasia with hypoplasia of the annulus and absence of commissural fusion may have minimal improvement after balloon valvuloplasty.[9] However, because a spectrum of pulmonary valve dysplasia exists, some patients with this disorder may derive substantial benefit from the balloon valvuloplasty procedure.[10]

Indications for Intervention

In contrast to balloon aortic valvuloplasty, the indications for intervention in balloon pulmonary valvuloplasty have been relatively constant over time and closely correlate with the surgical indications for valvuloplasty. Additionally, the peak instantaneous pressure gradients measured by echocardiography correlate more closely with resting peak systolic gradients in the catheterization laboratory. For this reason, most physicians refer patients for catheterization and balloon valvuloplasty once the echocardiographic peak instantaneous pressure gradient is 40 mm Hg or higher or symptoms develop. The current recommendations for performing balloon pulmonary valvuloplasty are as follows[11]:

- Critical pulmonary stenosis, defined as pulmonary stenosis in a cyanotic infant requiring a PDA to provide adequate pulmonary blood flow
- Resting catheterization peak systolic ejection gradient or echocardiographic peak instantaneous pressure gradient 40 mm Hg or greater
- Resting catheterization or echocardiographic gradient less than 40 mm Hg in the setting of RV dysfunction or symptoms

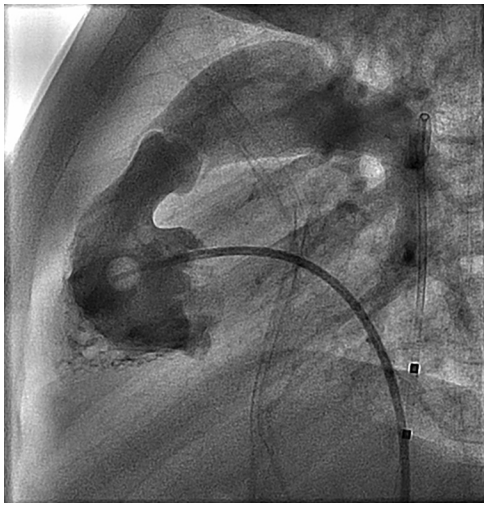

FIGURE 57-1 Lateral right ventricular angiogram in a child with congenital pulmonary valve stenosis. The valve is thickened and domed in systole. There is poststenotic dilation of the main pulmonary artery.

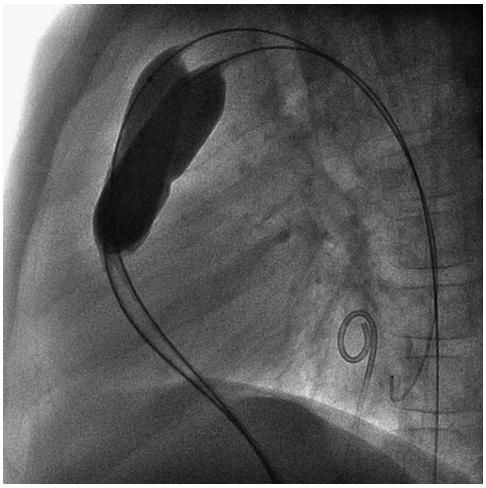

FIGURE 57-2 Double-balloon pulmonary valve dilation in a child with pulmonary valve stenosis. Two balloons may be used if a single-balloon catheter requires a sheath that is thought to be too large for the child's femoral vein or if the valve annulus is too large for a single balloon.

For patients with a dysplastic pulmonary valve who meet these criteria, balloon valvuloplasty is an acceptable option, although the results may not be satisfactory, as discussed later.

Other indications for balloon pulmonary valvuloplasty, which are not discussed in this text, include treatment for pulmonary atresia with an intact ventricular septum but without RV-dependent coronary circulation and as a palliative procedure for patients with cyanotic CHD associated with pulmonary stenosis (e.g., tetralogy of Fallot [TOF]).

Technique

Balloon pulmonary valvuloplasty is usually performed with a percutaneous transfemoral venous approach. Right heart catheterization documents the severity of the lesion. RV angiocardiography is performed to confirm the nature of the lesion and to measure the diameter of the pulmonary valve annulus. Typically, the lateral projection is best suited to this purpose. Once the decision is made to proceed with valvuloplasty, an end-hole catheter is advanced to the left PA. The left PA provides better wire and balloon stability than a right PA position. We recommend crossing the tricuspid valve with a balloon-tipped catheter, whenever possible. This helps to prevent positioning of the catheter and wire between tricuspid valve cords and lowers the risk of tricuspid valve injury during balloon valvuloplasty. An exchange-length guidewire is advanced to the distal left PA, and the end-hole catheter is removed. The balloon valvuloplasty catheter is then inserted over the exchange wire. A balloon valvuloplasty catheter is used whose inflated balloon diameter is approximately 15% to 25% larger than the pulmonary valve annulus diameter. Balloon oversizing improves valvuloplasty effectiveness, and injury to the pulmonary valve annulus is unlikely when balloons smaller than 140% of the annulus's diameter are used.[12,13]

If the pulmonary valve annulus exceeds 25 mm or if the single-balloon catheter required is too large for safe introduction into a patient's femoral vein, we recommend a double-balloon technique, with two balloons positioned across the valve and inflated simultaneously (Fig. 57-2). The effective dilating diameter of two equal-sized balloons can be calculated based on cross-sectional area or on circumference. The sum of the balloon diameters by the circumference method is 120% of the equivalent single-balloon diameters, and by the area method it is 130%. Therefore the operator first selects the optimal single-balloon size, multiplies this diameter by 1.2 or 1.3, and then selects two balloons whose diameters are half of that product. Once inserted, the balloon valvuloplasty catheter is advanced across the valve and positioned with the valve at the midportion of the balloon. Partial balloon inflation, with a mixture of saline and contrast, is helpful to determine the precise location of the valve on the balloon. Care should be taken to avoid inflating the balloon across the tricuspid valve, which can result in tricuspid valve injury.

The valvuloplasty balloon or balloons are then inflated by hand until the waist produced by the valve on the balloon disappears. The period of balloon inflation is kept as brief as possible to minimize obstruction to RV outflow. Typically, three or four balloon inflations are performed with minor adjustments in balloon position to ensure adequate dilation of the pulmonary valve. After the dilation is completed, the valvuloplasty catheter is withdrawn and replaced with a diagnostic catheter. The residual RVOT gradient and cardiac output are measured to document the effectiveness of the procedure. A repeat RV angiogram may be performed if necessary to document the degree of subvalvular infundibular narrowing (which may be increased immediately after valvuloplasty) present at this point (Fig. 57-3).

Infants

Newborns and infants with critical pulmonary stenosis or atresia are frequently critically ill and hypoxemic (because of a right-to-left atrial shunt) and may have associated hypoplasia of the RV and tricuspid valve (Fig. 57-4). Because of these factors, in addition to the presence of severe RVOT obstruction, it is a technical challenge to successfully catheterize the PA and properly position a valvuloplasty balloon across the RVOT in these infants.[14-18] In infants with critical pulmonary stenosis, we prefer to perform the procedure with the child receiving prostaglandin E_1 infusion, for three reasons: first, the infant is in a more stable hemodynamic state during the procedure; second, a left-to-right ductal shunt maintains pulmonary blood flow during balloon occlusion of the RVOT; and third, the presence of a PDA allows the exchange guidewire to be positioned across the pulmonary valve and into the descending aorta, a course that facilitates catheter exchanges and subsequent valve dilation.

Acute Results

In patients with isolated pulmonary valve stenosis, percutaneous balloon valvuloplasty can be expected to provide excellent relief of obstruction (Fig. 57-5). Numerous studies have clearly documented significant acute reduction in the peak systolic pulmonary valve gradient to 30 mm Hg or less (i.e., mild residual stenosis). In their landmark 1982 report, Kan and colleagues reported the acute effects

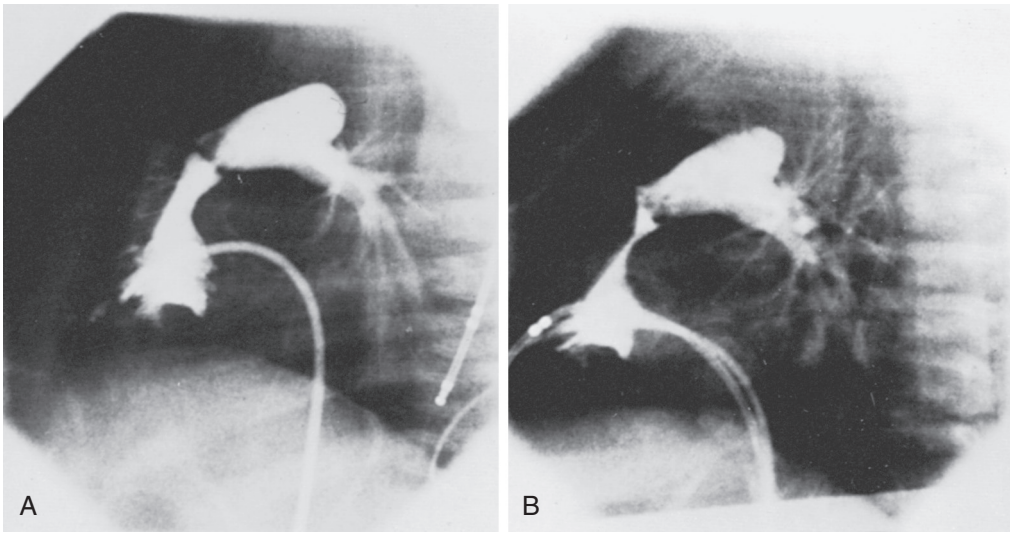

FIGURE 57-3 Lateral right ventricular angiogram before (**A**) and immediately after (**B**) valvuloplasty in an infant with pulmonary stenosis. There is marked systolic narrowing of the right ventricular infundibulum after valvuloplasty that was not present before the procedure. Such dynamic infundibular narrowing may account for some residual gradient that may be measured immediately after the procedure and typically improves with time.

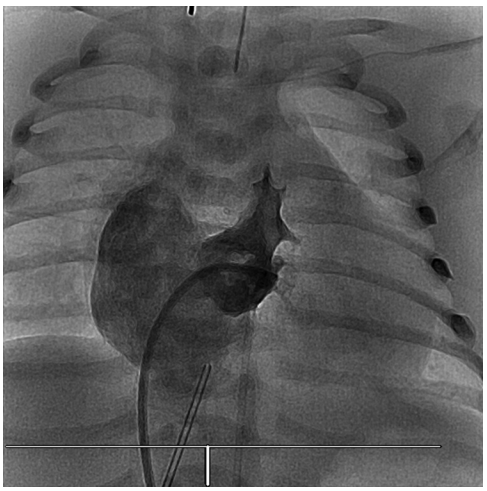

FIGURE 57-4 Anteroposterior right ventricular angiogram in a newborn with pulmonary valve atresia and right ventricular hypoplasia. The right ventricle is small, and its outflow tract is evident immediately beneath the imperforate pulmonary valve. There was significant tricuspid regurgitation.

of valvuloplasty in an 8-year-old child with pulmonary stenosis.[4] The procedure decreased the peak gradient from 48 to 14 mm Hg and was performed without significant complications. Other studies have confirmed this initial observation that valvuloplasty provides impressive gradient relief acutely.[12,14-16,19-24]

The largest published clinical series of balloon pulmonary valvuloplasty was reported by the Pediatric Valvuloplasty Registry.[19] This registry reported the acute results of pulmonary valvuloplasty performed in 784 patients between 1981 and 1986. Overall, balloon dilation resulted in an acute decrease in the peak systolic pressure gradient from 71 to 28 mm Hg. The residual pressure gradients immediately after valvuloplasty were ascribed in part to subvalvular infundibular obstruction related to RV hypertrophy. Effectiveness of the procedure was not related to age (the series included 35 adults older than 21 years), but a larger residual gradient was observed in patients with a dysplastic pulmonary valve. The Pediatric Valvuloplasty Registry described five major complications (0.6%), primarily confined to infancy. There were two procedure-related deaths (0.2%), and in one neonate RVOT perforation and tamponade occurred. Two children developed severe tricuspid regurgitation related to injury to the tricuspid valve apparatus. Minor complications included femoral venous thrombosis, hemorrhage, and transient arrhythmias.

Several other studies have shown similar results, including data from the Congenital Cardiac Catheterization Outcomes Project (C3PO),[23] which included 211 cases from eight institutions between 2007 and 2010. The overall procedural success rate was 91% with 88% of patients obtaining a reduction in the valve gradient to less than 25 mm Hg. The independent risk factors for procedural failure on multivariate analysis were the presence of supravalvular stenosis and evidence of a dysplastic pulmonary valve. Only one patient had a life-threatening adverse event (ventricular fibrillation). Although the overall rate of adverse events was 12%, most of these were mild; only 3% of patients experienced a more severe adverse event. An important finding of this study was that 6% of neonates and 2% of adults required reintervention.

Adults

Several reports have described the successful application of percutaneous balloon valvuloplasty for treatment of adults with pulmonary valve stenosis.[20,22,25-36] Table 57-1 summarizes the pertinent clinical and hemodynamic data from 14 publications describing the acute results of pulmonary valvuloplasty in adolescents and adults. Pulmonary valvuloplasty has been performed successfully in patients as old as 84 years. In most published cases, a single-balloon technique has been used. When a 20- to 25-mm-diameter balloon was insufficient, however, the double-balloon technique has often been necessary.

In these reports, balloon valvuloplasty acutely reduced the peak systolic gradient by 60% to 65%, from a range of 53 to 260 mm Hg before the procedure to 2 to 90 mm Hg after valvuloplasty. In most cases, the peak systolic gradient immediately after valvuloplasty was in the mild range (20 to 40 mm Hg). In one report, there was a significant improvement in New York Heart Association (NYHA) classification in adults 30 days after valvuloplasty.[36] Therefore the available data clearly indicate that percutaneous balloon valvuloplasty provides effective therapy in adults as well as in children with congenital pulmonary valve stenosis. Balloon valvuloplasty appears to be effective even in the oldest patients, in whom valve calcification may be present.[25]

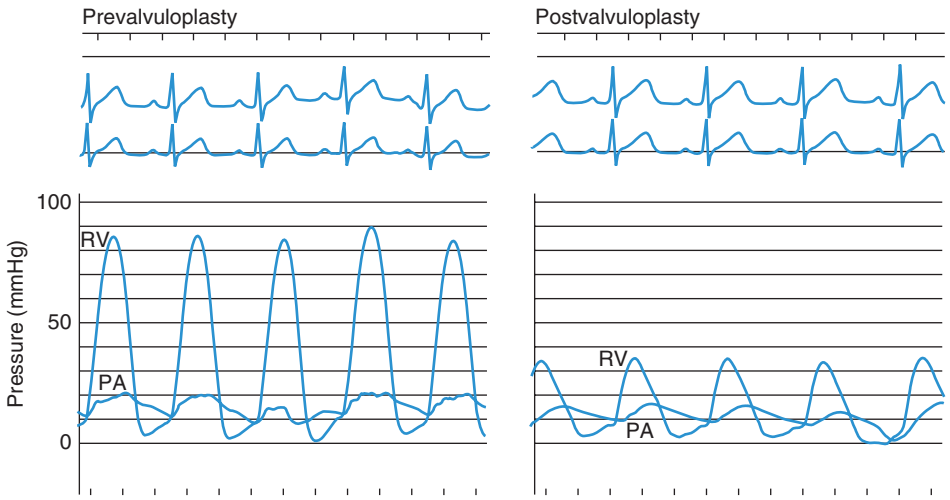

FIGURE 57-5 Simultaneous right ventricular (RV) and pulmonary artery (PA) pressure recordings before and immediately after pulmonary valve dilation in a 15-month-old boy with severe pulmonary stenosis. The right ventricular systolic pressure was reduced from 86 to 36 mm Hg. The pulmonary valve systolic gradient decreased from 66 to 20 mm Hg (pressure recordings were made on the same scale).

TABLE 57-1 Summary of Published Reports of Pulmonary Valvuloplasty in Adults

Study (Author)	No. of Patients	Age Range (yr)	Balloon Technique	PEAK SYSTOLIC GRADIENT (mm Hg)	
				Before	After
Tentolouris[25]	1	84	Double	70	34
Herrmann[26]	8	23-66	Single	66	22
Sherman[27]	4	48-67	Single (3) Double (1)	109	38
Al Kasab[22]	12	21-37	Double	86	28
Fawzy[28]	8	21-45	Double	107	36
Flugelman[29]	1	62	Single	260	90
Presbitero[30]	3	21-45	Single	130	29
Park[31]	3	24-40	Double	108	51
Cooke[32]	1	61	Single	105	13
Leisch[33]	6	21-59	Single	78	38
Shuck[34]	1	23	Single	30	2
Pepine[20]	1	59	Single	130	30
Chen[35]	53	13-55	Single	191	38
Taggart[36]	40	18-82	Single (12) Double (8)	54	22

Long-Term Results

Long-term studies of balloon pulmonary valvuloplasty have confirmed that the benefits of this procedure are durable and comparable to the results of surgical valvotomy.[24,37-41] In several studies, the degree of residual stenosis remained low (<40 mm Hg, below the current indications for intervention).[24,37-39,41] In the Pediatric Valvuloplasty Registry, 16% of patients required reintervention with either repeat valvuloplasty or surgical valvotomy during a follow-up period of 8.7 years.[38] Independent risk factors for a suboptimal late outcome included small valve annulus diameter, higher early residual gradient, smaller ratio of balloon-to-annulus diameter, and earlier year at initial intervention. This is similar to what we have found in our own long-term follow-up data.[39]

Pulmonary insufficiency, typically mild to moderate, is a common late complication of balloon pulmonary valvuloplasty.[24,40-41] Resultant RV dilation correlates with the degree of pulmonary insufficiency.[40-41] However, pulmonary valve replacement, even in patients who develop RV dilation, has typically not been required for these patients.[41] In a study we performed comparing patients undergoing balloon valvuloplasty to an age-matched cohort of surgical patients,[39] although the residual gradient was slightly less after surgery (16 vs. 24 mm Hg, respectively; $P = .01$), the surgical group had significantly more pulmonary valve insufficiency and late ventricular arrhythmias.

In one study,[40] mild or moderate pulmonary regurgitation was associated with impaired exercise capacity, specifically lower peak oxygen consumption, when compared with lesser amounts of regurgitation (85% ± 17% vs. 96% ± 16% of predicted; $P = .03$). In the same study, RV dilation (end-diastolic volume z-score >2) was present in 40% of the study group, and the indexed end-diastolic volume of the RV correlated with the pulmonary regurgitation fraction ($R = .79$; $P < .001$). These results suggest that relatively modest amounts of pulmonary regurgitation may result in long-term RV dilation and reduced exercise tolerance. Alternatively, these results may simply reflect the severe nature of the pulmonary stenosis in these patients before intervention and the aggressive balloon dilation procedures required: median age at intervention was 0.2 years; median RV-to-aorta pressure ratio was

110% before valvuloplasty; and median balloon-to-annulus diameter ratio was 1.3 (range 1.0 to 2.0).

Late follow-up data, therefore, document excellent long-term results after percutaneous pulmonary balloon valvuloplasty and support the use of this procedure as the treatment of choice for patients with isolated valvular pulmonary stenosis.

Complications

Beyond infancy, percutaneous balloon pulmonary valvuloplasty is a very safe procedure. In the Pediatric Valvuloplasty Registry, the only two deaths occurred in infants with critical pulmonary stenosis, and the single case of perforation and tamponade occurred in an 8-day-old neonate.[19] Minor complications were primarily related to vascular injury or hemorrhage and were also much more common during the first 12 months of life. Overall, the Pediatric Valvuloplasty Registry reported a 1.2% to 1.8% frequency of major complications and a 4.8% frequency of minor complications in 168 infants. In contrast, in 656 children and adults, the frequency of major complication was 0.8% and the frequency of minor complication was 1.7%.

In the C3PO study of 211 balloon pulmonary valvuloplasty procedures in the current era across several institutions,[23] the overall adverse event rate was 12%, and most of these (79%) were of low severity. Again, neonates were more likely to experience adverse events (19% vs. 6%). In the overall cohort, the most common type of adverse event was transient arrhythmias and conduction abnormalities, which were seen in 5% of patients.

There have been no reports of long-term arrhythmias after valvuloplasty. Valvuloplasty may cause injury to the femoral vein, especially when the procedure is performed in infancy. As discussed earlier, the mild pulmonary valve insufficiency commonly seen after pulmonary valvuloplasty, while perhaps not entirely benign,[40] is rarely of clinical importance and may be less severe than after surgical valvotomy.[39]

Conclusions and Recommendations

Percutaneous balloon pulmonary valvuloplasty is the treatment of choice for children and adults with isolated congenital valvular pulmonary stenosis. Valvuloplasty successfully reduces significant RVOT obstruction, with a residual gradient that is usually in the trivial to mild range (i.e., <30 mm Hg). Follow-up studies have documented long-term effectiveness, with little restenosis. Late pulmonary insufficiency is common and may cause RV dilation, but need for pulmonary valve replacement is atypical. Pulmonary valvuloplasty is indicated in neonates with critical pulmonary stenosis and in patients of any age with isolated pulmonary valve stenosis whose resting peak systolic pressure gradient exceeds 40 mm Hg in the presence of a normal cardiac output.

AORTIC BALLOON VALVULOPLASTY

Aortic valve stenosis accounts for 4% to 6% of all cases of CHD.[42] Left ventricular (LV) outflow tract obstruction elicits LV hypertrophy and myocardial fibrosis, which may eventually lead to LV dysfunction and congestive heart failure. Unlike most cases of congenital pulmonary valve stenosis, congenital aortic stenosis tends to progress over time.[38,43]

Successful percutaneous balloon valvuloplasty in children with congenital aortic valve stenosis was first reported in 1984 by Lababidi and colleagues.[44,45] Balloon valvuloplasty typically reduces the LV outflow tract obstruction to the mild range, and at most centers, it is the treatment of choice for children with congenital aortic stenosis who require intervention. In the last 30 years, there have been a few changes to the technique but considerable debate on the indications for percutaneous intervention.

Indications for Intervention

The current recommended indications for aortic valvuloplasty reflect the 2011 scientific statement from the American Heart Association.[11]

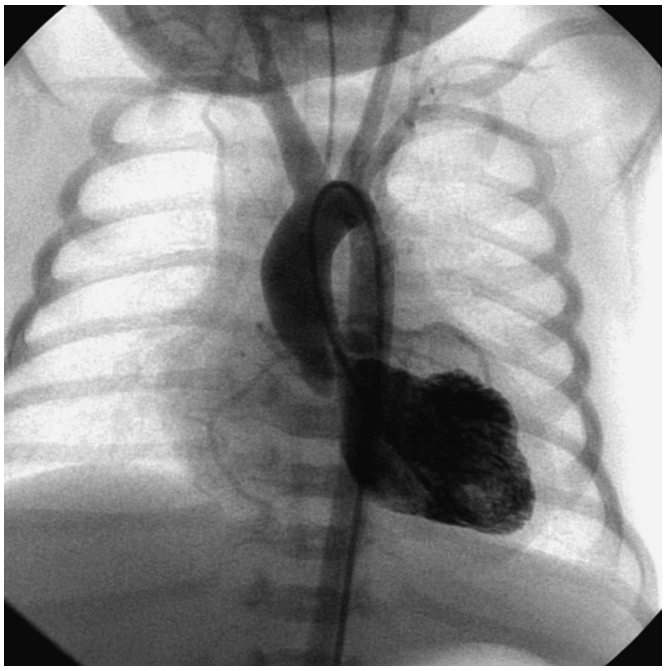

FIGURE 57-6 Anteroposterior left ventricular angiogram in a newborn with critical aortic valve stenosis. The aortic valve leaflets are thickened, and there is severe left ventricular dysfunction.

The gradient criteria listed are resting peak systolic gradients measured in the catheterization laboratory with the patient sedated. Extrapolation to echocardiogram-derived Doppler peak instantaneous pressure gradients or mean gradient is not reliable, especially in the setting of aortic insufficiency.[46] Additionally, given the impact of general anesthesia on systemic blood pressure, resting gradients should be obtained under light conscious sedation whenever possible.

Infants

Aortic balloon valvuloplasty is indicated for infants with critical aortic stenosis, which is defined as isolated aortic stenosis with either depressed LV systolic function or evidence of ductal dependency to maintain adequate cardiac output. Infants with critical aortic stenosis typically have severe congestive heart failure and shock with profound LV dysfunction (Fig. 57-6). Notably, the gradient across the aortic valve does not reflect the degree of aortic stenosis because of poor ventricular function and low anterograde flow across the aortic valve.

Children and Young Adults

In isolated valvular aortic stenosis, aortic balloon valvuloplasty is indicated in children with either of the following:

- Resting peak systolic gradient 50 mm Hg or higher
- Resting peak systolic gradient 40 mm Hg or higher if there are any symptoms (e.g., anginal chest pain, syncope) or ischemic changes on either resting or exercise electrocardiography (ECG)

Less well-established indications are:

- Resting peak systolic gradient 40 mm Hg or higher without symptoms or ischemic ECG changes in a patient who plans to become pregnant or to participate in competitive sports
- Resting peak systolic gradient less than 50 mm Hg in heavily sedated or anesthetized patients if the echocardiographically derived mean gradient is more than 50 mm Hg

Aortic valvuloplasty is not indicated in patients with a resting peak systolic gradient of less than 40 mm Hg who are without symptoms or ischemic ECG changes, nor in patients with severe insufficiency who have a surgical indication for aortic valve repair or replacement.

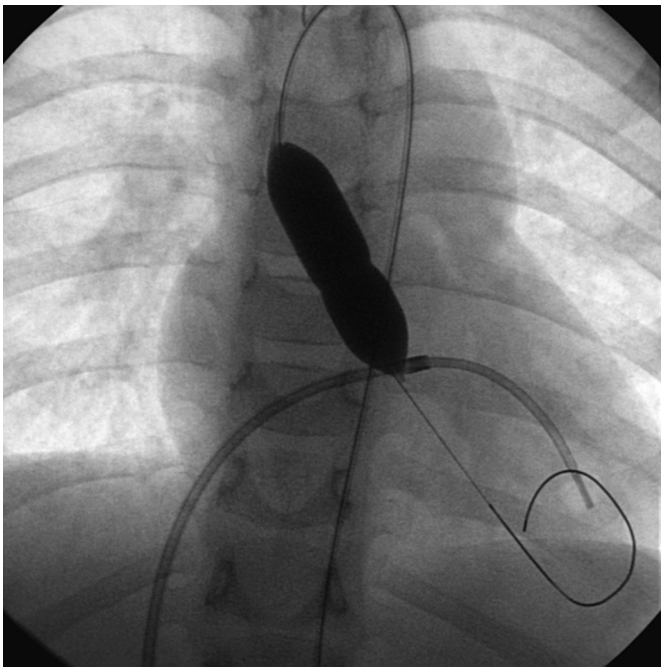

FIGURE 57-7 Balloon dilation in a child with severe aortic valve stenosis. The waist produced by the valve annulus on the balloon is evident. Ventricular pressure was monitored throughout the procedure by a catheter placed in the left ventricle through a transseptal puncture.

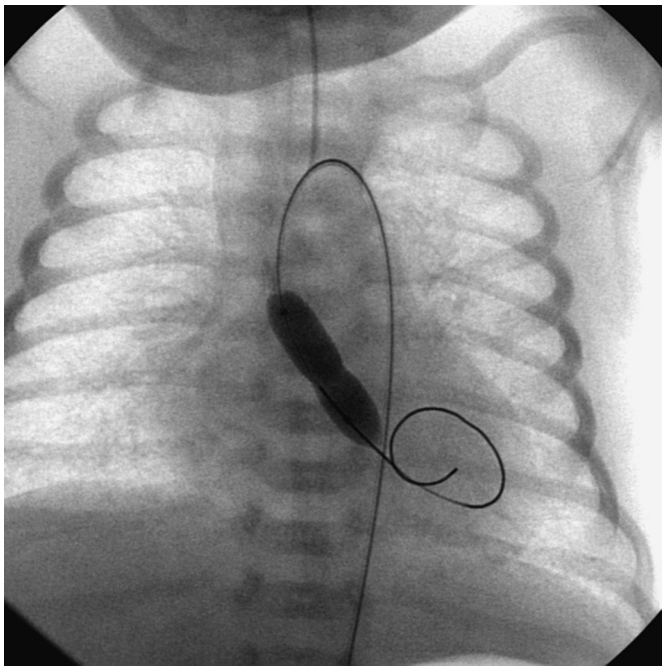

FIGURE 57-8 Balloon dilation in a newborn with critical aortic stenosis (same patient as in Fig. 57-6). The catheter was introduced through the umbilical artery, thereby avoiding potential femoral artery injury in a newborn with low cardiac output.

Technique

Percutaneous aortic valvuloplasty is usually performed from a retrograde transarterial approach, although the antegrade transseptal approach can also be used. In infants, alternative approaches include the carotid artery and the umbilical artery (see later discussion). We prefer the retrograde approach and use a transseptal catheter for continuous LV pressure monitoring throughout the procedure. After the transseptal puncture is accomplished, heparin is administered to increase the activated clotting time (ACT) to approximately 250 to 300 seconds. The aortic stenosis gradient is measured before angiography with simultaneous ventricular and aortic pressure recordings. Alternatively, a single catheter with both end and side holes can be used to simultaneously measure the LV and aortic pressures. Aortic root and LV angiography are helpful to determine the baseline aortic insufficiency and measure the aortic valve annulus.

Once the decision has been made to proceed with balloon valvuloplasty (see indications described previously), a balloon with the proper diameter is chosen. This diameter is based on the aortic valve annulus diameter, which can be measured by echocardiography or by angiography. Typically, the balloon diameter is 90% to 100% of the aortic valve diameter. Unlike pulmonary balloon valvuloplasty, oversized balloons are not used for aortic valvuloplasty because they have been shown to increase the risk of injury to the aortic valve and annulus.[47] The single-balloon technique, as opposed to the double-balloon technique (which requires two arterial access points) is chosen primarily after consideration of the femoral arterial size to minimize the risk of femoral arterial injury. In our experience, a double-balloon technique is rarely needed until the aortic annulus is larger than 25 mm.

The balloon or balloons are inflated until the waist produced on the balloon by the valve is relieved (Fig. 57-7). Balloon inflation is kept as brief as possible to minimize arterial hypotension during the procedure. To minimize balloon movement during inflation, which has been suggested to cause increased aortic insufficiency during valvuloplasty, rapid ventricular pacing may be performed via a venous access site to temporarily lower stroke volume.[48,49] After valvuloplasty, repeat measurements of LV and aortic pressures and aortic root angiography are performed to quantify the residual aortic stenosis gradient and degree of resultant aortic insufficiency.

Newborn Critical Aortic Stenosis

In newborns with critical aortic stenosis, prostaglandin E_1 infusion is initiated to maintain patency of the ductus arteriosus and support cardiac output. Intravenous inotropic support, and occasionally extracorporeal membrane oxygenation support, may be required to stabilize the patient before the procedure. Often, a transumbilical approach (Fig. 57-8) is used to spare the infant's femoral artery (which may be required for future percutaneous valve dilation procedures).

The carotid artery[50] and transvenous antegrade[51] approaches have also been reported as means to avoid femoral artery injury in small infants. The carotid approach can be accomplished by a cut-down procedure or by percutaneous access with ultrasound guidance. This route provides a relatively direct access to the aortic valve and is especially useful in low-birth-weight neonates with critical aortic stenosis. A single-balloon technique is employed with a single inflation. In contrast, McElhinney and colleagues[52] reported starting with smaller balloons and performing serial dilations with progressively larger balloons until the desired degree of relief was obtained.

Rapid ventricular pacing is not necessary to stabilize the balloon during inflation given the depressed LV function. The most challenging aspect of the procedure is often crossing the aortic valve. Special care must be taken to avoid perforation of an aortic valve leaflet (by crossing with a very soft wire), because severe aortic insufficiency due to leaflet tear is poorly tolerated.

Acute Results

Since its first description, the effectiveness of balloon valvuloplasty in children and adolescents with congenital aortic valve stenosis has been clearly demonstrated, and the results have proved comparable to those of surgical valvotomy.[43,47,53-61] The Pediatric Valvuloplasty Registry,[53,59]

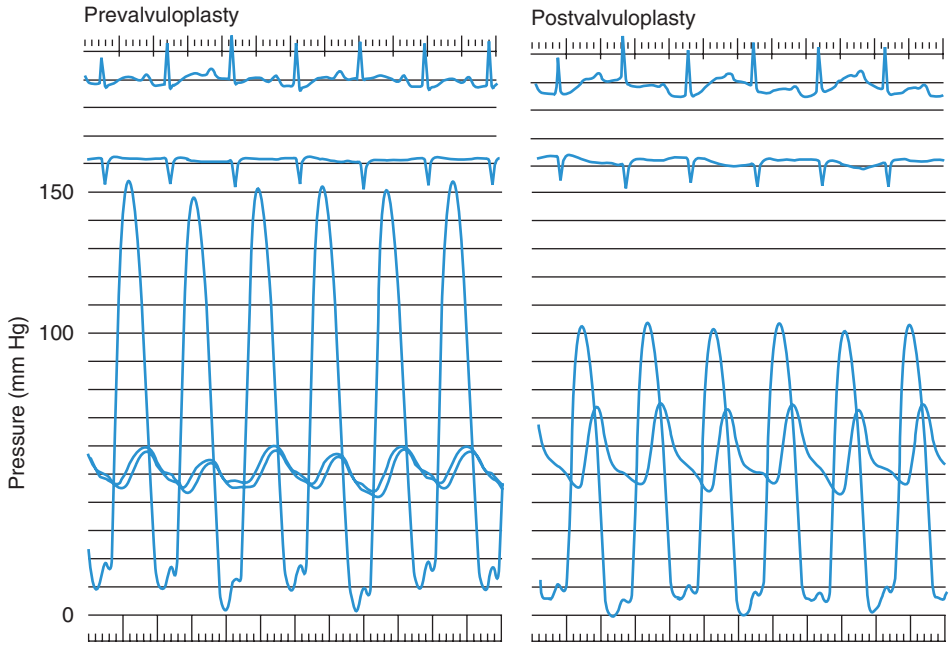

FIGURE 57-9 Aortic and left ventricular pressure tracings in an 11-day-old infant with critical aortic stenosis, measured before and immediately after balloon dilation. The peak systolic gradient decreased from 96 to 29 mm Hg. Notice the improved aortic pulse pressure after valvuloplasty, which is indicative of an improved cardiac output. (From Beekman RH, Rocchini AP, Andes A: Balloon valvuloplasty for critical aortic stenosis in the newborn: influence of new catheter technology. *J Am Coll Cardiol* 17:1172-1176, 1991.)

the largest series of balloon aortic valvuloplasty procedures for congenital aortic stenosis, reported the acute results of 630 balloon valvuloplasty procedures in 606 children (age 1 day to 18 years) at 23 institutions between 1984 and 1992. The procedure usually produced an immediate 60% decrease in peak systolic gradient across the aortic valve[53] (Fig. 57-9). The mortality rate was 2.4% and was primarily limited to newborns; there were no deaths in patients older than 3 months of age.

Severe aortic regurgitation is uncommon. Vascular complications have been limited primarily to neonates and young infants and have diminished in recent years with the development of lower-profile sheaths and catheters.

Traditionally, a good procedural result was a residual aortic valve gradient of 20 to 40 mm Hg[47,53-59] with little to no worsening of the aortic insufficiency. In single-center series, some degree of aortic insufficiency is common after aortic balloon valvuloplasty, and several studies have shown that the degree of aortic insufficiency, like the degree of aortic stenosis, progresses over time.[62-65] It is less clear how procedural technique (including the use of rapid ventricular pacing) and patient selection affect both the occurrence and the progression of aortic insufficiency after valvuloplasty.

Long-term follow-up data of 509 and 272 patients who underwent valvuloplasty at single institutions revealed relatively high rates of aortic reintervention and aortic valve replacement.[63,65] In the study by Brown and colleagues,[63] a very interesting finding was that patients with residual gradients less than 35 mm Hg and with moderate or severe aortic insufficiency immediately after dilation were no more likely to require late aortic valve replacement than patients with residual gradients greater than 35 mm Hg with mild insufficiency. These data suggest that a more aggressive balloon valvuloplasty to obtain lower residual gradients, even at the cost of creating more aortic insufficiency, may be better for patients in the long term. Similar results were found in the other large follow-up study.[65] However, there are limitations to generalizing the results of a single-center experience, especially when the primary outcome measures of aortic reintervention and aortic valve replacement are highly dependent on timing of referral. Timing of referral across the United States is largely influenced by era, surgeon preference, and heterogenous practice variation even within institutions.

The effectiveness of balloon dilation, in terms of both acute success and long-term freedom from reintervention, likely relates to the underlying morphologic substrate.[66] If a technically adequate balloon dilation fails to achieve a satisfactory hemodynamic result in a patient with congenital aortic valve stenosis, a more complex diagnosis is suggested; such patients may be found to have annular hypoplasia or valve leaflet calcification. Most congenitally stenotic aortic valves are bicuspid, involving a single central or eccentric commissure with a variable degree of fusion of its edges. The valve leaflets themselves are thickened but are rarely calcified in childhood. In older patients and in children with prior valve surgery, the leaflets may calcify, becoming less mobile and less amenable to balloon dilation. In congenital aortic valve stenosis, as in pulmonary valve stenosis, balloon valvuloplasty reduces the degree of stenosis by separating valve leaflets along the lines of commissural fusion (Fig. 57-10). In marked contrast, balloon valvuloplasty has proved to be much less successful in older patients with calcific aortic stenosis.[60,67-70] In these patients, the aortic valve stenosis is acquired, primarily as a result of calcium deposition within the leaflets, and little or no commissural fusion is present.[71,72]

Based on the Pediatric Valvuloplasty Registry, several other factors are associated with suboptimal results during balloon aortic valvuloplasty. A suboptimal result is defined as failure to perform the valvuloplasty (which occurred in 4.1% of registered patients), an immediate residual gradient of 60 mm Hg or more, an LV systolic pressure exceeding the aortic systolic pressure by 60% or more, mortality, or major morbidity.[59] Overall, a suboptimal outcome was reported for 17% of the 630 valvuloplasty procedures. Independent predictors for a suboptimal outcome included age younger than 3 months, a greater predilation systolic gradient, a balloon-annulus diameter ratio of less than 0.9, the coexistence of an unrepaired coarctation, and earlier year of the procedure. The effect of the balloon-annulus diameter ratio has been thoroughly evaluated, and the optimal ratio was found to be between 0.90 and 0.99. Smaller ratios were associated with an increased risk of suboptimal gradient relief. Larger ratios were associated with a greater risk of aortic insufficiency after valvuloplasty.

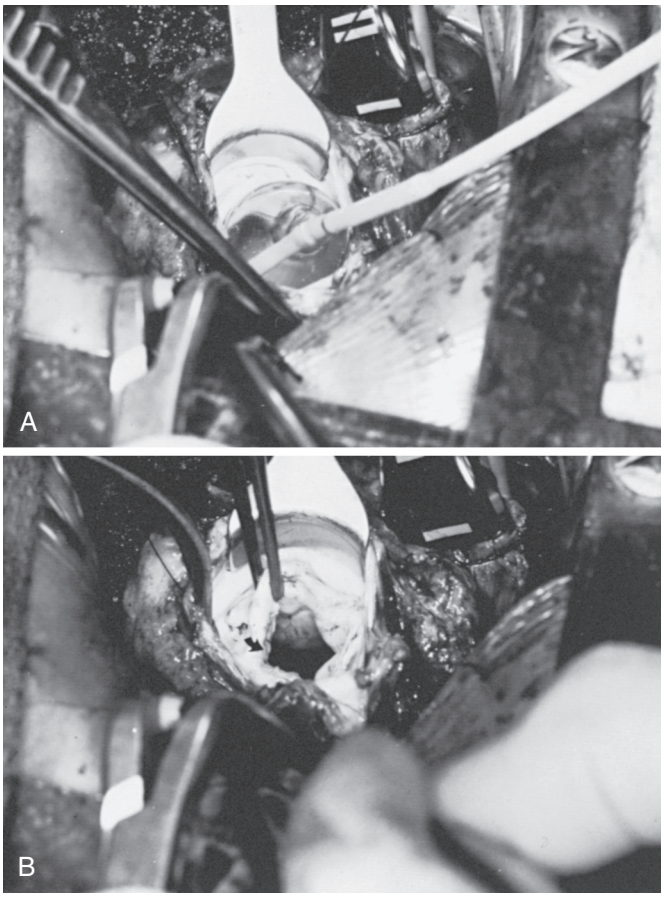

FIGURE 57-10 The mechanism of balloon aortic valvuloplasty is demonstrated during surgery in an 18-year-old woman with congenital aortic valve stenosis. A 20-mm balloon had been inflated across the valve (**A**), producing a 3- to 4-mm tear across the line of commissural fusion (*black arrow*) (**B**). The valve leaflets are thick and dysplastic.

Critical Aortic Stenosis

In newborns with critical aortic stenosis, balloon aortic valvuloplasty has proved to be remarkably successful, with results comparable to those of surgical intervention at several premier institutions.[52,73-75] The Congenital Heart Surgeons Society reported the results of intervention in 110 neonates with critical aortic stenosis from 18 institutions.[74] Balloon aortic valvuloplasty was the initial procedure in 82 patients, and surgical valvotomy in the remaining 28. Relief of aortic stenosis was significantly better in the balloon valvuloplasty group (gradient reduction of 65% ± 17% and median residual gradient of 20 mm Hg vs. 41% ± 32% and 36 mm Hg in the surgical group), although there was also a trend toward more aortic insufficiency in the balloon group. Early mortality was 18%, with no difference between groups.

In a study from our center,[73] 30 neonates were assigned to balloon valvuloplasty and 17 to surgical intervention on an intent-to-treat basis; early mortality was 13% in both groups. Early mortality was 14% in a series of 113 neonates treated with balloon aortic valvuloplasty, with about one third of survivors requiring repeat intervention within 1 year.[52] Echocardiographic estimates of valve thickness or mobility have not correlated with valvuloplasty success in neonates.

Long-Term Results

Percutaneous balloon valvuloplasty and all other forms of therapy for congenital aortic valve stenosis should be regarded as palliative therapeutic procedures. As is the case after surgical aortic valvotomy,[76] late restenosis (5 to 20 years) should be expected after a successful balloon dilation procedure. As stated earlier, we caution against comparing follow-up peak instantaneous gradients determined by Doppler echocardiography against catheter-based measurements of peak systolic gradient obtained immediately after valvuloplasty because a false impression of restenosis may be obtained from echocardiography-derived assessments of valve gradients.[46]

Several studies have examined aortic restenosis requiring reintervention during middle- and long-term follow-up, including a prospective study examining the intermediate effectiveness of balloon valvuloplasty at our institution.[51,63,65,77-80] The recent study by Brown and coworkers represents the largest series of patients with 20-year follow-up data.[63] The rate of survival free from any aortic reintervention was 89% at 1 year and steadily declined to 27% at 20 years. Similarly, the rate of survival free from aortic valve replacement was 47% at 20 years. Predictors of reintervention and aortic valve replacement included a higher postvalvuloplasty gradient, whereas a higher grade of acute aortic insufficiency was associated only with shorter time to aortic valve replacement. Long-term mortality was low (88% survival at 20 years), and the highest hazard for death was during the first year after valvuloplasty. These results are similar to what has been found in other long-term follow-up studies.[65]

Critical Aortic Stenosis

Neonates with critical aortic stenosis appear to have a substantially higher risk of restenosis and progressive aortic insufficiency after balloon valvuloplasty: the reintervention-free survival rate has been approximately 50% at 5 years,[52,73-74] with aortic valve replacement or surgical repair of aortic insufficiency required in approximately 50% of patients at 10 years.[52,73]

Studies have found significant abnormalities during exercise testing and cardiac magnetic resonance imaging (MRI) in patients who have undergone aortic valvuloplasty.[81-82] This underscores the importance of ongoing medical supervision, particularly for patients who require intervention early in life.

Complications

Percutaneous balloon aortic valvuloplasty is a relatively safe procedure, and mortality is rare outside of early infancy.[53] Early mortality after balloon valvuloplasty in neonates has ranged from 13% to 18%; l5-year mortality has ranged between 5% and 28%[52,63,73-74] These data compare favorably with the surgical experience, in which morbidity and mortality rates have been relatively high in neonates with critical aortic stenosis. Other complications reported in the Pediatric Valvuloplasty Registry were rare and included potentially life-threatening arrhythmias, cardiac perforation, and mitral valve injury. As described in detail earlier, valvuloplasty-induced aortic valve insufficiency may be an important complication of the procedure, but its relative incidence and importance in long-term patient outcomes is controversial.[63,83]

Femoral artery injury, thrombosis, and occlusion were relatively common in the past, particularly in infants, but their incidence has improved with current low-profile sheaths and angioplasty catheters.[84] We prefer not to exceed a 4-Fr exit profile in neonatal femoral arteries and to use the transumbilical approach for neonatal critical aortic stenosis if possible. Newer, 3-Fr sheaths are commonly used in infants who weigh less than 4 kg. Because future transfemoral valvuloplasty procedures (for restenosis) are likely to be necessary in these patients, femoral artery access should be preserved if at all possible.

A more recently recognized complication of neonatal aortic balloon valvuloplasty is aortic wall injury, in particular the creation of an intimal flap.[85] This diagnosis is made by angiography, echocardiography, or direct observation by the surgeon or pathologist. The complication was found in 28 (15%) of 187 procedures performed over a 23-year period, with no change in frequency over the study period. In one instance, a flap in the proximal ascending aorta extended into a coronary artery ostium, causing death, and another patient died suddenly at home. Multivariate analysis showed that aortic wall injury was more

likely in patients with severe ventricular dysfunction at the time of the procedure, in procedures with greater numbers of balloon dilation attempts, and in procedures supervised by less experienced interventional staff.

Current Controversies

Several articles have compared the outcomes of aortic balloon valvuloplasty and surgical valvotomy for neonatal and infant congenital aortic stenosis.[78,79] Citing improved gradient reduction, a lesser degree of resultant aortic insufficiency, and less need for reintervention during follow-up, these authors have questioned the use of aortic balloon valvuloplasty as first-line therapy in infants and children. Again, retrospective, single-center studies are subject to several important limitations, probably the most important of which is center-related biases and the generalizability of the results to all patients.

The technique for aortic balloon valvuloplasty has improved over time with innovations such as rapid ventricular pacing and lower-profile catheters and sheaths. Additionally, understanding of the relative importance of residual aortic stenosis and resultant aortic insufficiency is changing with time. Surgical valvotomy has additional long-term risks that are just beginning to be understood, including the impact of cardiopulmonary bypass and circulatory arrest on neonatal and infant neurodevelopment. Predicting which patients (i.e., which valves) would most benefit from aortic balloon valvuloplasty versus surgical valvotomy or repair is likely the next most important step to ensuring the highest quality of care in these challenging patients.

Fetal Intervention

Balloon valvuloplasty has been proposed for fetuses with aortic stenosis for the purpose of preventing the development of hypoplastic left heart syndrome. Research has focused on accurately identifying fetuses at risk for this progression, developing techniques for in utero intervention, reducing the risks of technical failure and of fetal demise, and predicting which fetuses are most likely to benefit from intervention.[86]

Conclusions and Recommendations

Percutaneous balloon aortic valvuloplasty provides effective palliative treatment for congenital valvular aortic stenosis in infants, children, and young adults. At most pediatric cardiology centers, it is the treatment of choice. Valvuloplasty successfully reduces the peak systolic aortic stenosis gradient to the 20- to 40-mm Hg range, a result that compares favorably with open surgical valvotomy. Aortic insufficiency is not significantly increased in most patients. Mortality is uncommon and has been limited to critically ill neonates and young infants.

We recommend balloon valvuloplasty for patients whose resting peak systolic pressure gradient exceeds 50 mm Hg, for those whose resting peak gradient exceeds 40 mm Hg in association with symptoms or ischemic ECG changes, and for patients with heart failure and low cardiac output regardless of gradient. Balloon valvuloplasty is effective in neonates, children, and young adults with congenital aortic valve stenosis in whom commissural fusion is the primary anatomic cause of outflow obstruction. The procedure is less likely to be effective in patients with a hypoplastic valve annulus or with valve leaflet calcification.

BALLOON-EXPANDABLE STENTING FOR PULMONARY ARTERY STENOSIS

PA stenosis occurs commonly in patients with CHD. It is encountered as an isolated lesion in patients with arteriopathies such as Williams or Alagille syndrome or as a feature of complex CHD (e.g., TOF) both before and after surgery. Balloon angioplasty of PA stenosis or hypoplasia has yielded mixed results. Numerous reports document an immediate success rate of only 60% to 70% after balloon angioplasty of this lesion,[87-89] with restenosis rates in follow-up as high as 35%.[89]

Failure of angioplasty alone is often related to elastic recoil of the PA. These observations have led to the application of stent therapy to treat PA stenosis or hypoplasia. Since Mullins and colleagues first reported the use of balloon-expandable stents in the pulmonary arteries and systemic veins in 1988,[90] transcatheter stenting has become the treatment of choice for many patients with PA stenosis and has demonstrated excellent early and long-term effectiveness.

Technical Considerations

PA stenosis is considered significant when the measured gradient across the area of stenosis is greater than 20 to 30 mm Hg, the RV pressure is greater than one half to two thirds of systemic pressure due to distal obstruction, or there is relative flow discrepancy of greater than 35%/65% to each lung.[91] In low pulmonary flow states such as palliated single-ventricle lesions, gradients may be much lower, and the subjective angiographic appearance instead may determine the need for intervention. Stent use in pediatrics is complicated by a wide range of patient sizes and the need to account for somatic growth of young patients over time. The implantation of stents in older children who are capable of accommodating stents that can ultimately be dilated to adult size in the future is well accepted. The implantation of small stents in infants and small children is more controversial but is generally considered as a palliative approach in cases when angioplasty has been unsuccessful or other options are limited.[91] Data evaluating PA interventions from a multicenter prospective registry, the C3PO study, found that 46% of all stent implantations used smaller, premounted stents.[92] Use of these stents was more common in younger patients and in nonelective or emergent cases and provides evidence of the relatively widespread use of small- and medium-diameter stents within the pediatric population in current practice.

There are no stents developed specifically for use in pediatric patients with CHD, and therefore all stents used in this setting represent off-label use of coronary and peripheral stents developed for adult purposes.[93-95] Ideally, large stents, which ultimately can be dilated to a diameter of 18 mm, are appropriate for use in the pulmonary arteries of a patient who can accommodate the appropriate delivery sheath. In some smaller patients, the internal jugular vein may accommodate a larger sheath than is possible with the femoral venous approach. Additionally, a hybrid surgical approach, either with direct stent placement during cardiac surgery or via sternotomy and sheath placement in the main PA, can allow for placement of larger stents in smaller patients.

The balloon size chosen for stent implantation is typically up to 3 times the narrowest vessel dimension, not to exceed the dimension of the adjacent normal vessel. Although it is usually recommended that vessel side branches not be "jailed" in the process of stent placement, if jailing is necessary to address the stenosis, the use of an open cell stent can allow for later angioplasty through the stent struts to reopen these side branches in the event of restricted flow. In very proximal branch PA stenosis or distal main PA stenosis, techniques such as the simultaneous implantation of bilateral proximal PA stents[96] ("kissing stents") or implantation of a single stent crimped onto two balloons, extending from the main PA into both the proximal branch pulmonary arteries ("bifurcating" or "flowering" stent), may be used.[97]

New imaging technologies such as rotational angiography and three-dimensional (3-D) reconstruction can be useful in some cases of PA stenosis. This technology can augment traditional biplane angiography and allow for more complete understanding of the 3-D anatomy of the stenotic area, can help determine ideal angles for profiling an area of stenosis, and can be used as a roadmap to guide stent placement (Fig. 57-11; Videos 57-1 and 57-2).

Acute and Intermediate Outcomes

Early clinical studies of PA stenting used the Palmaz (Cordis, Bridgewater, NJ) stainless steel balloon-expandable stent[98-101] (Figs. 57-12 and 57-13). A multiinstitutional study of percutaneous stenting in the pediatric population was reported by O'Laughlin and colleagues in 1993.[98]

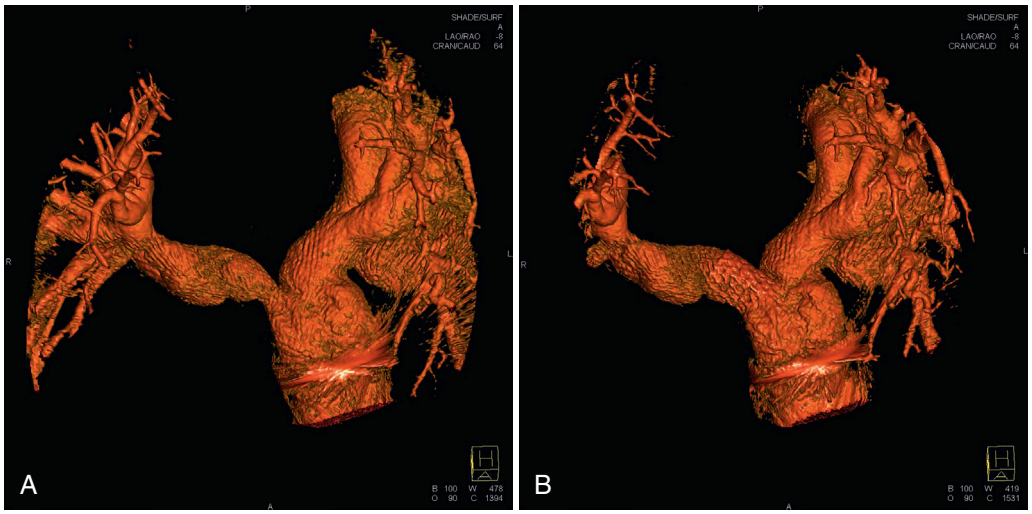

FIGURE 57-11 Three-dimensional (3-D) reconstruction of 64-slice computed rotational angiogram (CRA-64) performed on a 15-year-old boy with tetralogy of Fallot obtained after complete repair and placement of a 25-mm Hancock valved conduit, with proximal right pulmonary artery (RPA) stenosis before (**A**) and after (**B**) RPA stenting. These single views of the 3-D reconstruction displayed at 8-degree left anterior oblique (LAO-8) profile the proximal RPA stenosis well. (See also Videos 57-1 and 57-2.) (Courtesy Dr. Aimee Armstrong, University of Michigan, Ann Arbor.)

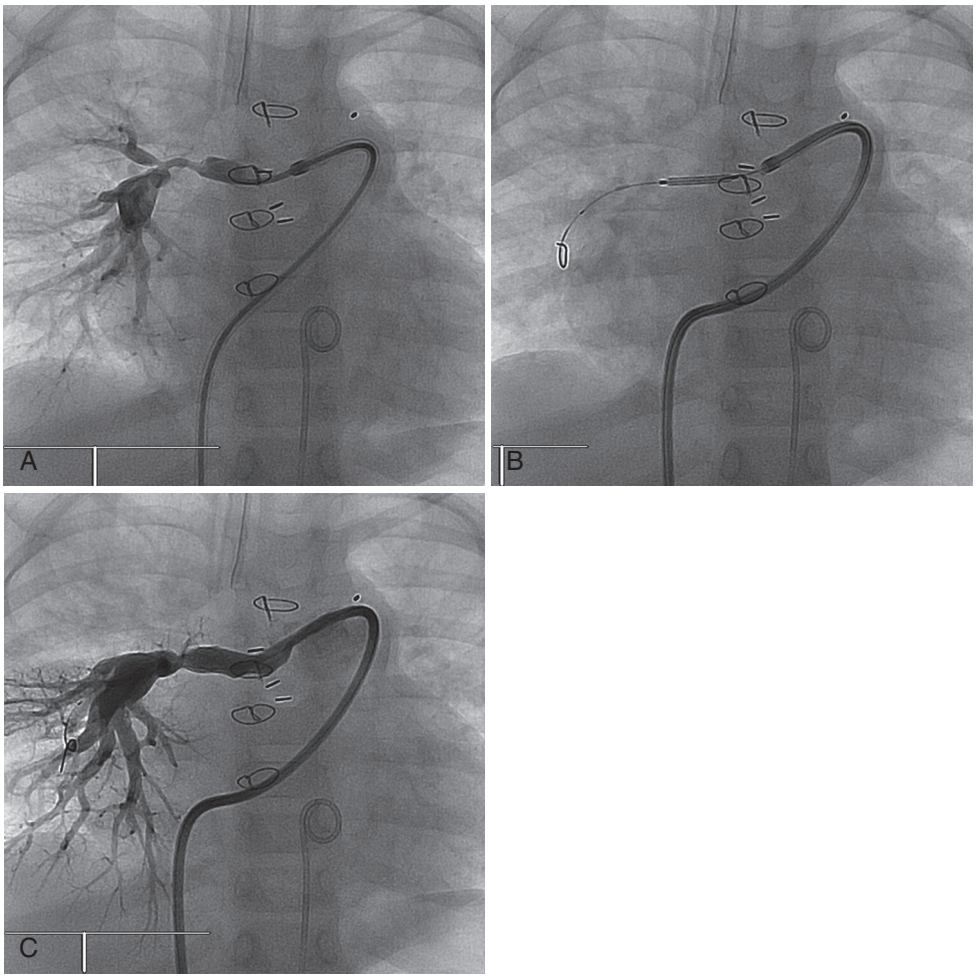

FIGURE 57-12 Anteroposterior pulmonary artery angiograms before (**A**), during (**B**), and after (**C**) right pulmonary artery stenting in a 5-month-old infant after repair of pulmonary atresia and ventricular septal defect. There is severe proximal right pulmonary artery stenosis before stenting. After stent implantation, there is improvement in the stenosis, but a small upper lobe branch has been jailed.

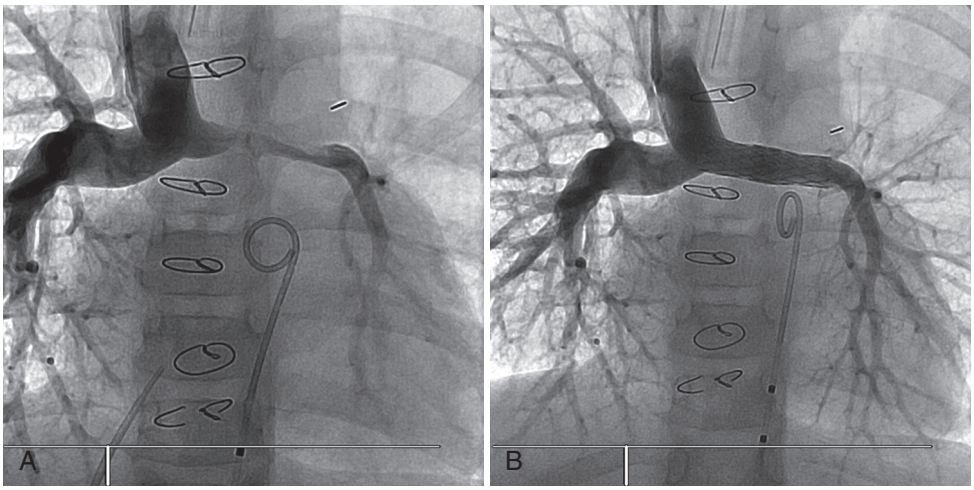

FIGURE 57-13 Anteroposterior pulmonary artery angiograms obtained before and after left pulmonary artery stenting in an infant with hypoplastic left heart syndrome and left pulmonary artery hypoplasia. **A,** Before stenting, there is diffuse hypoplasia of the proximal left and central pulmonary artery. **B,** After stenting with two balloon-expandable stents, there is significant improvement in the pulmonary artery diameter and flow. The patient has a bidirectional Glenn shunt (superior vena cava–to–pulmonary artery anastomosis).

A total of 121 Palmaz stents, 80 for branch PA stenosis, were implanted in 58 patients, most of whom had undergone repair of TOF. In this series, stenting resulted in an increase in PA diameter from 4.6 to 11.3 mm, with an immediate decrease in RV systolic pressure. A follow-up cardiac catheterization was performed in 25 patients 8 months after stenting, and restenosis was identified in only 1 patient. The clinical benefits derived from PA stenting in children, including alleviation of symptoms and deferral of surgical intervention, were further validated in a large single-institution series by Fogelman and associates.[99] The largest series of PA stenting in children was reported by McMahon and colleagues in 2002.[102] Over a 12-year period, 664 Palmaz stents were implanted in 338 patients, most with a diagnosis of repaired TOF; the mean age was 12.2 years. After stenting, the systolic pressure gradient across the stenosis decreased from 41 to 9 mm Hg, and the mean diameter of the stented vessels more than doubled. With improved techniques and increased experience, morbidity and mortality decreased significantly during the second half of this series.

The adverse events associated with PA angioplasty and stenting collected in the C3PO registry were reported by Holzer and coworkers.[92] From 2007 to 2009, 1315 cases of PA rehabilitation were performed in 969 patients, 495 (38%) of which involved stent placement. The authors found an adverse event rate of 22%, with high-severity (moderate, major, or catastrophic) events in 10%. There was no significant difference between stent placement and standard balloon angioplasty alone. There were two procedure-related deaths (0.015%). The most common adverse events were reperfusion injury/endotracheal tube bleeding in 40 patients (12% of the adverse events), heart block in 37 patients (11%), confined vascular tears in 23 patients (7%), and stent malposition/embolization in 21 patients (6%). Unconfined tears occurred in 9 patients (3%), and aneurysm formation occurred in 5 patients (2%). Independent risk factors for a high-severity adverse event included hemodynamic vulnerability, age less than 1 month, use of cutting balloons for angioplasty, and operator experience of less than 10 years.

Long-Term Outcomes

The longest follow-up series was reported in 2009 by Law and colleagues,[103] who described the long-term outcome of children who were originally enrolled in the investigational device exemption (IDE) PA stent trial approved by the U.S. Food and Drug Administration (FDA) between 1989 and 1992. Their data, with a mean follow-up time of 13.2 ± 2.3 years, confirmed the lasting hemodynamic benefits in these children and documented the feasibility of late stent redilation. Although nonobstructive neointimal proliferation was seen almost universally, clinically important in-stent restenosis was uncommon. Repeated stent dilation in these patients was primarily indicated to accommodate somatic growth. There were no late complications. Despite this and many studies reporting a low rate of late in-stent restenosis, a 2014 study by Hallbergson and coworkers used a more defined criterion for restenosis (>25% narrowing of contrast-filled lumen–to–stent diameter), reported an incidence of 24%.[104] These authors found that patients with TOF who had multiple aortopulmonary collaterals, Williams syndrome, or Alagille syndrome had the highest incidence of in-stent restenosis; no association was found with stent type.

As previously mentioned, it is important that stents implanted into the pulmonary arteries of children can be safely and effectively redilated to a larger diameter as the child grows. Reports from several institutions confirm the experimental observations that PA stents can be safely redilated to a larger diameter.[98-99,101,103-106] In 2003, Duke and colleagues[106] reported safe and effective stent redilation in 12 children with PA stenosis. Redilation was required because of a combination of patient growth and neointimal proliferation. Redilation increased the PA stent diameter to beyond its initial implantation size and effectively decreased the systolic gradient. These authors found neointimal proliferation to be precipitated by overdilation of stents at the time of implantation, in agreement with the practice of placing stents at a size that is no larger than the size of the normal adjacent vessel.

Conclusions and Recommendations

Experimental and clinical data from several centers indicate that balloon-expandable stenting provides an effective form of therapy for many patients with PA stenosis or hypoplasia. Because balloon angioplasty alone is initially unsuccessful in as many as 30% to 40% of patients, stenting is now considered standard first-line therapy for most children with PA stenosis. If at all possible, implanted stents should have the capacity for later redilation when the child has grown. In infants and small children in whom larger stents may be difficult to implant, a hybrid approach for implantation and/or an understanding that small stents will require later surgical intervention is necessary. Despite these techniques, angioplasty alone may be preferable in selected situations in an attempt to avoid implanting smaller stents with limited growth potential.

BALLOON-EXPANDABLE STENTING FOR COARCTATION OF THE AORTA

Coarctation of the aorta accounts for 8% to 10% of all CHD. For 7 decades, surgical repair has been a conventional therapy for patients with a native (unoperated) or recurrent postoperative coarctation. Coarctation balloon angioplasty has been available since the mid-1980s, but its effectiveness has been diminished by restenosis (15% to 20% of patients) and aneurysm formation (approximately 5% of patients). As a result, in the late 1980s, balloon-expandable stenting emerged as the most recent transcatheter therapy for coarctation (Fig. 57-14). A stent's radial strength opposes elastic aortic wall recoil and may improve vessel integrity, thereby decreasing the risk of aneurysm formation at the dilation site. The availability of covered stents may provide an even safer therapy for coarctation in patients with a vulnerable aortic wall (e.g., Turner syndrome) and in older adults.

Technical Considerations

Stent therapy can benefit patients who have a native unoperated coarctation or a recurrent postoperative coarctation with equal effectiveness (Figs. 57-15 and 57-16). Most interventionalists attempt to limit stenting to older children and adolescents so as to maximize initial implant diameter and minimize the need for later stent redilation after somatic growth has occurred. Stent placement for native or recurrent coarctation of the aorta is indicated in patients who have a peak systolic ejection gradient greater than 20 mm Hg or a gradient of less than 20 mm Hg with associated systemic hypertension or LV dysfunction.[91]

Mild coarctation (i.e., resting systolic gradient <20 mm Hg) posed a therapeutic dilemma in the past because it was generally thought that the benefits did not outweigh the risks of surgery. However, more recent data suggest that mild coarctation may be associated with long-term rest and exercise hypertension and perhaps LV hypertrophy and diastolic dysfunction. Marshall and colleagues[107] reported the results of stent treatment in 33 patients with mild native or residual coarctation. At follow-up catheterization after stent placement, LV end-diastolic pressure had decreased significantly, from 17 to 14 mm Hg. Although larger clinical studies with longer follow-up periods are necessary, these data do suggest that there may be a place for nonsurgical intervention for mild degrees of coarctation.

Transcatheter stent therapy may also provide a reasonable treatment strategy for anatomic variations of coarctation that pose difficult surgical dilemmas. For example, hypoplasia of the transverse aortic arch is responsible for residual obstruction in a small proportion of patients after surgical coarctation repair. These lesions can be difficult to manage surgically because the operative procedure may require a period of hypothermic circulatory arrest. Pihkala and colleagues[108] reported the successful use of stent therapy in four children with transverse arch hypoplasia. Successful stenting in infants with complex aortic arch obstruction after the Norwood operation for hypoplastic left heart syndrome has also been described.[109] In these infants, an antegrade approach via the femoral vein or a carotid cutdown may be used to avoid femoral artery injury while allowing for implantation of a relatively large-sized stent with larger diameter potential to

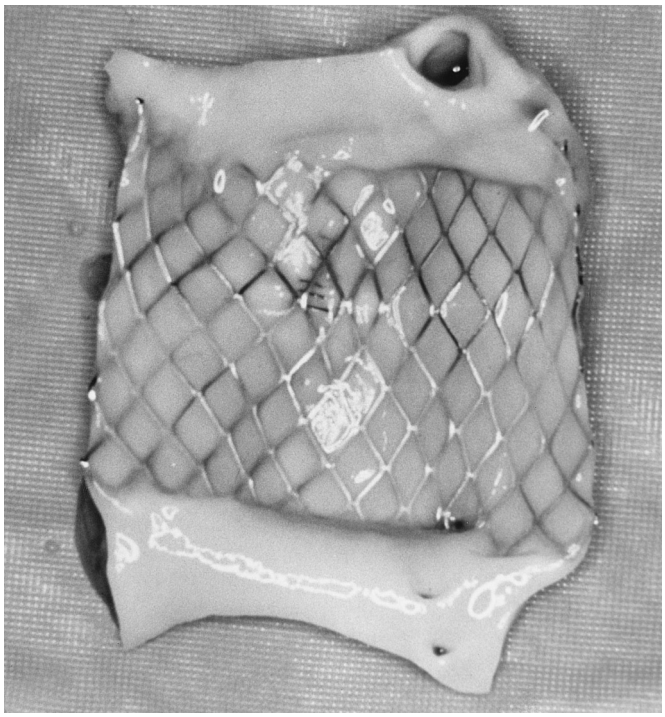

FIGURE 57-14 Aortic stent explanted 6 weeks after stenting of an experimental coarctation in a canine model. The Palmaz P-308 stainless steel stent is almost completely covered with a thin layer of neointima. The sutures used to create the experimental coarctation are evident.

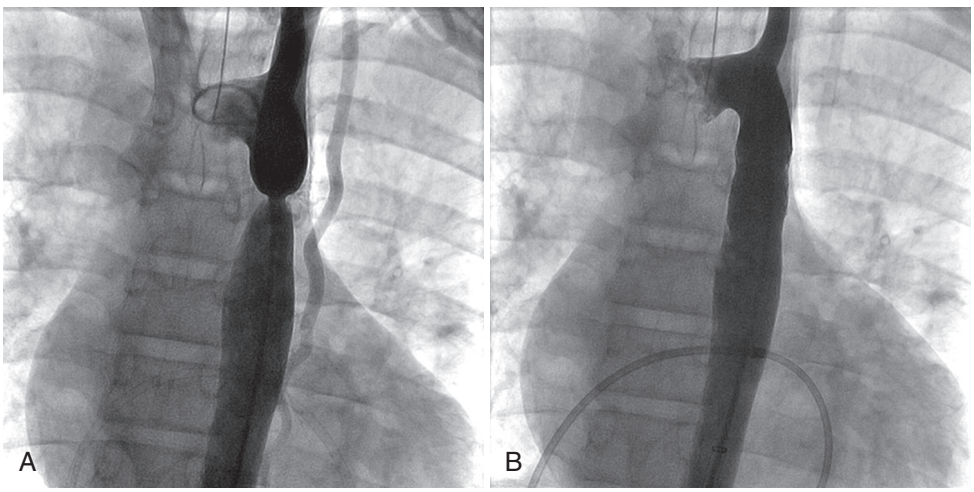

FIGURE 57-15 Anteroposterior aortograms obtained before and after stenting in a 14-year-old teenager with a discrete native (unoperated) coarctation of the aorta. **A,** Before stenting, there is a severe stenosis, and a systolic gradient of 41 mm Hg was measured. **B,** After stenting with a balloon-expandable stainless steel stent dilated to a diameter of 16 mm, the pressure gradient is entirely eliminated.

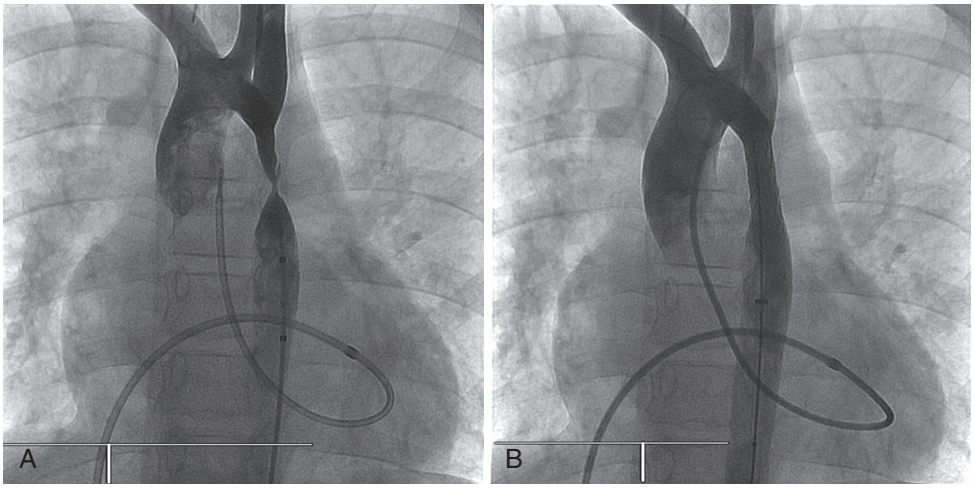

FIGURE 57-16 Anteroposterior aortograms obtained before and after stenting in an 11-year-old child with a severe native coarctation of the aorta. **A,** Before stenting, there was a severe stenosis that measured approximately 2 mm in diameter. **B,** After the coarctation was stented with a bare-metal stainless steel stent intentionally dilated to a subtherapeutic diameter (8 mm) in an attempt to avoid undue aortic wall trauma, the gradient decreased from 31 to 10 mm Hg.

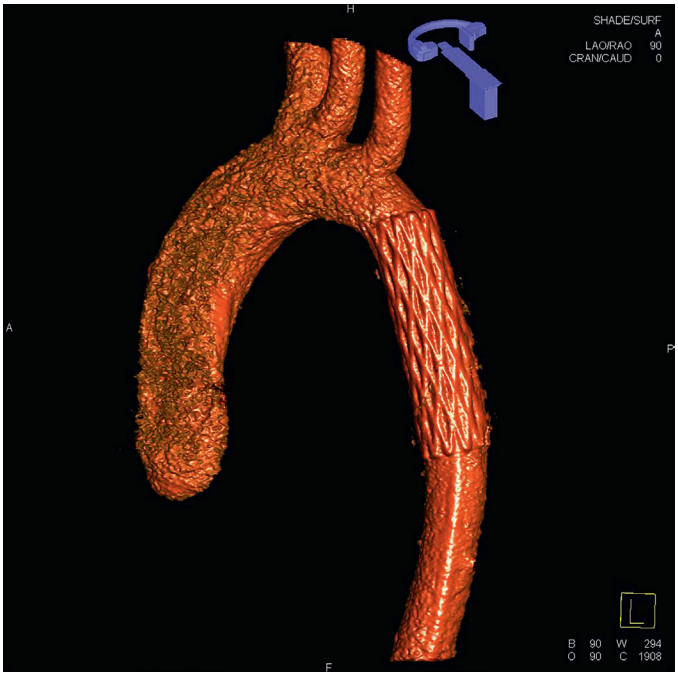

FIGURE 57-17 Three-dimensional reconstruction of rotational angiogram performed on a 10-year-old boy with mild transverse arch hypoplasia, and long-segment coarctation of the aorta distal to the left subclavian artery after placement of a Palmaz 4010 stent (see also Video 57-3.) (Courtesy Dr. Jeffrey Zampi, University of Michigan, Ann Arbor.)

accommodate somatic growth. Imaging of the aortic arch with rotational angiography and 3-D reconstruction can be of great value in visualization of complex or atypical coarctation anatomy (Fig. 57-17; Video 57-3).

In most reported series, balloon-expandable bare-metal stents have been used. More recently, use of the covered Cheatham platinum (CP) stent (NuMed, Hopkinton, NY) has been reported (Fig. 57-18). Initially described to treat vessel complications as a bail-out procedure, this covered stent is currently available in the United States only in clinical trials or under compassionate use approval. In 2014, Sohrabi and colleagues described the first prospective randomized trial comparing bare-metal and covered CP stents in patients with native coarctation.[110] In their experience with 120 patients with a mean age of 23.6 years, procedural success was 100% in both groups with similar overall complication rates. However, patients undergoing covered CP stent implantation experienced a nonsignificantly lower recoarctation rate and a higher occurrence of psuedoaneurysm compared with the bare-metal stent group. Whereas covered stents may indeed be useful in preventing recurrent stenosis by preventing ingrowth within the stent, the association with pseudoaneurysm is less clear and may have been related to case-specific technical issues in this study.

Although this study does not support the routine use of covered stents compared with bare-metal stents, selective use of covered stents may be particularly effective in stenting of complex coarctation anatomy and in patients in whom the aortic wall is more fragile (e.g., arteriopathies, advanced age).[111-112] With the use of covered stents, more complex and tighter coarctation can be treated with lower rates of complications.[113]

Clinical Outcomes

Numerous clinical studies in the last 2 decades have documented the effectiveness and relative safety of transcatheter stenting of coarctation of the aorta in both pediatric and adult populations.[107,114-121] A prospective, observational, multiinstitutional study carried out by 36 centers from the Congenital Cardiovascular Interventional Study Consortium (CCISC) compared the safety and efficacy of stent placement with that of balloon angioplasty and surgery for native coarctation of the aorta in patients weighing more than 10 kg.[122] Although all three arms of the study showed significant improvement in follow-up resting systolic blood pressure and coarctation gradient, the stent group achieved a lower gradient compared with the angioplasty group. Of the three, the stent group had the lowest likelihood of any complication (2.3% vs. 9.8% for angioplasty and 18.1% for surgery). In particular, aortic wall injury was significantly greater on follow-up imaging in the angioplasty group (21.4%) compared with the stent group (3.1%), primarily because of an increased risk of aneurysm formation. Stent patients were more likely to require a planned reintervention, most often for stent redilation as part of a staged approach or secondary to patient somatic growth. There was no difference in unplanned reinterventions between the treatment groups. Although these results must be interpreted with some caution given the nonrandomized nature of the

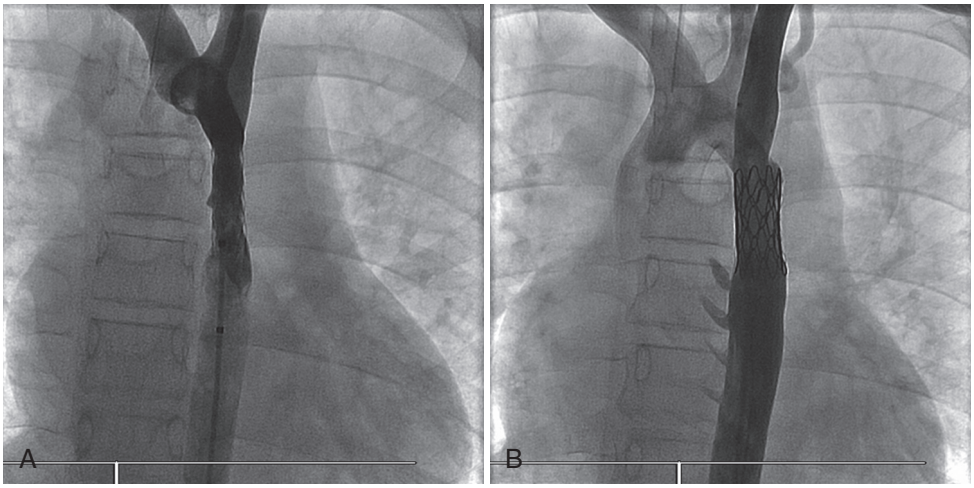

FIGURE 57-18 Anteroposterior aortograms obtained before and 10 months after bare-metal stenting of a severe coarctation (same patient as in Fig. 57-16). **A,** The initial angiogram demonstrates a small saccular aneurysm on the medial aspect of the stented area. **B,** After stenting with a covered Cheatham platinum (CP) stent under compassionate use approval, the aneurysm is excluded and the residual coarctation stenosis is relieved. Reflux of contrast material into several intercostal arteries is evident.

study, the findings suggest that stent therapy may be the lowest-risk intervention available to this patient population.

The largest series of coarctation stenting to date was reported in 2007 by Forbes for the CCISC.[117] In that multiinstitutional study, 627 stents were placed in 555 patients for native (52.3%) or recurrent postoperative coarctation. The median age was 15 years, and the median weight was 56.4 kg. A successful treatment outcome was achieved in 97.9% of procedures, with the systolic gradient decreasing from 32 to 3 mm Hg acutely. Complications occurred in 14.3% of procedures and included aortic wall injury (intimal tear, dissection/rupture, and aneurysm) in 3.9%, stent migration in 5%, and cerebral vascular accident in 0.7%. Acute aortic aneurysm formation was observed in six procedures (1.1%). Two patients (0.4%) with severe aortic wall injury were sent emergently to surgery but experienced severe neurologic injury and later died. Acute aortic wall complications were associated with performance of prestenting balloon angioplasty (odds ratio [OR], 4.18), location of coarctation in the abdominal aorta versus the isthmus or transverse aorta (OR, 5.74), and age greater than 40 years (OR, 2.95). At intermediate follow-up (median of 12 months), about one quarter of patients in the CCISC study underwent additional aortic arch imaging, with identification of an abnormality in 29% of patients.[116] These abnormalities included aneurysm (9%), intimal tear/dissection (3%), stent fracture (4%), and stent reobstruction (11%). The authors identified an increased risk of aortic wall pathology in follow-up if the ratio of balloon diameter to coarctation diameter exceeded 3.5, but they found no association between age and late development of aortic wall pathology.

Data on long-term outcomes of stent implantation for aortic coarctation are limited, with the longest reported follow-up being 15 years.[113,120,123-125] Butera and associates[113] reported their long-term, single-center experience using both bare and covered stents in patients with coarctation. Recoarctation occurred as a result of neointimal hyperplasia, somatic growth, or stent fracture. In the bare-metal stent group, over a median follow-up period of 81.7 months, 23.9% of patients required reintervention due to restenosis, at a mean of 49.4 months from initial stent placement. Three patients (4.5%) required reintervention with covered stent implantation due to late aneurysm formation. There was a 100% success rate with reintervention. The covered stent group had a similar reintervention rate (22.4%) at an earlier mean follow-up time of 18.4 months. Three of 15 of these patients underwent staged redilation due to the severity of the initial lesion, and this may have contributed to the earlier time at reintervention in this group. Independent risk factors for reintervention included complex lesions, use of a balloon smaller than 14 mm in diameter for initial stent delivery, and an immediate poststent residual gradient of more than 10 mm Hg. Neointimal hyperplasia was present in 8.4% at follow-up, with a similar incidence in the two stent groups. Stent fracture was more common in the bare-metal group (5%), and the majority of these patients required reintervention due to restenosis. Somatic growth as a cause of reintervention was significantly associated with age younger than 15 years and use of a balloon diameter smaller than 14 mm at initial stent implantation.

Another long-term issue with patients after coarctation repair is systemic hypertension. Many studies have found that patients with coarctation continue to exhibit elevated blood pressure after their initial intervention or develop hypertension over time, even in the setting of a good anatomic result of intervention.[114,123] Holzer and coworkers[120] reported the intermediate and long-term follow-up results (up to 60 months) in patients included in the multiinstitution CCISC study. Twenty-three percent of patients continued to have systolic blood pressure greater than the 95th percentile, 9% had an upper-to-lower limb blood pressure gradient greater than 20 mm Hg, and 32% were taking antihypertensive medications. Eighty percent of patients studied a mean of 5.3 years after stent implantation for coarctation also exhibited abnormally elevated exercise blood pressure response.[125]

Lifelong surveillance for these patients, even after successful anatomic relief of coarctation, is therefore warranted for regular assessment of blood pressure, monitoring with cross-sectional imaging for late development of aneurysm formation or recurrent coarctation, and assessment of ventricular systolic and diastolic function.

Conclusions and Recommendations

Coarctation stenting is an effective approach to native and postoperative recurrent coarctation of the aorta. Most pediatric interventionalists limit stent implantation for coarctation to large children and adolescents to avoid the need for aortic stent redilation after somatic growth in a smaller child. Stent implantation is a promising intervention for more difficult variations on coarctation anatomy, particularly transverse arch hypoplasia, arch obstruction after the Norwood operation, and mild degrees of coarctation that have not warranted surgery in the past. In older adults in whom the aortic wall is friable, covered stents may provide a safer alternative because of the increased risk of aortic wall injury with coarctation dilation. Longer-term follow-up studies are necessary to more precisely define the late risks of stent restenosis, aortic aneurysm formation, the safety of late stent redilation

after somatic growth in children, and blood pressure response to exercise in the face of a rigid, stented aortic segment.

TRANSCATHETER CLOSURE OF THE SECUNDUM ATRIAL SEPTAL DEFECT

ASDs result from deficient development of the intraatrial septum. Sinus venosus defects result from abnormal development of either the superior or the inferior horns of the sinus venosus and are located superiorly or inferiorly along the posterior margin of the atrial septum. Superior sinus venosus defects frequently have associated anomalous drainage of the right upper pulmonary vein. Primum ASDs result from deficiencies of the septum secundum, frequently as part of the complex of maldevelopment of the endocardial cushions (atrioventricular canal [AVC] defects). In the most severe form (complete AVC), the primum defect is part of a complex that includes an inlet ventricular septal defect (VSD) and a common atrioventricular valve. In the least severe form, the primum ASD defect is associated with a cleft in the anterior mitral valve leaflet.

Secundum ASDs result from deficiencies of the central portion of the atrial septum, the septum primum. These defects, usually in the region of the fossa ovalis, may be extensive in size, varied in shape, and often multiple in number (fenestrated atrial septum). It is secundum-type defects, often with substantial peridefect margins and positioned some distance from other vital structures, that lend themselves well to percutaneous device closure. Further discussion in this section focuses on secundum ASDs.

Physiology

ASDs represent one of the most common forms of acyanotic CHD.[126] Although the left atrial pressure is typically higher than that in the right atrium, flow across the atrial septum is determined in large part by the end-diastolic pressure within each ventricle, which reflects relative ventricular compliance. The net size of the atrial-level shunt is therefore only in part dependent on the size of the ASD. Elevation of either left or RV systolic pressure in the face of ventricular outflow tract obstruction will not affect atrial-level shunting if ventricular relaxation is not adversely impacted.

With persistence of atrial-level shunting, the right atrial and ventricular end-diastolic volumes are chronically increased, and both atrial and ventricular dimensions increase accordingly.[126] Additional RV volume results first in delayed pulmonary valve closure compared with the aortic valve (causing the clinical sign of the fixed, split second heart sound) and a flow murmur across a normal pulmonary valve (identical to that of pathologic pulmonary valve stenosis, but without an ejection click).[127] The additional pulmonary blood flow is well tolerated in most cases but rarely can lead to pulmonary hypertension and pulmonary vasoocclusive disease.

Ultimately, Eisenmenger-type physiology prevails, at which point the shunt flow is right to left, and the patient becomes cyanotic.[128,129,130] That pathologic end point should not be confused with right-to-left shunting resulting from a decrease in RV compliance with long-standing RV dilation. This latter scenario carries a substantially better prognosis than pulmonary vasoocclusive disease and can be diagnosed either on the basis of relatively normal RV and PA pressures determined by echocardiography or at cardiac catheterization.

Clinical Presentation and Diagnosis

ASDs are typically asymptomatic during the first 2 decades of life. Diagnosis is most often made after detection of a murmur, which is indistinguishable from that of pulmonary valve stenosis, or with auscultation of a fixed, split second heart sound.[127] Infrequently, infants or children exhibit failure to thrive or other more overt signs of congestive heart failure or have recurrent lower respiratory tract infections. Later, in the third and fourth decades of life, the symptoms of previously undiagnosed ASD may include undue fatigue, increased dyspnea on exertion, and a frequent sensation of palpitations.[126,130] The electrocardiographic (ECG) findings may be normal early in childhood or at any age if right atrial enlargement or RV dilation has not yet occurred. Over time, typical ECG changes with right axis deviation, right atrial enlargement, and RV dilation become more clearly apparent.

Transthoracic (TTE) or transesophageal (TEE) echocardiography remains the mainstay of diagnosis.[131] In standard long-axis views, the first indication of an ASD may be dilation of the anteriorly located RV. In short-axis views, that dilation may again be noticed, especially in the region of the infundibulum. In four-chamber views, both the right atrium and the RV will be seen to be dilated. However, the ASD is best seen and evaluated in both long- and short-axis subcostal views. These views allow for complete evaluation of the total septal length and provide excellent visualization of the defect margins. Color flow mapping is of great importance. This allows determination of the direction of flow across the defect (left-to-right or right-to-left) and provides further assessment to exclude the possibility of multiple defects (Fig. 57-19).

Occasionally, poor acoustic windows preclude clear TTE images. This is more likely in the adult patient, in the presence of obesity or with chronic lung disease. At those times, elective TEE should be performed to confirm the diagnosis before further discussion regarding possible defect closure and repair.[132] Echocardiography is also invaluable in achieving a noninvasive measure of RV and PA pressures. Excessive elevation of right-sided pressures should introduce some caution before proceeding with defect repair, especially if there is color flow evidence of right-to-left shunting across the ASD. Other causes of pulmonary vascular disease should be excluded before attributing the cause to an ASD.

Treatment and Outcomes

Surgical repair has long been the mainstay of treatment for ASDs.[129,130,133] However, over the last 2 decades, substantial advances have been made with percutaneous closure devices. At this time, an initial attempt at percutaneous closure of appropriate secundum ASDs is considered the standard of care.[134,135,136] Currently, in the United States, two devices are approved for use by the FDA: the Amplatzer Septal Occluder (St. Jude Medical, St. Paul, MN) and the Helex Septal Occluder (W. L. Gore & Associates, Flagstaff, AZ).[137,138] Although they are different in design and construction, the principles of function, deployment, and follow-up are similar for the two devices (Figs. 57-20 and 57-21). After deployment, both devices are designed to have two discs separated by a central core or waist. One disc is positioned on the left atrial side of the defect, with the core or waist straddling the defect, and the other disc apposed to the atrial membrane from the right atrial side of the atrial septum. The devices have intrinsic recoil that apposes both discs to each other, holding the devices in place on the atrial septum.

Irrespective of the device used, defect sizing is required before deployment. Reliance may be placed on the TTE measurements with an empiric factor adjustment (e.g., 115% of the TTE measurement). However, most operators continue to rely on balloon sizing of the defect before choosing a particular device size.[135,136] That is accomplished by using a large, compliant balloon inflated across the atrial septum, with the narrowest area ("stretched diameter" or "waist") measured by angiographic calibration (Fig. 57-22). The current recommendation is to employ a "stop-flow" technique for defect sizing. Once the sizing balloon is positioned across the atrial septum, it is slowly inflated while careful observation is maintained with TEE or intracardiac echocardiography (ICE). As soon as color flow across the defect is arrested, no further inflation occurs, and an angiographic measurement of that balloon waist size is used to choose the closure device. This technique is used to avoid oversizing of the closure device, the main factor thought to contribute to both early and late erosions of closure devices.[139]

Both devices are deployed though a delivery sheath that typically is extended from the femoral region, although other access sites have been used. The left atrial disc is initially deployed, and the device is

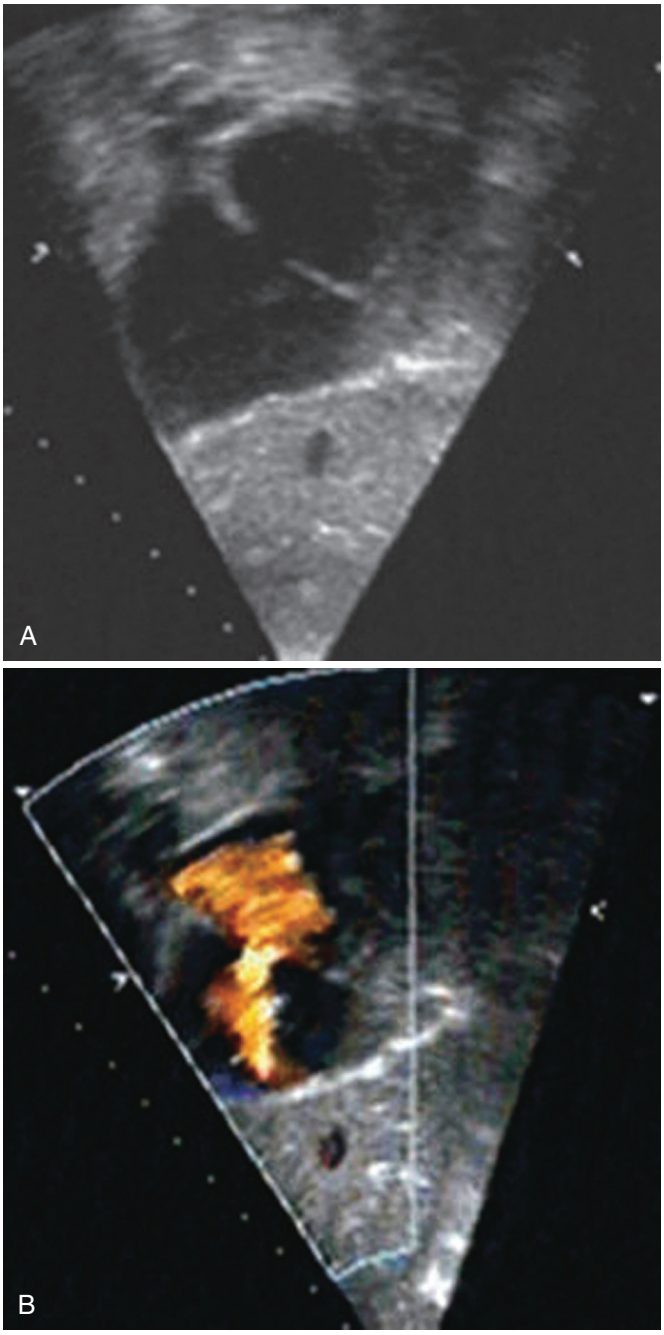

FIGURE 57-19 Subcostal short-axis transthoracic echocardiographic images show a secundum atrial septal defect in two dimensions (**A**) and with color flow mapping (**B**). The defect is central in the septum and has excellent margins for device support.

FIGURE 57-20 Amplatzer septal occluder. The device is constructed from an alloy of nickel and titanium. The two atrial discs are separated by the central waist. In this photograph, the tethering cable, covered by the delivery sheath, remains attached to the device. (Courtesy AGA Medical, Golden Valley, MN.)

FIGURE 57-21 The Helex septal occluder. The device is composed of a nickel-titanium wire with a patch of microporous expanded polytetrafluoroethylene attached along its length. The elastic properties of the wire form the device into two equal-sized opposing disks that reside on either side of the atrial septum after deployment, thus occluding the defect. (Courtesy W.L. Gore & Associates, Flagstaff, AZ.)

retracted back onto the atrial septum with both fluoroscopic and echocardiographic guidance. The remainder of the device is then deployed within the right atrium so that the waist or core of the device straddles the defect. The delivery cable remains attached to the device until the time of release and can be used to retract the device if positioning is not acceptable (Fig. 57-23). Even after release, the device can be retrieved with various intravascular snares if necessary.

To ensure adequate device deployment, echocardiographic imaging is used in addition to fluoroscopy.[131] Most pediatric institutions continue to use TEE, but ICE has increased in popularity. Use of ICE avoids the necessity of general anesthesia in most patients, but an additional femoral venous access site is required for positioning of the ICE probe within the right atrium. Deployment of the devices with echocardiography alone has also been described.[132] 3-D echocardiographic imaging is frequently used with device placement.[140] This modality provides an en face view of the septum, allowing the interventionalist to better appreciate the true shape and size of the defect. Whichever echocardiographic modality is used, it is imperative to

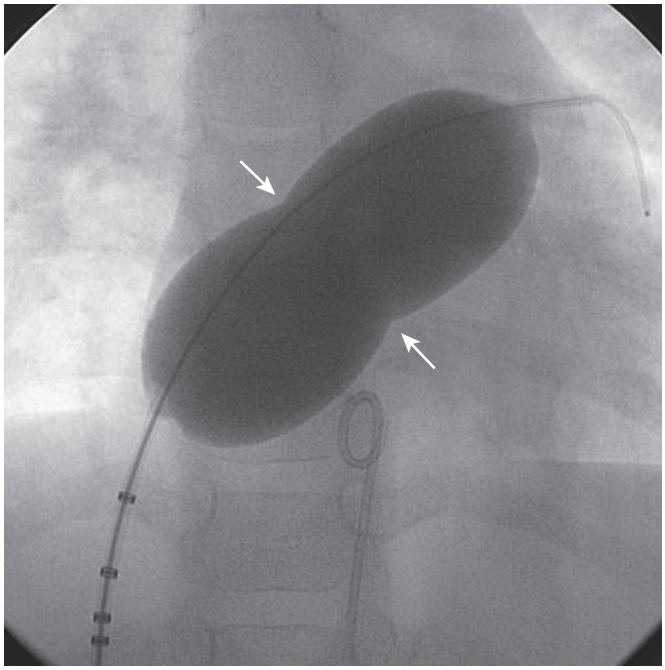

FIGURE 57-22 Still frame of an angiogram demonstrating inflation of the balloon sizing catheter across the atrial septum. The indentations on the balloon *(white arrows)* indicate the stretched margin of the atrial septal defect. That diameter is measured, and an appropriately sized septal occluder is chosen accordingly.

ensure that atrial septal tissue is present between the left and right atrial device discs in all different planes to ensure proper and safe device deployment before the device is released from the delivery cable.

Percutaneous device closure has proved effective in repair of ASDs, with minimal morbidity and no effective mortality. Closure rates are comparable to those achieved with surgery over similar time periods (97% to 99% at 12 months), but procedural morbidity is considerably lower.[134,140,141] Percutaneous closure avoids the necessity of a sternotomy, cardiopulmonary bypass, or mediastinal and chest-tube drainage, but it does have the disadvantage of some limited exposure to ionizing radiation. However, fluoroscopy times are typically brief, and low-dose adjustments can be used. The risk of device embolization is also small and in most cases is related to operator inexperience. The incidence of this complication is in the region of 0.1%.[135,136] Most acute complications have been related to rhythm disturbances, usually atrial flutter or intermittent supraventricular tachycardia. However, these complications are also rare, occurring less than 1% of the time. Thrombus formation on the device, with distal embolization, is of great concern and justifies the recommendation for aspirin therapy until device endothelialization has occurred.[141,142] Collective review of this potential problem, including evaluation of various generations of early septal occluder devices, reveals a low incidence (54 patients over a 14-year period).

Cardiac erosion with possible hemodynamic compromise, particularly by the Amplatzer Septal Occluder, is the most significant short- and long-term complication of percutaneous ASD closure.[143,144] The incidence appears to be low (<0.11%), according to both the manufacturer and published data, and in most cases is related to device oversizing.[143] Deficiency of the retroaortic rim, with resulting need to position the device in a manner that straddles the aorta, may also be a risk factor.[139] Deficiency of that rim or oversizing of the device can cause either aortic compression or direct impingement of the wall of the aorta by either left or right atrial margins of the device (Fig. 57-24). Additionally, oversizing of the device or placement of a device that is too large to be accommodated by the total septal length can cause part

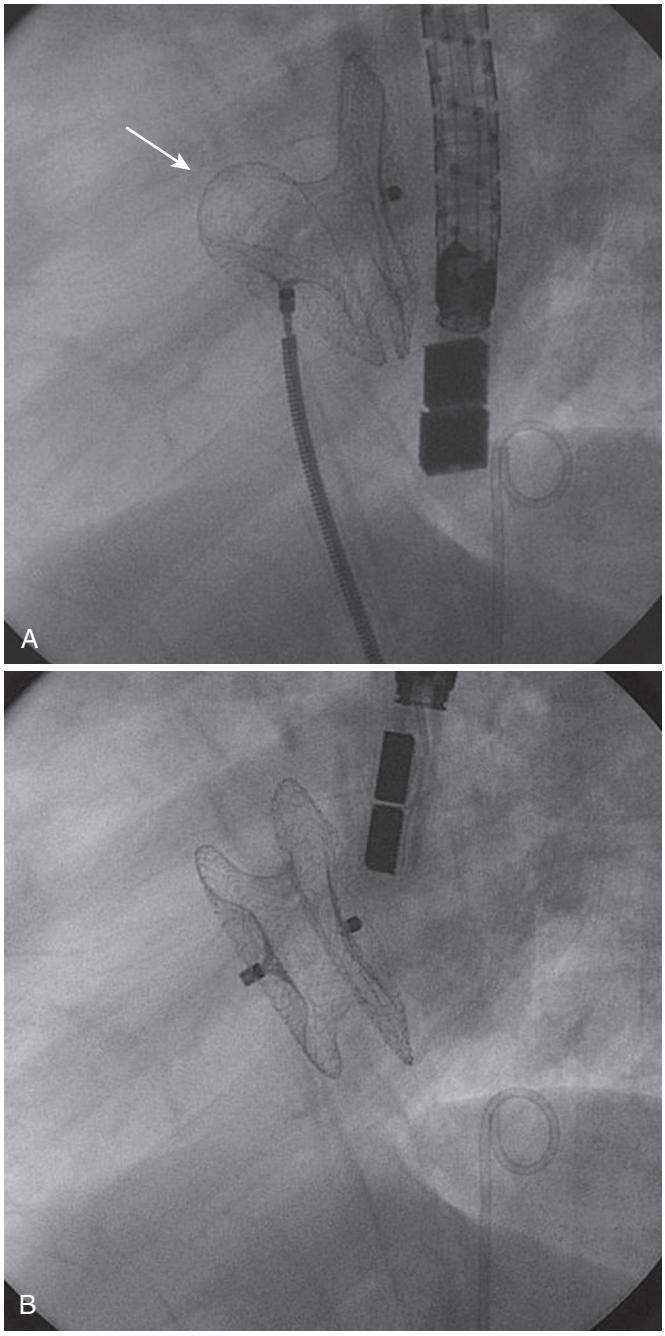

FIGURE 57-23 Still-frame lateral image (**A**) demonstrates full deployment of an Amplatzer Septal Occluder with the cable still attached. Distortion of the superior margin of the right atrial disk of the device *(solid white arrow),* resulting from downward tension by the delivery cable, is typical at this stage of deployment. Retraction and redeployment of the device is easily achieved while it is still attached to the delivery cable. A transesophageal echocardiographic probe is visible in the image. **B,** Still-frame lateral image after release of the Amplatzer Septal Occluder from the delivery cable. The septal occluder immediately assumes the typical position, with the right and left atrial disks parallel to each other.

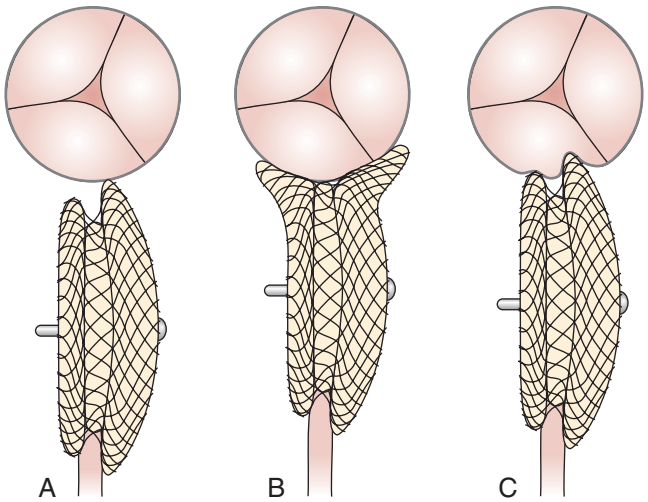

FIGURE 57-24 Diagram demonstrates different relations of the Amplatzer Septal Occluder to the aorta after deployment. **A,** Close proximity, possibly touching. **B,** Straddling the aortic root. **C,** Distortion of the aorta, which may increase the risk of erosion.

of the superior margin of the left atrial disc to abut against the roof of the left atrium. Continuous rocking motion of the device against either the aorta or the atrial wall may result in erosion. If any of these findings become apparent, either during device deployment or after complete deployment, the device should be withdrawn, and attempts to reposition or resize the device should be made. If the findings persist despite these attempts, the device should be removed.[139]

Follow-Up

An echocardiogram should be performed within 24 hours of ASD device closure to exclude the presence of a pericardial effusion. After device implantation, patients should remain on aspirin for at least 6 months, during which time complete device endothelialization occurs. Prophylaxis against subacute bacterial endocarditis is also recommended during that period and should be continued if residual atrial-level shunting is apparent at the time of the 6-month echocardiogram. After that, follow-up should be done at least on an annual basis, with echocardiography obtained during those visits. The right atrial and RV dimensions return to normal within 6 months if no significant atrial-level shunting remains.[145]

TRANSCATHETER CLOSURE OF PATENT DUCTUS ARTERIOSUS

The ductus arteriosus is a muscular artery that extends from the undersurface of the aortic arch to the roof of the main PA but is mostly directed to the left. Although some degree of anatomic variation does occur (e.g., a right aortic arch, in which the ductus arises from the base of the left innominate artery), the relationship is generally consistent. It provides a vital function during fetal life, allowing blood that has entered the main PA via the RV to be redirected into the aorta. At birth, with an increase in arterial oxygen content and a decrease in circulating prostaglandins, the ductus arteriosus spasms and later becomes fibrotic with permanent closure. This occurs usually by 5 to 7 days in full-term infants, but may not occur for up to 3 weeks. Persistence of the ductus arteriosus after that time occurs in 1 of every 2500 to 5000 live births.[146,147] After closure, the ductus arteriosus has no further significance, unless it is associated with a right aortic arch and aberrant origin of the left subclavian artery. Those anatomic associations result in a vascular ring that could prove clinically significant with airway compromise or feeding difficulty in infancy.

Physiology

Discussion regarding the influence of the PDA on the physiology of the neonate, particularly with regard to prematurity and hyaline membrane disease, is beyond the scope of this text. The discussion here will be confined to the effect of the PDA on older children and adults, in whom the impact is similar. The main factors contributing to the effects of a PDA are the size of the vessel and the relative resistance of the systemic and pulmonary vascular beds. When it is small, the hemodynamic effect is negligible, with flow occurring only during systole and limited by the resistance of flow through the narrow ductus. As the PDA increases in size, flow through the PDA continues to be from left to right as long as the pulmonary vascular resistance is lower than that of the systemic vascular bed (even in the presence of a completely unrestrictive vessel). Under those circumstances, PA pressures are equal to aortic pressures, and the flow is left to right during both systole and diastole.

With persistent shunting through a large ductus, the left atrium and LV become increasingly volume loaded and dilated. Further, owing to this increased runoff into a lower-resistance pulmonary vascular bed, the aortic pulse pressure (i.e., the difference between the aortic systolic and diastolic pressures) widens considerably. With continued LV dilation, wall stress and end-diastolic pressures continue to increase, which in turn increases the myocardial oxygen requirement. With the decrease in aortic diastolic pressure, coronary perfusion pressure can at times become narrowed. Although this is theoretically important, it is usually of little clinical concern, and the presence of coronary ischemia with only an isolated PDA has not been described.

Like other shunt lesions that expose the pulmonary vascular bed to persistently high-pressure and high-flow situations, large PDAs can ultimately result in the development of pulmonary vasoocclusive disease.[148] At that time, flow direction across the PDA reverses, and Eisenmenger physiology prevails.[149] Development of those changes depends on ductal size and the duration of its presence, resistance to flow across the vessel, and individual patient susceptibility.

Clinical Presentation and Diagnosis

In infancy and childhood, the clinical presentation of PDA may vary from completely asymptomatic to the full spectrum of congestive heart failure. Symptoms may thus be completely absent but could include failure to thrive, dyspnea, poor feeding, and excessive perspiration. In older children, adolescents, and adults, congestive symptoms are less likely. It is not uncommon for the diagnosis to be suspected when an incidental murmur is heard during a well-child examination. Rarely, patients undiagnosed in infancy may have presenting symptoms of endocarditis or pulmonary vasoocclusive disease if the PDA is sufficiently unrestrictive.

Clinical signs may be absent if the PDA is small and hemodynamically insignificant; with increasing size of the PDA, more typical clinical features become apparent. The pulse pressure may be wider than expected (by palpation and blood pressure measurement), and a murmur of variable grade and duration may be auscultated. If the PDA is small, flow may occur only during systole, and a systolic regurgitant murmur will be present. In the larger PDA, flow occurs throughout the entire cardiac cycle, and the more typical multiphasic continuous machinery murmur is present. As with all left-to-right shunt lesions, if flow is substantial, a middiastolic tricuspid flow murmur may also be audible. These clinical features remain the same if the PDA is sufficiently stenotic. However, if the PDA offers little resistance to flow and PA pressures remain significantly elevated over time, the murmur may become diminished and disappear altogether as pulmonary vascular resistance increases to systemic levels. At that point, with Eisenmenger physiology present, flow across the PDA becomes right to left, and measured oxygen saturations in the lower extremities become lower than those in the upper extremities.[150]

Confirmation of the diagnosis relies on echocardiography. The PDA is well seen in many different views, but the parasternal short-axis view

obtained immediately above the level of the pulmonary valve is ideal. If the PDA is small, two-dimensional imaging may not be helpful; in those cases, color flow mapping in the main PA reveals the flow occurring in an opposite direction to the antegrade PA flow. Caution should be used to avoid confusing a pulmonary insufficiency color jet with that of the PDA. Doppler interrogation of the ductal flow can also help in determining the degree of stenosis across the PDA and in estimating the PA pressure.

Treatment and Outcomes

During the last 3 decades, percutaneous therapy for patients with an isolated PDA has become the standard of care at most institutions in the United States.[151] The exceptions are premature neonates and those patients in early infancy who have particularly large, hemodynamically significant lesions. In those cases, surgical therapy is still regarded as routine. However, the advent of newer generations of ductal closure devices and occlusive plugs has begun to extend the age and size at which PDA closure is now attempted.[152,153]

When necessary, surgical PDA repair is performed, in most cases via the left lateral thoracotomy approach. Usually, the PDA is identified, tied off, and ligated. A left-sided chest tube drain remains in place for a brief period after surgery, and hospitalization may extend for 3 to 4 days. The most significant, but fortunately rare, complications are damage to the recurrent laryngeal nerve and inadvertent ligation of the left PA or descending aorta (the latter with often catastrophic consequences if not immediately identified).[154,155] There is a low but not unexpected morbidity from wound and skin infections. Pain and discomfort are not insignificant, and in most cases opioid analgesics are required during the first 24 hours. There is also a low incidence of vascular recanalization, but that may depend on surgical technique.

Transcatheter device closure of the PDA has been available for about 30 years. Various methods have been prominent during this time, but with evolution of device technology and operator technique, two categories of devices are currently in use: coils and occluder devices. Given the differences in their design and delivery, these are discussed separately.

Coils

Stainless steel Gianturco coils (Cook, Bloomington, IN), of various thicknesses, lengths, and loop diameters, were initially available for general vascular occlusion (Fig. 57-25).[156-158] The application of these coils for small PDA closure began in the early 1990s, and since then, various techniques for their safe delivery and variations on the initial design and delivery have occurred. In general, after basic angiography of the PDA is complete, an appropriately sized coil is chosen. The PDA deemed ideal for coil closure should narrow significantly along its course (to <2 mm), be sufficiently long to accommodate the multiple loops of the coil, and have a sufficient aortic ductal diverticulum. In that way, the loops of the coil on the aortic end of the PDA do not cause flow disturbance in the proximal descending aorta once deployed.

Gianturco coils are delivered in a retrograde manner from the aortic end. Once the delivery catheter (typically a right coronary artery catheter or a similarly shaped catheter) has crossed the PDA, approximately two thirds of a loop of coil is extruded beyond the catheter tip (within the main PA) by a pusher wire of appropriate diameter. The entire catheter-coil complex is then slowly withdrawn until the partially extruded coil is seen to "catch" on the PA wall. At that point, the catheter is retracted back over the pusher wire into the aorta, with the coil held statically in place. As the catheter is withdrawn, the body of the coil straddles the length of the PDA until it is completely extruded from the delivery catheter, when it springs back into the aortic ductal diverticulum and coils appropriately. With correct delivery, approximately two thirds of the coil remains on the pulmonary end of the PDA, a portion of the coil straddles the narrowest section of the vessel, and the remainder of the coil is tightly looped within the aortic ampulla. Repeat angiography is performed at a variable time after delivery to confirm appropriate placement and complete closure.

The risk of coil embolization has resulted in modifications of both the coil design and the delivery method. Detachable coils (Cook) used a screw mechanism on a modified Gianturco coil that allowed repositioning and retrieval if the initial positioning was incorrect.[159,160] However, that modification did not completely alleviate the risk of coil embolization after deployment. Snare techniques to control coil delivery have also been described.[161] Once the initial loop of coil is advanced into the main PA, and before retraction of the delivery catheter back into the aorta, a gooseneck-type snare is positioned on the coil to maintain control at the time of delivery. Although this technique is successful in experienced hands, greater coordination between the primary catheterizer and the assistant is necessary. Difficulty loosening the snare from the coil after complete delivery may also result in displacement after an apparently successful initial coil deployment.

The snare technique is now rarely required since the advent of the Nit-Occlud PDA closure device (PFM Medical, Cologne, Germany). This device is a further modification of the detachable coil but has a unique cone shape that is available in different sizes and lengths

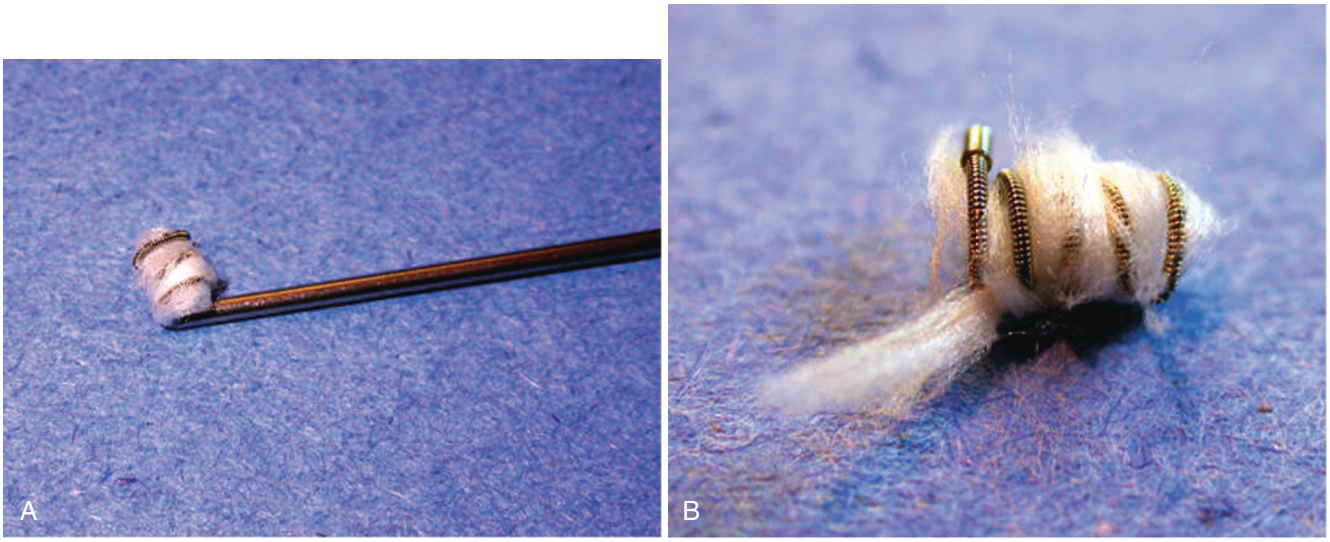

FIGURE 57-25 Partial (**A**) and full (**B**) extrusion of a Gianturco coil from its delivery sleeve. The coil has polyester fibers attached that promote thrombosis once deployed.

FIGURE 57-26 The Nit-Occlud PDA occlusion device. The device consists of a preformed coil in a conical shape and is designed to be positioned in the aortic ductal ampulla, with a section of coil that straddles the patent ductus arteriosus and a smaller counter-coil that resides in the pulmonary ductal ampulla after release. (Courtesy PFM Medical, Cologne, Germany.)

FIGURE 57-27 Amplatzer Duct Occluder I. The device is constructed from an alloy of nickel and titanium. The larger end with the cap is designed to be placed on the aortic end of the patent ductus arteriosus, within the ductal diverticulum. The other end tapers slightly and houses the screw thread for placement of the delivery cable. This image shows the device attached to the delivery cable and the delivery sheath. (Courtesy AGA Medical, Golden Valley, MN.)

(Fig. 57-26). The device is typically deployed in the descending aorta with a tethering cable passed antegrade from the pulmonary side. The body of the device is extruded into the descending aorta. The extruded device and delivery catheter are then retracted until the body of the closure device is lodged within the ductal ampulla. The delivery catheter is withdrawn back across the ductal vessel, deploying the remainder of the device but maintaining control. Confirmatory angiography can then be performed, and if the position is acceptable, the device is released from the tethering delivery cable. Until that point, the device can easily be retracted and redeployed if necessary.[162,163]

Previously, simultaneous deployment of multiple coils was used for closure of large PDAs.[164,165] Since the advent of the newer duct occluder devices and plugs, this technique is largely of historical significance.

In general, coil occlusion has been successful in occluding small PDAs, with closure rates between 95% and 100% at 2 years.[166,167] Duct size has been shown to be the single most important factor in predicting complete early and late closure. Small, residual shunts that are present early after attempted closure raise the prospect of persistent hemolysis with resulting anemia.[168] In most cases, this resolves within 72 hours; if not, a repeat catheterization with further coil placement may be necessary. Early experience with coil occlusion was also associated with mild stenosis of the left PA or descending aorta.[169] However, with refinement of technique and appropriate patient selection for coil placement, this is of less clinical concern in the current era of PDA closure.

Duct Occluder Devices

Currently, the only FDA-approved noncoil device is the Amplatzer Ductal Occluder family of devices (ADO I and ADO II; St Jude Medical).[170,171] The ADO I is a cone-shaped device that tapers from a larger-circumference rimmed edge ("cap"). This device is designed to be delivered through a sheath via the antegrade venous approach, and it has a delivery cable that remains attached until release (Fig. 57-27). The cable can also be used for retraction and repositioning of the device if necessary. Once the delivery sheath has been placed across the PDA and in the proximal descending aorta, the larger, aortic end with the cap is advanced out of the aortic end of the sheath. The device and sheath complex is then pulled back, with the cap positioned on the side wall of the aorta or within the ductal diverticulum. At that point, the delivery cable and device are kept exactly in place and the sheath is pulled back to deploy the remainder of the device within the body of the PDA. Before final release, repeat angiography is performed to ensure adequate positioning of the device. The delivery cable is then unscrewed from the device (Fig. 57-28).

This device has proved to be highly effective in closing larger PDAs, with success rates exceeding 98% at 6 to 12 months after closure.[163,170] The complication profile for this device has also been low, with few serious side effects. Similar concerns regarding left PA or aortic coarctation apply, but in practice, this has not been a large concern.[170,172,173] Patient selection is important in avoiding those complications, and this device should be avoided if the PDA is smaller than 1 to 1.5 mm in the narrowest diameter or the PDA is an aortopulmonary window-type defect with no obvious ampulla. Under those circumstances, a modification of device delivery can be employed, with the aortic cap positioned within the PDA itself and not against the side wall of the aorta. Hemolysis occurring immediately after delivery of Amplatzer occluder devices has also been rarely described, but it has either been self-limited or has resolved with coil placement within the device.[171]

The ADO II is a "biconical" modification of the original device. It is manufactured from a thinner-bore nitinol mesh and can be delivered through smaller guide catheters. The softer nature of the device allows improved conformation on both the aortic and the pulmonary end of the ductus, making it more suitable for smaller patients.[173,174]

FDA approval of other vascular occlusion plugs—the Amplatzer Vascular Plugs (AVP) I, II, and IV (St. Jude Medical)—has also widened the spectrum of devices available for PDA closure.[152,153] These plugs are available in many different sizes. Although they are mostly applicable

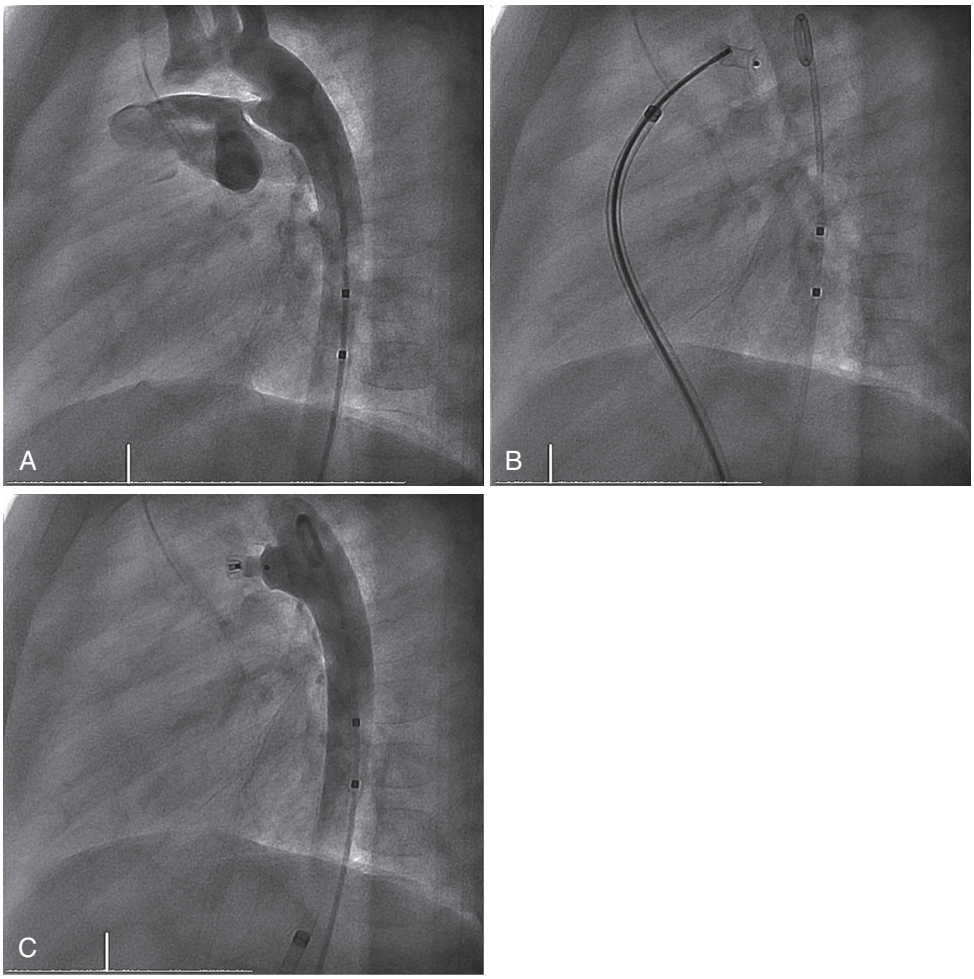

FIGURE 57-28 **A,** Still-frame lateral aortogram of a moderate-sized patent ductus arteriosus (PDA). A well-formed ductal diverticulum is present. **B,** The Amplatzer Duct Occluder has been deployed within the PDA but remains attached to its delivery cable. Retraction and redeployment is still possible at this point. **C,** Still-frame view of lateral aortogram after device release. The ductus is completely occluded, and the device's cap is well positioned within the ductal ampulla.

in smaller patients, they are on occasion suitable for adult-sized patients. Ductal closure rates with these devices appear similar to those achieved with other available means.[163,171]

Follow-Up

Anticoagulation is not required after PDA occlusion with either coils or other devices. Prophylaxis for subacute bacterial endocarditis remains indicated for at least the first 6 months and as long as residual PDA shunting is present. Follow-up echocardiography should be performed at least 6 months after PDA closure; thereafter, if no murmur is present, further testing is not necessary.

TRANSCATHETER PULMONARY VALVE REPLACEMENT

Disruption, removal, and replacement of the native pulmonary valve are common to a number of palliative and reparative surgeries for treatment of CHD. Placement of an RV-PA RVOT conduit is common in surgical palliation of some forms of TOF, transposition of the great arteries, truncus arteriosus, and aortic valve disease treated with the Ross procedure. Even more commonly, in "typical" TOF with pulmonary stenosis, surgical palliation involves enlargement of the pulmonary valve annulus with a transannular patch; this results in long-term pulmonary valve incompetence, which can be associated with late RV dilation and dysfunction. Over the past decade, there has been increasing clinical emphasis on restoration of pulmonary valve function with surgical pulmonary valve replacement before the development of irreversible RV dysfunction. Common long-term limitations to both RV-PA conduits and BPVs include recurrent stenosis and regurgitation. There is strong evidence that such dysfunction can be associated with exercise intolerance, arrhythmias, RV dysfunction, and an increased risk of late sudden death.[175,176] There is also evidence to show that intervention on a dysfunctional RV-PA conduit or BPV can halt or even reverse the risk of these adverse outcomes.[177-179] The long-established standard of care for clinically important RV-PA conduit or BPV stenosis or regurgitation is reoperation involving cardiopulmonary bypass and its attendant risks. Such patients face a lifetime of repeat RVOT operations.[180,181]

TPVR within an existing RV-PS conduit or BPV is one of the newest transcatheter interventions for structural heart disease and has continued to evolve rapidly since its introduction to the field. The goal of this novel therapy is to prolong the interval between surgical RVOT interventions (either RV-PA conduit or BPV replacement), with the intention to reduce the total number of open heart operations required over the lifetime of a patient. A second goal is to reduce the overall time during which a patient lives with some degree of clinically important RVOT dysfunction (valvular stenosis or insufficiency). Percutaneous pulmonary valve implantation was introduced in the year 2000 by

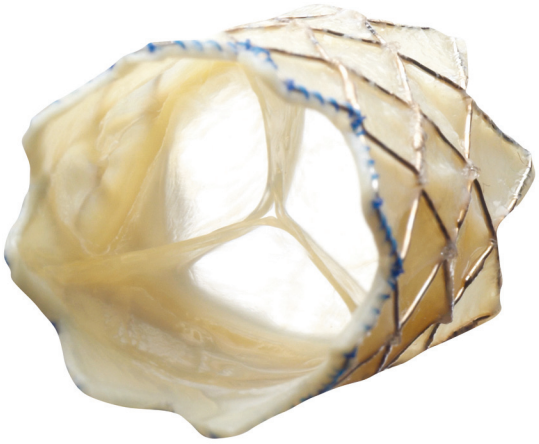

FIGURE 57-29 The Medtronic Melody transcatheter pulmonary valve consists of a bovine jugular venous valve sutured onto a 28-mm balloon-expandable stent. (Courtesy Medtronic, Minneapolis, MN.)

FIGURE 57-30 The Medtronic Ensemble transcatheter valve delivery system is designed to percutaneously deliver the Melody valve. It consists of a 16-Fr delivery catheter with a 22-Fr distal pod that encloses the crimped Melody valve. (Courtesy Medtronic, Minneapolis, MN.)

Bonhoeffer and colleagues.[182,183] This technology was subsequently acquired by Medtronic (Minneapolis, MN) and marketed as the Melody transcatheter pulmonary valve and the Ensemble delivery system (Figs. 57-29 and 57-30). In 2010, based on the results from the U.S. pivotal trial, Medtronic received humanitarian device exemption (HDE) approval from the FDA to market the device in the United States. It has been used in other countries since 2006. As of August 2014, approximately 7000 Melody valves have been implanted in more than 180 centers worldwide. The Edwards SAPIEN transcatheter heart valve (Edwards Lifesciences LLC, Irvine, CA) has FDA approval for transcatheter aortic valve replacement but currently remains an investigational device for TPVR.[184]

Physiology

RVOT obstruction is common in native as well as repaired CHD. Patients who undergo surgical repair that involves the placement of an RV-PA valved conduit or BPV require long-term monitoring (including echocardiography and cardiac MRI) to detect recurrent RVOT dysfunction, specifically stenosis or regurgitation, which eventually occurs in most. The physiology of conduit or BPV stenosis is similar to that of native pulmonary valve stenosis. There is an increase in RV systolic pressure directly related to the severity of the stenosis and the RV stroke volume. This elevated RV systolic pressure stimulates myocardial hypertrophy and also, over time, fibrosis. Eventually, if it is not relieved, severe stenosis will result in RV systolic and diastolic dysfunction. If there is an associated atrial-level communication, the patient will become cyanotic as a right-to-left atrial shunt develops in response to the decreased RV compliance associated with progressive myocardial hypertrophy and fibrosis. Similarly, the physiology of conduit or BPV insufficiency can be compared with that of native pulmonary valve insufficiency. It results in an increased volume load on the RV that causes dilation and can eventually lead to the development of systolic and diastolic dysfunction. If left untreated, RV-PA conduit stenosis and insufficiency can also lead to LV dysfunction secondary to septal shift and adverse ventricular/ventricular interactions.[185]

Clinical Presentation and Diagnosis

Patients with RV-PA conduit or BPV stenosis or insufficiency may be detected early by the presence of a systolic or diastolic murmur, respectively, often without symptoms. As conduit dysfunction progresses in severity or duration, patients may report exercise intolerance and shortness of breath with modest aerobic exercise.[175] Eventually, with progressive RVOT dysfunction, patients may develop with right-sided heart failure. RV dysfunction is known to increase the risk of late arrhythmia and sudden death.[176] Echocardiography and cardiac MRI are the noninvasive diagnostic studies of choice for assessment of conduit or BPV regurgitation or stenosis. For RVOT stenosis, Doppler peak systolic gradients lower than 30 mm Hg are considered mild and those between 30 and 50 mm Hg are moderate (in the face of normal RV systolic function). For RVOT insufficiency, cardiac MRI is the imaging modality of choice to quantify RV systolic and diastolic volumes.

Studies with cardiac MRI show that RV size and function can predict which patients may benefit from intervention for a dysfunctional RV-PA conduit or BPV.[186,187] Intervention is probably indicated for an RVOT with stenosis and/or regurgitation if the RV ejection fraction is diminished or if RV diastolic volume exceeds 160 to 180 mL/m^2. Geva and colleagues showed that all patients who had an RV end-systolic volume greater than 95 mL/m^2 had evidence of RV dysfunction by MRI.[185] Studies of patients with repaired TOF have found that elevation of B-type natriuretic peptide correlates with RV size, ejection fraction, diastolic function, and exercise capacity.[188]

Once the decision has been made that a dysfunctional RVOT conduit warrants intervention, the feasibility of TPVR must be evaluated. Currently, TPVR with the Melody valve is recommended only for RV-PA conduits that were 16 mm or larger in diameter at surgical implantation and that have clinically important stenosis or insufficiency. Valved homograft or heterograft conduits are equally suitable for Melody valve implantation. Precatheterization evaluation typically includes cardiac MRI to evaluate the anatomic dimensions of the surgical RVOT (conduit or BPV),[189,190] the anatomy of the more distal pulmonary artery, and the size and function of the RV. Cardiac MRI also can provide valuable information regarding the proximity of the RVOT to underlying coronary arteries. This is critical information, because RVOT rehabilitation before or during valve implantation can rarely cause coronary artery compression, occasionally with fatal results.[191]

Patients with significant RVOT stenosis or insufficiency after repair of TOF using a transannular patch who have not undergone surgical PVR are infrequently candidates for TPVR. However, some centers have recently demonstrated occasional success with TPVR in this population.[192] Efforts to develop new TPVR technology designed for the patch-augmented or native RVOT, which is typically quite dilated and dynamic throughout the cardiac cycle, are ongoing.

Treatment and Outcomes

In the United States, the only FDA-cleared option for TPVR is the Medtronic Melody valve. The valve is a trileaflet bovine jugular venous valve that has been treated and preserved with glutaraldehyde and sutured into a 34-mm-long platinum-iridium stent (see Fig. 57-29). The stent is covered throughout its length by venous tissue. The valve is supplied in two versions: a 16-mm valve, which is indicated for dilation from 18 to 20 mm, and an 18-mm valve for dilation from 18 to

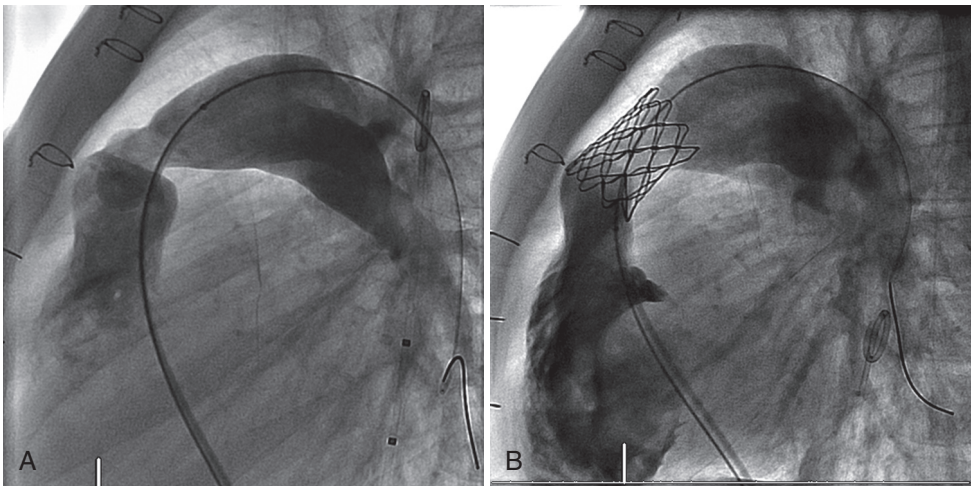

FIGURE 57-31 Lateral angiograms in a 10-year-old boy 8 years after a Ross procedure following aortic valve endocarditis. **A,** Before Melody valve implantation, there is significant stenosis and regurgitation of the right ventricle–to–pulmonary artery (RV-PA) homograft. **B,** After Melody valve implantation, there is relief of the stenosis, and Doppler echocardiography documents only trace valve regurgitation.

22 mm. Some have found these valves to function well at smaller implant diameters and to be expandable to 24 mm, but these implant diameters are not listed on the FDA-cleared instructions for use. Valve implantation is performed with the 22-Fr sheathed Ensemble delivery system on an 18-, 20-, or 22-mm outer balloon catheter with a balloon-in-balloon design to facilitate a more controlled deployment (see Fig. 57-30).

Technique

TPVR is most commonly performed from a femoral venous approach, but the internal jugular venous approach has also been used successfully, as have other central venous and hybrid perventricular strategies, when indicated. After baseline hemodynamic measurements are obtained, RV angiography is performed to assess RV function, the anatomy of the RVOT, and the branch pulmonary arteries; all are important for determining the valve implantation site and the need for concomitant procedures (e.g., branch pulmonary artery rehabilitation).

Although there are a number of approaches to the procedure, existing RVOT stenosis is typically treated with a combination of serial ultra-high-pressure angioplasty and large-diameter bare-metal stent implantation. It is important to establish that there will be no coronary artery compression with RVOT rehabilitation before the implantation of any stent. Therefore during balloon angioplasty of the RVOT, the spatial relationship of the RVOT and coronary arteries is assessed with aortography or selective coronary angiography.[193] Once the possibility of coronary compression is ruled out, the RVOT is rehabilitated to the desired TPVR implant diameter, with placement of large-diameter bare-metal stents (frequently several telescoped within one another for added radial strength). Early data suggested that inadequate conduit preparation (prestenting) resulted in an increased incidence of TPVR stent fracture and valve dysfunction, prompting a shift in approach to more comprehensive RVOT preparation.[194] An existing BPV, in contrast to an RV-PA conduit, rarely requires placement of a preparatory bare-metal stent because the BPV itself typically prevents compressive forces from interacting with the TPV when it is placed in a "valve-in-valve" fashion.

After RVOT preparation, and with an ultrastiff exchange wire positioned in a distal pulmonary artery, the Melody valve is serially rinsed in normal saline baths to adequately dilute the gluteraldehyde solution. The stent is hand-crimped onto the 18-, 20-, or 22-mm balloon of the Ensemble delivery system and loaded into a self-sheathing mechanism. It is of vital importance to be certain that the Melody valve is oriented properly on the delivery balloon (implanting the valve "upside down" will cause complete RVOT obstruction that could be fatal). A formal intraprocedural "time out" at this step is recommended to ensure and document that the TPVR is properly oriented on the delivery system before implantation. The delivery system is advanced over the ultrastiff guidewire into the target implant site within the RVOT. Once it is in the desired position, the delivery sheath is retracted to uncover the valve and balloon. The Melody valve is then implanted with sequential inflation of the inner and then the outer balloon of the Ensemble delivery system. The dilation balloons are then deflated, and the delivery system is withdrawn over the guidewire. Repeat hemodynamic measurements and angiography are performed to document the immediate outcome (Figs. 57-31 and 57-32). If significant residual stenosis is present or a paravalvular leak is noticed, a high-pressure balloon can be used to postdilate the TPVR. Adequate RVOT preparation before TPVR typically obviates this need. It is recommended that the patient be heparinized throughout the procedure.

Variations on the technique described here, particularly prestenting of a stenotic conduit before Melody valve implantation, have become widespread. Evidence suggests that prestenting of the RV-PA conduit with at least one bare-metal stent (in some cases, multiple stents) before TPVR may improve the hemodynamic outcome and decrease the incidence of late Melody stent fracture.[194,195] As experience with this procedure continues to grow, new techniques and changes in the device will undoubtedly occur to make TPVR safer, more successful, and applicable to a larger range of RVOTs and patients.

Results

After an initial report on the first 34 patients, McElhinney and colleagues reported the short- and medium-term follow-up results from the expanded U.S. Melody valve trial in 136 patients over a period of almost 30 months.[196,197] This study evaluated the safety, procedural success, and short- and medium-term effectiveness of the Melody valve in patients with dysfunctional RV-PA conduits or BPVs. TPVR was attempted in 124 (91%) of 136 patients; of the remaining 12 patients, TPVR was not attempted in 6 because there was evidence of coronary artery compression during provocative testing. Melody valve implantation was successful in 123 of the 124 attempts (conduit rupture occurred in one patient, necessitating emergent surgical conduit replacement). Among the cohort with a primary TPVR indication of pulmonary stenosis or mixed pulmonary stenosis and pulmonary regurgitation, the median peak RV-PA pressure gradient was acutely reduced from 43.5 to 14 mm Hg. Pulmonary regurgitation was graded as none or

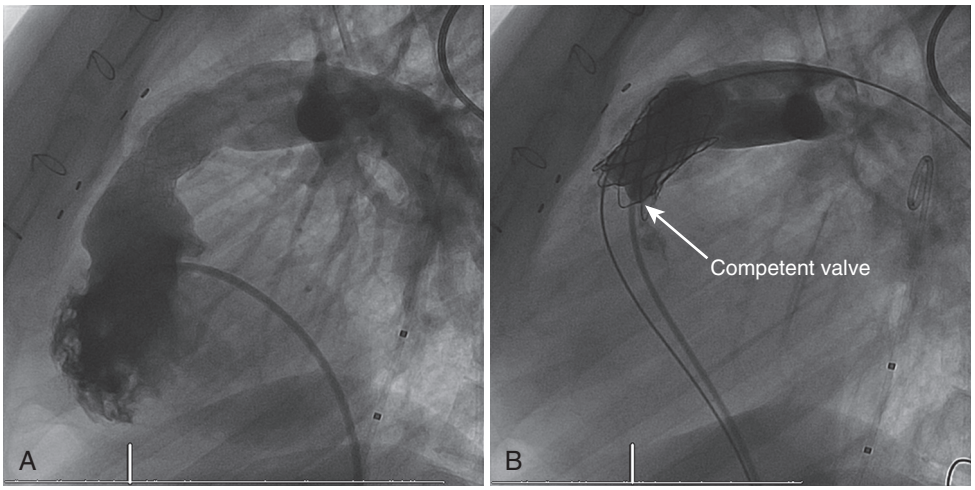

FIGURE 57-32 Lateral angiograms in a 14-year-old girl who had undergone a Rastelli procedure for complex transposition. Two years earlier, she had undergone bare-metal stenting of the right ventricle–to–pulmonary artery (RV-PA) homograft for stenosis but was left with free regurgitation (**A**). After Melody valve implantation (**B**), there is no residual conduit stenosis or regurgitation *(white arrow)*.

trivial in all patients immediately after TPVR. The RV end-diastolic volume, as measured by cardiac MRI, demonstrated substantial reduction at the 6-month follow-up, whereas the RV ejection fraction was not changed. Although medium-term follow-up was limited, no patient had evidence of moderate or severe pulmonary regurgitation at 1 or 2 years of follow-up. Most patients remained in NYHA class I at 2 years. Improvements in cardiopulmonary exercise capacity were modest.[198] Freedom from recurrent RVOT intervention was 95.4% at 1 year and 87.6% at 2 years, which closely matched freedom from valve dysfunction (93.5% and 85.6% at 1 and 2 years, respectively). Ten of the 11 patients requiring RVOT reintervention received transcatheter therapy (90% received a second Melody implant, all in the presence of stent fracture with associated RVOT obstruction).

More recently, Gillespie and associates published their multicenter experience of Melody valve specifically within failed BPVs in the pulmonary position.[199] Acute procedural success was high in this cohort, with no major procedural morbidity, and only two stent fractures identified at a median follow-up of 12 months.

There is a far more extensive international experience with TPVR, and the Melody valve received a CE mark in the European Union and a Canadian Medical Device License in 2006. One review by Lurz and colleagues reported results in 155 consecutive patients, with a median follow-up period of 28 months.[200] The procedure resulted in an immediate decrease in RVOT gradient from 37 to 17 mm Hg ($P < .001$) with no more than mild angiographic pulmonary regurgitation in any patient. Freedom from reintervention was achieved in 95% of these patients at 10 months after implantation.

Complications

TPVR has proved to be safe, with a procedural mortality of less than 0.2%.[201] Acute complications typically relate to RV-PA conduit injury (ranging from mild tear with associated pseudoaneurysm formation to frank conduit rupture with life-threatening hemorrhage), distal guidewire pulmonary artery injury, or more commonly, catheterization-related adverse events such as vascular injury or arrhythmia.[197] A trial is ongoing in the United States to evaluate the use of covered stents in the RVOT for treatment of clinically relevant conduit injury. Coronary artery compression is identifiable during prestent provocative testing and is therefore avoidable, but stent- and valve-related coronary artery compression has been described, occasionally with catastrophic results. Coronary compression can be anticipated in approximately 5% of TPVR candidates and is more common in patients with abnormal coronary artery anatomy.[202]

The most common complication in follow-up has been Melody stent fracture. In the expanded U.S. experience of 150 patients, freedom from Melody stent fracture was 77% at 14 months and 60% at 39 months.[194] Transcatheter implantation within a prestented RV-PA conduit or a BPV was associated with a longer freedom from Melody stent fracture, whereas transcatheter pulmonary valve compression behind the anterior chest wall was associated with shorter freedom from Melody stent fracture. Among patients with a Melody stent fracture, freedom from RVOT intervention was 49% at 2 years. The European experience described by Lurz reported a 21% incidence of late stent fracture.[200] These data have strongly shifted clinical practice toward the placement of RVOT stents before Melody valve implantation.

The most common complication in follow-up has been Melody stent fracture. In the U.S. experience reported by Zahn, implantation of a second Melody valve within a fractured first valve stent (i.e., a "valve-in-valve" procedure) appeared to provide safe and effective treatment for recurrent stenosis secondary to stent fracture in some patients.[203]

Fever after catheterization seems to be a relatively common occurrence, seen in as many as 40% to 80% of patients in some early studies, but is infrequently associated with infection.[204] The development of Melody valve endocarditis has been reported; risk factors have not yet been determined.[205,206]

Conclusion

Similar to advances in transcatheter aortic valve replacement, the availability of TPVR is a remarkable advance for many patients. This technology provides a transcatheter intervention for the dysfunctional RVOT (at this time, in the presence of a dysfunctional RV-PA conduit or BPV) that has the ability to ameliorate both stenosis and regurgitation. Studies have shown that TPVR improves RV hemodynamics and extends the lifespan of the existing RVOT. Although early data demonstrate excellent effectiveness and low complication rates, TPVR remains a work in progress, with only a single first-generation device currently available in the United States. Device competition within the transcatheter pulmonary valve marketplace and development of new devices intended for the patch-augmented RVOT can be expected to expand the population of patients who will benefit from this minimally invasive therapy.

REFERENCES

1. Emmanouilides GC, Baylen BG: Pulmonary stenosis. In Adams FH, Emmanouilides GC, editors: *Heart disease in infants, children, and adolescents*, ed 3, Baltimore, 1983, Williams & Wilkins, p 234.
2. Perloff JK: Postpediatric congenital heart disease: natural survival patterns. In Roberts WC, editor: *Congenital heart disease in adults*, Philadelphia, 1979, Davis, pp 27–51.
3. Nugent EW, Freedom RM, Nora JJ, et al: Clinical course in pulmonary stenosis. *Circulation* 56(Suppl I):I-38–I-47, 1977.
4. Kan JS, White RI, Mitchell SE, et al: Percutaneous balloon valvuloplasty: a new method for treatment of congenital pulmonary-valve stenosis. *N Engl J Med* 307:540, 1982.
5. Becker AE, Anderson AH: Anomalies of the ventricular outflow tracts. In Becker AE, Anderson AH, editors: *Cardiac pathology*, New York, 1983, Raven Press, pp 13.1–13.22.
6. Jeffery RF, Moller JH, Amplatz K: The dysplastic pulmonary valve: a new roentgenographic entity. *Am J Roentgenol Radium Ther Nucl Med* 114:322, 1972.
7. Lababidi Z, Wu JR: Percutaneous balloon pulmonary valvuloplasty. *Am J Cardiol* 52:560–562, 1983.
8. Walls JT, Lababidi Z, Curtis JJ: Morphologic effects of percutaneous balloon pulmonary valvuloplasty. *South Med J* 80:475–477, 1987.
9. DiSessa TG, Alpert BS, Chase NA, et al: Balloon valvuloplasty in children with dysplastic pulmonary valves. *Am J Cardiol* 60:405–407, 1987.
10. Rocchini AP, Beekman RH: Balloon angioplasty in the treatment of pulmonary valve stenosis and coarctation of the aorta. *Tex Heart Inst J* 13:377–385, 1986.
11. Feltes TF, Bacha E, Beekman RH, et al: Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. *Circulation* 123:2607–2652, 2011.
12. Radtke W, Keane JF, Fellows KE, et al: Percutaneous balloon valvotomy of congenital pulmonary stenosis using oversized balloons. *J Am Coll Cardiol* 8:909–915, 1986.
13. Ring JC, Kulik TJ, Burke BA, et al: Morphologic changes induced by dilation of the pulmonary valve annulus with overlarge balloons in normal newborn lambs. *Am J Cardiol* 55:210–214, 1985.
14. Zeevi B, Keane JF, Fellows K, et al: Balloon dilation of critical pulmonary stenosis in the first week of life. *J Am Coll Cardiol* 11:821–824, 1988.
15. Rey C, Marache P, Francart C, et al: Percutaneous transluminal balloon valvuloplasty of congenital pulmonary valve stenosis, with a special report on infants and neonates. *J Am Coll Cardiol* 11:815–820, 1988.
16. Khan MAA, Al-Yousef S, Huhta JC, et al: Critical pulmonary valve stenosis in patients less than 1 year of age: treatment with percutaneous gradational balloon pulmonary valvuloplasty. *Am Heart J* 117:1008–1014, 1989.
17. Fedderly RT, Lloyd TR, Mendelsohn AM, et al: Determinants of successful balloon valvotomy in infants with critical pulmonary stenosis or membranous pulmonary atresia with intact ventricular septum. *J Am Coll Cardiol* 25:460–465, 1995.
18. Colli AM, Perry SB, Lock JE, et al: Balloon dilation of critical valvar pulmonary stenosis in the first month of life. *Cathet Cardiovasc Diagn* 34:23–28, 1995.
19. Stanger P, Cassidy SC, Girod DA, et al: Balloon pulmonary valvuloplasty: results of the Valvuloplasty and Angioplasty of Congenital Anomalies Registry. *Am J Cardiol* 65:775–783, 1990.
20. Pepine CJ, Gessner IH, Feldman RL: Percutaneous balloon valvuloplasty for pulmonary valve stenosis in the adult. *Am J Cardiol* 50:1442–1445, 1982.
21. Rocchini AP, Kveselis DA, Crowley D, et al: Percutaneous balloon valvuloplasty for treatment of congenital pulmonary valvular stenosis in children. *J Am Coll Cardiol* 3:1005–1012, 1984.
22. Al Kasab S, Ribeiro PA, al Raibag M, et al: Percutaneous double balloon pulmonary valvotomy in adults. *Am J Cardiol* 62:822–824, 1988.
23. Holzer RJ, Gauvreau K, Kreutzer J, et al: Safety and efficacy of balloon pulmonary valvuloplasty: a multicenter experience. *Catheter Cardiovasc Interv* 80:663–672, 2012.
24. Behjati-Ardakani M, Forouzannia SK, Abdollahi MH, et al: Immediate, short, intermediate and long-term results of balloon valvuloplasty in congenital pulmonary valve stenosis. *Acta Med Iran* 51:324–328, 2013.
25. Tentolouris CA, Kyriakidis MK, Gaualiatsis IP, et al: Percutaneous pulmonary valvuloplasty in an octogenarian with calcific pulmonary stenosis. *Chest* 101:1456–1458, 1992.
26. Herrmann HC, Hill JA, Krol J, et al: Effectiveness of percutaneous balloon valvuloplasty in adults with pulmonic valve stenosis. *Am J Cardiol* 68:1111–1113, 1991.
27. Sherman W, Hershman R, Alexopoulos D, et al: Pulmonic balloon valvuloplasty in adults. *Am Heart J* 119:186–190, 1990.
28. Fawzy ME, Mercer EN, Dunn B: Late results of pulmonary balloon valvuloplasty in adults using double balloon technique. *J Interv Cardiol* 1:35–42, 1998.
29. Flugelman MY, Halon DA, Lewis BS: Pulmonary balloon valvuloplasty in the seventh decade of life. *Isr J Med Sci* 24:112–113, 1998.
30. Presbitero P, Orzan F, Defilippi G, et al: Percutaneous pulmonary valvuloplasty in adults. *G Ital Cardiol* 18:155–159, 1988.
31. Park JH, Yoon YS, Yeon KM, et al: Percutaneous pulmonary valvuloplasty with a double-balloon technique. *Radiology* 164: 715–718, 1987.
32. Cooke JP, Seward JB, Holmes DR: Transluminal balloon valvotomy for pulmonic stenosis in an adult. *Mayo Clin Proc* 62:306–311, 1987.
33. Leisch F, Schutzenberger W, Kerschner K, et al: Percutaneous pulmonary valvuloplasty in adults. *Z Kardiol* 75:426–430, 1986.
34. Shuck JW, McCormick DJ, Cohen IS, et al: Percutaneous balloon valvuloplasty of the pulmonary valve: role of right to left shunting through a patent foramen ovale. *J Am Coll Cardiol* 4:132–135, 1984.
35. Chen CR, Cheng TO, Huang T, et al: Percutaneous balloon valvuloplasty for pulmonary stenosis in adolescents and adults. *N Engl J Med* 335:21–25, 1996.
36. Taggart NW, Cetta F, Cabalka AK, et al: Outcomes for balloon pulmonary valvuloplasty in adults: comparison with a concurrent pediatric cohort. *Catheter Cardiovasc Interv* 82:811–815, 2013.
37. McCrindle BW, Kan JS: Long-term results after balloon pulmonary valvuloplasty. *Circulation* 83:1915–1922, 1991.
38. McCrindle BW: Independent predictors of long-term results after balloon pulmonary valvuloplasty. *Circulation* 89:1751–1759, 1994.
39. O'Connor BK, Beekman RH, Lindauer A, et al: Intermediate-term outcome after pulmonary balloon valvuloplasty: comparison to a matched surgical control group. *J Am Coll Cardiol* 20:169–173, 1992.
40. Harrild DM, Powell AJ, Trang TX, et al: Long-term pulmonary regurgitation following balloon valvuloplasty for pulmonary stenosis. *J Am Coll Cardiol* 55:1041–1047, 2010.
41. Merino-Ingelmo R, Santos-de Soto J, Coserria-Sánchez F, et al: Long-term results of percutaneous balloon valvuloplasty in pulmonary valve stenosis in the pediatric population. *Rev Esp Cardiol* 67:374–379, 2014.
42. Friedman WF: Aortic stenosis. In Adams FH, Emmanouilides GC, editors: *Heart disease in infants, children, and adolescents*, ed 3, Baltimore, 1983, Williams & Wilkins, p 224.
43. Wagner HR, Ellison RC, Keane JF, et al: Clinical course in aortic stenosis. *Circulation* 56(Suppl I):I-47–I-56, 1977.
44. Lababidi Z, Wu J, Walls JT: Percutaneous balloon aortic valvuloplasty: results in 23 patients. *Am J Cardiol* 53:194–197, 1984.
45. Walls JT, Lababidi Z, Curtis JJ, et al: Assessment of percutaneous balloon pulmonary and aortic valvuloplasty. *J Thorac Cardiovasc Surg* 88:352–356, 1984.
46. Beekman RH, Rocchini AP, Gillon JH, et al: Hemodynamic determinants of the peak systolic pressure gradient in children with valvar aortic stenosis. *Am J Cardiol* 69:813–815, 1992.
47. Helgason H, Keane JF, Fellows KE, et al: Balloon dilation of the aortic valve: studies in normal lambs and in children with aortic stenosis. *J Am Coll Cardiol* 9:816–822, 1987.
48. Ing FF, Boramand NK, Mathewson J, et al: Transcatheter aortic valvuloplasty assisted by right ventricular pacing. *J Am Coll Cardiol* 39(Suppl 2):412A, 2002.
49. Mehta C, Desai T, Shebani S, et al: Rapid ventricular pacing for catheter interventions in congenital aortic stenosis and coarctation: effectiveness, safety, and rate titration for optimal results. *J Interv Cardiol* 23:7–13, 2010.
50. Fischer DR, Ettedgui JA, Park SC, et al: Carotid artery approach for balloon dilation of aortic valve stenosis in the neonate: a preliminary report. *J Am Coll Cardiol* 15:1633–1636, 1990.
51. Galal O, Rao PS, Al-Fadley F, et al: Follow-up results of balloon aortic valvuloplasty in children with special reference to causes of late aortic insufficiency. *Am Heart J* 133:418–427, 1997.
52. McElhinney DB, Lock JE, Keane JF, et al: Left heart growth, function, and reintervention after balloon aortic valvuloplasty for neonatal aortic stenosis. *Circulation* 111:451–458, 2005.
53. Rocchini AP, Beekman RH, Ben Shachar G, et al: Balloon aortic valvuloplasty: results of the valvuloplasty and angioplasty of congenital anomalies registry. *Am J Cardiol* 65:784–789, 1990.
54. Beekman RH, Rocchini AP, Crowley DC, et al: Aortic balloon valvuloplasty: two balloons are better than one. *Circulation* 76:266, 1987.
55. Sholler GF, Keane JF, Perry SB, et al: Balloon dilation of congenital aortic valve stenosis: results and influences of technical and morphological features on outcome. *Circulation* 78:351–360, 1988.
56. Meliones JN, Beekman RH, Rocchini AP, et al: Balloon valvuloplasty for recurrent aortic stenosis after surgical valvotomy in childhood: immediate and follow-up studies. *J Am Coll Cardiol* 13:1106–1110, 1989.
57. Vogel M, Benson LN, Burrows P, et al: Balloon dilatation of congenital aortic valve stenosis in infants and children: short and intermediate term results. *Br Heart J* 62:148–153, 1989.
58. Keane JF, Perry SB, Lock JE: Balloon dilation of congenital valvular aortic stenosis. *J Am Coll Cardiol* 16:457–458, 1990.
59. McCrindle BW: Independent predictors of immediate results of percutaneous balloon aortic valvotomy in childhood. *Am J Cardiol* 77:286–293, 1996.
60. Sandhu SK, Lloyd TR, Crowley DC, et al: Effectiveness of balloon valvuloplasty in the young adult with congenital aortic stenosis. *Cathet Cardiovasc Diagn* 36:122–127, 1995.
61. Jones M, Barnhart GR, Morrow AG: Late results after operations for left ventricular outflow tract obstruction. *Am J Cardiol* 50: 569–579, 1982.
62. Balmer C, Beghetti M, Fasnacht M, et al: Balloon aortic valvoplasty in paediatric patients: progressive aortic regurgitation is common. *Heart* 90:77–81, 2004.
63. Brown DW, Dipilato AE, Chong EC, et al: Aortic valve reinterventions after balloon aortic valvuloplasty for congenital aortic stenosis intermediate and late follow-up. *J Am Coll Cardiol* 56:1740–1749, 2010.
64. Hamidi-Manesh L, Tibby SM, Herman R, et al: Influence of balloon size on aortic regurgitation in neonates undergoing balloon aortic valvuloplasty: a retrospective study over an 11-year period. *J Interv Cardiol* 26:200–207, 2013.
65. Maskatia SA, Ing FF, Justino H, et al: Twenty-five year experience with balloon aortic valvuloplasty for congenital aortic stenosis. *Am J Cardiol* 108:1024–1028, 2011.
66. Maskatia SA, Justino H, Ing FF, et al: Aortic valve morphology is associated with outcomes following balloon valvuloplasty for congenital aortic stenosis. *Catheter Cardiovasc Interv* 81:90–95, 2013.
67. NHLBI Balloon Valvuloplasty Registry Participants: Percutaneous balloon aortic valvuloplasty: acute and 30-day follow-up results in 674 patients from NHLBI Balloon Valvuloplasty Registry. *Circulation* 84:2383–2397, 1991.
68. Safian RD, Berman AD, Diver DJ, et al: Balloon aortic valvuloplasty in 170 consecutive patients. *N Engl J Med* 319:125–130, 1988.
69. Block PC, Palacios IF: Clinical and hemodynamic follow-up after percutaneous aortic valvuloplasty in the elderly. *Am J Cardiol* 62:760–763, 1988.
70. Del Core MG, Nair CK, Peetz D, Jr, et al: Early restenosis following successful percutaneous balloon valvuloplasty for calcific valvular aortic stenosis. *Am Heart J* 118:118–182, 1989.
71. McKay RG, Safian RD, Lock JE, et al: Balloon dilation of calcific aortic stenosis in elderly patients: postmortem, intraoperative, and percutaneous valvuloplasty studies. *Circulation* 74:119–125, 1986.
72. Berdoff RL, Strain J, Crandall C, et al: Pathology of aortic valvuloplasty: findings after postmortem successful and failed dilatations. *Am Heart J* 117:688–690, 1989.
73. Cowley CG, Dietrich M, Mosca RS, et al: Balloon valvuloplasty versus transventricular dilation for neonatal critical aortic stenosis. *Am J Cardiol* 87:1125–1127, 2001.
74. McCrindle BW, Blackstone EH, Williams WG, et al: Are outcomes of surgical versus transcatheter balloon valvotomy equivalent in neonatal critical aortic stenosis? *Circulation* 104(Suppl I):I-152–I-158, 2001.
75. Magee AG, Nykanen D, McCrindle BW, et al: Balloon dilation of severe aortic stenosis in the neonate: comparison of anterograde and retrograde catheter approaches. *J Am Coll Cardiol* 30:1061–1066, 1997.
76. Hsieh K, Keane JF, Nadas AS, et al: Long-term follow-up of valvotomy before 1968 for congenital aortic stenosis. *Am J Cardiol* 58:338–341, 1986.
77. O'Connor BK, Beekman RH, Rocchini AP, et al: Intermediate-term effectiveness of balloon valvuloplasty for congenital aortic stenosis: a prospective follow-up study. *Circulation* 84:732–738, 1991.
78. Brown JW, Rodefeld MD, Ruzmetov M, et al: Surgical valvuloplasty versus balloon aortic dilation for congenital aortic stenosis: are evidence-based outcomes relevant? *Ann Thorac Surg* 94:146–153, 2012.
79. Siddiqui J, Brizard CP, Galati JC, et al: Surgical valvotomy and repair for neonatal and infant congenital aortic stenosis achieves better results than interventional catheterization. *J Am Coll Cardiol* 62:2134–2140, 2013.
80. Petit CJ, Maskatia SA, Justino H, et al: Repeat balloon aortic valvuloplasty effectively delays surgical intervention in children with recurrent aortic stenosis. *Catheter Cardiovasc Interv* 82:549–555, 2013.
81. Kipps AK, McElhinney DB, Kane J, et al: Exercise function of children with congenital aortic stenosis following aortic valvuloplasty during early infancy. *Congenit Heart Dis* 4:258–264, 2009.
82. Robinson JD, del Nido PJ, Geggel RL, et al: Left ventricular diastolic heart failure in teenagers who underwent balloon aortic valvuloplasty in early infancy. *Am J Cardiol* 106:426–429, 2010.
83. Bacha EA, Satou GM, Moran AM, et al: Valve-sparing operation for balloon-induced aortic regurgitation in congenital aortic stenosis. *J Thorac Cardiovasc Surg* 122:162–168, 2001.
84. Beekman RH, Rocchini AP, Andes A: Balloon valvuloplasty for critical aortic stenosis in the newborn: influence of new catheter technology. *J Am Coll Cardiol* 17:1172–1176, 1991.
85. Brown DW, Chong EC, Gauvreau K, et al: Aortic wall injury as a complication of neonatal aortic valvuloplasty: incidence and risk factors. *Circ Cardiovasc Interv* 1:53–59, 2008.
86. McElhinney DB, Marshall AC, Wilkins-Haug LE, et al: Predictors of technical success and postnatal biventricular outcome after in utero aortic valvuloplasty for aortic stenosis with evolving hypoplastic left heart syndrome. *Circulation* 120:1482–1490, 2009.
87. Rothman A, Perry SB, Keane JF, et al: Early results and follow-up of balloon angioplasty for branch pulmonary artery stenoses. *J Am Coll Cardiol* 15:1109–1117, 1990.
88. Kan JS, Marvin WJ, Bass JL, et al: Balloon angioplasty for branch pulmonary artery stenosis: results from the valvuloplasty and

angioplasty of congenital anomalies registry. *Am J Cardiol* 65:798–801, 1990.
89. Bush DM, Hoffman TM, Rosario JD, et al: Frequency of restenosis after balloon pulmonary arterioplasty and its causes. *Am J Cardiol* 86(11):1205–1209, 2000.
90. Mullins CE, O'Laughlin MP, Vick GW, et al: Implantation of balloon-expandable intravascular grafts by catheterization in pulmonary arteries and systemic veins. *Circulation* 77(1):188–199, 1988.
91. Feltes TF, Bacha E, Beekman RH, et al: Indications for cardiac catheterization and intervention in pediatric cardiac disease. *Circulation* 123(22):2607–2652, 2011.
92. Holzer RJ, Gauvreau K, Kreutzer J, et al: Balloon angioplasty and stenting of branch pulmonary arteries: adverse events and procedural haracteristics. Results of a multi-institutional registry. *Circ Cardiovasc Interv* 4(3):287–296, 2011.
93. Ing F: Stents: what's available to the pediatric interventional cardiologist? *Catheter Cardiovasc Interv* 57(3):374–386, 2002.
94. Peters B, Ewert P, Berger F: The role of stents in the treatment of congenital heart disease: current status and future perspectives. *Ann Pediatr Cardiol* 2(1):3–23, 2009.
95. Quandt D, Ramchandani B, Bhole V, et al: Initial experience with the cook formula balloon expandable stent in congenital heart disease. *Catheter Cardiovasc Interv* 85:259–266, 2015.
96. Stapleton GE, Hamzeh R, Mullins CE, et al: Simultaneous stent implantation to treat bifurcation stenoses in the pulmonary arteries: initial results and long-term follow up. *Catheter Cardiovasc Interv* 73(4):557–563, 2009.
97. Stumper O, Bhole V, Anderson B, et al: A novel technique for stenting pulmonary artery and conduit bifurcation stenosis. *Catheter Cardiovasc Interv* 78(3):419–424, 2011.
98. O'Laughlin MP, Slack MC, Grifka RG, et al: Implantation and intermediate term follow-up of stents in congenital heart disease. *Circulation* 88:605–614, 1993.
99. Fogelman R, Nykanen D, Smallhorn JF, et al: Endovascular stents in the pulmonary circulation: clinical impact on management and medium-term follow-up. *Circulation* 92:881–885, 1995.
100. O'Laughlin MP, Perry SB, Lock JE, et al: Use of endovascular stents in congenital heart disease. *Circulation* 83:1923–1939, 1991.
101. Ing FF, Grifka RG, Nihill MR, et al: Repeat dilation of intravascular stents in congenital heart defects. *Circulation* 92:893–897, 1995.
102. McMahon CJ, El Said HG, Vincent JA, et al: Refinements in the implementation of pulmonary arterial stents. *Cardiol Young* 12:445–452, 2002.
103. Law MA, Shamszad P, Nugent AW, et al: Pulmonary artery stents: long-term follow-up. *Catheter Cardiovasc Interv* 75:757–764, 2010.
104. Hallbergson A, Lock JE, Marshall AC: Frequency and risk of in-stent stenosis following pulmonary artery stenting. *Am J Cardiol* 113(3):541–545, 2014.
105. Shaffer KM, Mullins CE, Grifka RG, et al: Intravascular stents in congenital heart disease: short and long-term results from a large single-center experience. *J Am Coll Cardiol* 31:661–667, 1998.
106. Duke C, Rosenthal E, Qureshi SA: The efficacy and safety of stent redilation in congenital heart disease. *Heart* 89:905–912, 2003.
107. Marshall AC, Perry SB, Keane JF, et al: Early results and medium-term follow-up of stent implantation for residual aortic coarctation. *Am Heart J* 139:1054–1060, 2000.
108. Pihkala J, Pedra CA, Nykanen D, et al: Implantation of endovascular stents for hypoplasia of the transverse arch. *Cardiol Young* 10:3–7, 2000.
109. Schaeffler R, Sarikouch S, Peuster M: Anterograde stent implantation for treatment of recurrent coarctation after Norwood operation. *Pediatr Cardiol* 29(2):388–392, 2008.
110. Sohrabi B, Jamshidi P, Yaghoubi A, et al: Comparison between covered and bare Cheatham-platinum stents for endovascular treatment of patients with native post-ductal aortic coarctation: immediate and intermediate-term results. *JACC Cardiovasc Interv* 7(4):416–423, 2014.
111. Tzifa A, Ewert T, Brzezinska-Rajszys G, et al: Covered Cheatham-platinum stents for aortic coarctation. *J Am Coll Cardiol* 47:1457–1463, 2006.
112. Varma C, Benson LN, Butany J, et al: Aortic dissection after stent dilatation for coarctation of the aorta: a case report and literature review. *Catheter Cardiovasc Interv* 59:528–535, 2003.
113. Butera G, Manica JLL, Marini D, et al: From bare to covered. *Catheter Cardiovasc Interv* 83(6):953–963, 2014.
114. Ebeid MR, Prieto LR, Latson LA: Use of balloon expandable stents for coarctation of the aorta. *J Am Coll Cardiol* 30:1847–1852, 1997.
115. Suarez de Lezo J, Pan M, Romero M, et al: Immediate and follow-up findings after stent treatment for severe coarctation of the aorta. *Am J Cardiol* 83:400–406, 1999.
116. Forbes TJ, Moore P, Pedra CAC, et al: Intermediate follow-up following intravascular stenting for treatment of coarctation of the aorta. *Catheter Cardiovasc Interv* 70:569–577, 2007.
117. Forbes TJ, Garekar S, Amin Z, et al: Procedural results and acute complications in stenting native and recurrent coarctation of the aorta in patients over 4 years of age: a multi-institutional study. *Catheter Cardiovasc Interv* 70:276–285, 2007.
118. Mohan UR, Danon S, Levi D, et al: Stent implantation for coarctation of the aorta in children <30 kg. *JACC Cardiovasc Interv* 2:877–883, 2009.
119. Ringel RE, Vincent J, Jenkins KJ, et al: Acute outcome of stent therapy for coarctation of the aorta: results of the coarctation of the aorta stent trial. *Catheter Cardiovasc Interv* 82(4):503–510, 2013.
120. Holzer R, Qureshi S, Ghasemi A, et al: Stenting of aortic coarctation: acute, intermediate, and long-term results of a prospective multi-institutional registry. Congenital Cardiovascular Interventional Study consortium (CCISC). *Catheter Cardiovasc Interv* 76(4):553–563, 2010.
121. Harrison DA, McLaughlin PR, Lazzam C, et al: Endovascular stents in the management of coarctation of the aorta in the adolescent and adult: one year follow-up. *Heart* 85:561–566, 2001.
122. Forbes TJ, Kim DW, Du W, et al: Comparison of surgical, stent, and balloon angioplasty treatment of native coarctation of the aorta: an observational study by the CCISC (Congenital Cardiovascular Interventional Study Consortium). *J Am Coll Cardiol* 58(25):2664–2674, 2011.
123. Krasemann T, Bano M, Rosenthal E, et al: Results of stent implantation for native and recurrent coarctation of the aorta: follow-up of up to 13 years. *Catheter Cardiovasc Interv* 78(3): 405–412, 2011.
124. Sadiq M, Rehman AU, Qureshi AU, et al: Covered stents in the management of native coarctation of the aorta: intermediate and long-term follow-up. *Catheter Cardiovasc Interv* 82(4):511–518, 2013.
125. Morgan GJ, Lee KJ, Chaturvedi R, et al: Systemic blood pressure after stent management for arch coarctation: implications for clinical care. *JACC Cardiovasc Interv* 6(2):192–201, 2013.
126. Brassard M, Fouron JC, van Doesburg NH, et al: Outcome of children with atrial septal defect considered too small for surgical closure. *Am J Cardiol* 83:1552–1555, 1999.
127. Tabery S, Daniels O: How classical are the clinical features of the "ostium secundum" atrial septal defect? *Cardiol Young* 7:294–301, 1997.
128. Andrews R, Tulloh R, Magee A, Anderson D: Atrial septal defect with failure to thrive in infancy: hidden pulmonary vascular disease? *Pediatr Cardiol* 23:528–530, 2002.
129. Shah D, Azhar M, Oakley CM, et al: Natural history of secundum atrial septal defect in adults after medical or surgical treatment: a historical prospective study. *Br Heart J* 71:224–228, 1994.
130. Konstantinides S, Geibel A, Olschewski M, et al: A comparison of surgical and medical therapy for atrial septal defect in adults. *N Engl J Med* 333(8):469–514, 1995.
131. Salaymeh K, Taeed R, Michelfelder EC, et al: Unique echocardiographic features associated with deployment of the Amplatzer atrial septal defect device. *J Am Soc Echocardiogr* 14(2): 128–137, 2001.
132. Ewert P, Daehnert I, Berger F, et al: Transcatheter closure of atrial septal defects under echocardiographic guidance without x-ray: initial experiences. *Cardiol Young* 9:136–140, 1999.
133. Formigari R, Di Donato RM, Mazzera E, et al: Minimally invasive or interventional repair of atrial septal defects in children: experience in 171 cases and comparison with conventional strategies. *J Am Coll Cardiol* 37(6):1707–1712, 2001.
134. Cowley CG, Lloyd TR, Bove EL, et al: Comparison of results of closure of secundum atrial septal defect by surgery versus Amplatzer septal occluder. *Am J Cardiol* 88:589–591, 2001.
135. Berger F, Ewett P, Björnstad PG, et al: Transcatheter closure as standard treatment for most interatrial defects: experience in 200 patients treated with the Amplatzer septal occluder. *Cardiol Young* 9:468–473, 1999.
136. Bilkis AA, Alwi M, Hasri S, et al: The Amplatzer duct occluder: experience in 209 patients. *J Am Coll Cardiol* 37(1):258–261, 2001.
137. Chan KC, Godman MJ, Walsh K, et al: Transcatheter closure of atrial septal defect and interatrial communications with a new self expanding nitinol double disc device (Amplatzer septal occluder): multicentre UK experience. *Heart* 82:300–306, 1999.
138. Zahn EM, Wilson N, Cutright W, et al: development and testing of the Helex septal occluder, a new expanded polytetrafluoroethylene atrial septal defect occlusion system. *Circulation* 104:711–716, 2001.
139. Moore J, Hegde S, El-Sais H, et al: Transcatheter device closure of atrial septal defects: a safety review. *JACC Cardiovasc Interv* 6(5):433–442, 2013.
140. Perk G, Lang RM, Garcia-Fernandez MA, et al: Use of real time three-dimensional transesophageal echocardiography in intracardiac catheter based interventions. *J Am Soc Echocardiogr* 22(8):865–882, 2009.
141. Berger F, Vogel M, Alexi-Meskishvili V, et al: comparison of results and complications of surgical and Amplatzer device closure of atrial septal defects. *J Thorac Cardiovasc Surg* 118(4): 674–680, 1999.
142. Sherman JM, Hagler DJ, Cetta F: Thrombosis after septal closure device placement: a review of the current literature. *Catheter Cardiovasc Interv* 63:486–489, 2004.
143. Amin Z, Hijazi ZM, Bass JL, et al: Erosion of Amplatzer septal occluder device after closure of secundum atrial septal defects: review of registry of complications and recommendations to minimize future risk. *Catheter Cardiovasc Interv* 63:496–502, 2004.
144. Divekar A, Gaamangwe T, Shaikh N, et al: Cardiac perforation after device closure of atrial septal defects with the Amplatzer septal occluder. *J Am Coll Cardiol* 45(8):1213–1218, 2005.
145. Veldtman GR, Razack V, Siu S, et al: Right ventricular form and function after percutaneous atrial septal defect device closure. *J Am Coll Cardiol* 37(8):2108–2113, 2001.
146. Arlettaz R, Archer N, Wilkinson AR: Natural history of innocent murmurs in newborn babies: controlled echocardiography study. *Arch Dis Child Fetal Neonatal Ed* 78(3):F166–F170, 1998.
147. Jan SL, Hwang B, Fu YC, et al: Prediction of ductus arteriosus closure by neonatal screening echocardiography. *Int J Cardiovasc Imaging* 20(5):349–356, 2004.
148. Waddell TK, Bennett L, Kennedy R, et al: Heart-lung or lung transplantation for Eisenmenger syndrome. *J Heart Lung Transplant* 21(7):731–737, 2002.
149. Sahn DW, Kim YJ, Zo JH, et al: The value of contrast echocardiography in the diagnosis of patent ductus arteriosus with Eisenmenger's syndrome. *J Am Soc Echocardiogr* 14(1):57–59, 2001.
150. Panetta G, Schiller N: Evidence of patent ductus arteriosus and right-to-left shunt by finger pulse oximetry and Doppler signals of agitated saline in abdominal aorta. *J Am Soc Echocardiogr* 12(9):763–765, 1999.
151. Moore JW, Levi DS, Moore SD, et al: Interventional treatment of patent ductus arteriosus in 2004. *Catheter Cardiovasc Interv* 64:91–101, 2005.
152. Delaney JW, Fletcher SE: Patent ductus arteriosus closure using the Amplatzer vascular plug II for all anatomic variants. *Catheter Cardiovasc Interv* 81(5):820–824, 2013.
153. Sungur M, Karakurt C, Ozbarlas N, Baspinar O: Closure of patent ductus arteriosus in children, small infants, and premature babies with Amplatzer duct occluder II additional sizes: multicenter study. *Catheter Cardiovasc Interv* 82(2):245–252, 2013.
154. Strychowsky JE, Rukholm G, Gupta MK, Reid D: Unilateral vocal fold paralysis after congenital cardiothoracic surgery: a meta-analysis. *Pediatrics* 133(6):e1708–e1723, 2014.
155. Hutchings K, Vasquez A, Price D, et al: Outcomes following neonatal patent ductus arteriosus ligation done by pediatric surgeons: a retrospective cohort analysis. *J Pediatr Surg* 48(5):915–918, 2013.
156. Rothman A, Lucas VW, Sklansky MS, et al: Percutaneous coil occlusion of patent ductus arteriosus. *J Pediatr* 130:447–454, 1997.
157. Wang J-K, Liau C-S, Huang J-J, et al: Transcatheter closure of patent ductus arteriosus using Gianturco coils in adolescents and adults. *Catheter Cardiovasc Interv* 55:513–518, 2002.
158. Alwi M, Kang LM, Samion H, et al: Transcatheter occlusion of native persistent ductus arteriosus using conventional Gianturco coils. *Am J Cardiol* 79(10):1430–1432, 1997.
159. Uzun O, Hancock S, Parsons JM, et al: Transcatheter occlusion of the arterial duct with Cook detachable coils: early experience. *Heart* 76:269–273, 1996.
160. Bermudez-Canete R, Santoro G, Bialkowsky J, et al: Patent ductus arteriosus occlusion using detachable coils. *Am J Cardiol* 82:1547–1549, 1998.
161. Ing FF, Sommer RJ: The snare-assisted technique for transcatheter coil occlusion of moderate to large patent ductus arteriosus: immediate and intermediate results. *J Am Coll Cardiol* 33:1710–1718, 1999.
162. Ghasemi A, Pandya S, Reddy SV, et al: Trans-catheter closure of patent ductus arteriosus: what is the best device? *Catheter Cardiovasc Interv* 76(5):703–704, 2010.
163. Masura J, Tittel P, Gavora P, et al: Long-term outcome of transcatheter patent ductus arteriosus closure using Amplatzer duct occluders. *Am Heart J* 151(3):755.e7–755.e10, 2006.
164. Hijazi ZM, Lloyd TR, Beekman RH, III, et al: Transcatheter closure with single or multiple Gianturco coils of patent ductus arteriosus in infants weighing ≤8 kg: retrograde versus antegrade approach. *Am Heart J* 132:827–835, 1996.
165. Hijazi ZM, Geggel RL: Transcatheter closure of large patent ductus arteriosus (≥4 mm) with multiple Gianturco coils: immediate and mid-term results. *Heart* 76:536–540, 1996.
166. Goyal VS, Fulwant MC, Ramakantan R, et al: Follow-up after coil closure of patent ductus arteriosus. *Am J Cardiol* 83:463–466, 1999.
167. Shim D, Fedderly RT, Beekman RH, III, et al: Follow-up of coil occlusion of patent ductus arteriosus. *J Am Coll Cardiol* 28(1): 207–211, 1996.
168. Radha S, Sivakumar K, Philip AK, et al: Clinical course and management strategies for hemolysis after transcatheter closure of patent arterial ducts. *Catheter Cardiovasc Interv* 59:538–543, 2003.
169. Carey LM, Vermilion RKP, Shim D, et al: Pulmonary artery size and flow disturbances after patent ductus arteriosus coil occlusion. *Am J Cardiol* 78:1307–1309, 1996.
170. Pass RH, Hijazi Z, Hsu DT, et al: Multicenter USA Amplatzer patent ductus arteriosus occlusion device trial: initial and one-year results. *J Am Coll Cardiol* 44(3):513–519, 2004.
171. Joseph G, Mandalay A, Zacharias TU, et al: Severe intravascular hemolysis after transcatheter closure of a large patent ductus arteriosus using the Amplatzer duct occluder: successful resolution by intradevice coil deployment. *Catheter Cardiovasc Interv* 55:245–249, 2002.
172. Thanopoulos BV, Eleftherakis N, Tzannos K, et al: Further experience with catheter closure of patent ductus arteriosus using the new Amplatzer duct occluder in children. *Am J Cardiol* 105(7):1005–1009, 2010.
173. Saliba Z, El-Rassi I, Abi-Warde MT, et al: The Amplatzer Duct Occluder II: a new device for percutaneous ductus arteriosus closure. *J Interv Cardiol* 22(6):496–502, 2009.

174. Bhole V, Miller P, Mehta C, et al: Clinical evaluation of the new Amplatzer duct occluder II for patent arterial duct occlusion. *Catheter Cardiovasc Interv* 74(5):762–769, 2009.
175. Carvalho JS, Shinebourne EA, Busst C, et al: Exercise capacity after complete repair of tetralogy of Fallot: deleterious effects of residual pulmonary regurgitation. *Br Heart J* 67(6):470–473, 1992.
176. Gatzoulis MA, Balaji S, Webber SA, et al: Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet* 356(9234):975–981, 2000.
177. Bove EL, Kavey RE, Byrum CJ, et al: Improved right ventricular function following late pulmonary valve replacement for residual pulmonary insufficiency or stenosis. *J Thorac Cardiovasc Surg* 90(1):50–55, 1985.
178. Eyskens B, Reybrouck T, Bogaert J, et al: Homograft insertion for pulmonary regurgitation after repair of tetralogy of Fallot improves cardiorespiratory exercise performance. *Am J Cardiol* 85(2):221–225, 2000.
179. Therrien J, Siu SC, Harris L, et al: Impact of pulmonary valve replacement on arrhythmia propensity late after repair of tetralogy of Fallot. *Circulation* 103(20):2489–2494, 2001.
180. Bielefeld MR, Bishop DA, Campbell DN, et al: Reoperative homograft right ventricular outflow tract reconstruction. *Ann Thorac Surg* 71(2):482–487, discussion 487–488, 2001.
181. Stark J, Bull C, Stajevic M, et al: Fate of subpulmonary homograft conduits: determinants of late homograft failure. *J Thorac Cardiovasc Surg* 115(3):506–514, discussion 514–506, 1998.
182. Bonhoeffer P, Boudjemline Y, Saliba Z, et al: Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. *Lancet* 356(9239):1403–1405, 2000.
183. Bonhoeffer P, Boudjemline Y, Saliba Z, et al: Transcatheter implantation of a bovine valve in pulmonary position: a lamb study. *Circulation* 102(7):813–816, 2000.
184. Kenny D, Hijazi ZM, Kar S, et al: Percutaneous implantation of the Edwards SAPIEN transcatheter heart valve for conduit failure in the pulmonary position: early phase 1 results from an international multicenter clinical trial. *J Am Coll Cardiol* 58(21): 2248–2256, 2011.
185. Geva T, Sandweiss BM, Gauvreau K, et al: Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. *J Am Coll Cardiol* 43(6):1068–1074, 2004.
186. Karamlou T, Silber I, Lao R, et al: Outcomes after late reoperation in patients with repaired tetralogy of Fallot: the impact of arrhythmia and arrhythmia surgery. *Ann Thorac Surg* 81(5): 1786–1793, discussion 1793, 2006.
187. Therrien J, Provost Y, Merchant N, et al: Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. *Am J Cardiol* 95(6):779–782, 2005.
188. Norozi K, Buchhorn R, Bartmus D, et al: Elevated brain natriuretic peptide and reduced exercise capacity in adult patients operated on for tetralogy of Fallot is due to biventricular dysfunction as determined by the myocardial performance index. *Am J Cardiol* 97(9):1377–1382, 2006.
189. Schievano S, Coats L, Migliavacca F, et al: Variations in right ventricular outflow tract morphology following repair of congenital heart disease: implications for percutaneous pulmonary valve implantation. *J Cardiovasc Magn Reson* 9(4):687–695, 2007.
190. Schievano S, Migliavacca F, Coats L, et al: Percutaneous pulmonary valve implantation based on rapid prototyping of right ventricular outflow tract and pulmonary trunk from MR data. *Radiology* 242(2):490–497, 2007.
191. Mauri L, Frigiola A, Butera G: Emergency surgery for extrinsic coronary compression after percutaneous pulmonary valve implantation. *Cardiol Young* 23(3):463–465, 2013.
192. Meadows JJ, Moore PM, Berman DP, et al: Use and performance of the Melody transcatheter pulmonary valve in native and post-surgical, nonconduit right ventricular outflow tracts. *Circ Cardiovasc Interv* 7(3):374–380, 2014.
193. Sridharan S, Coats L, Khambadkone S, et al: Images in cardiovascular medicine. Transcatheter right ventricular outflow tract intervention: the risk to the coronary circulation. *Circulation* 113(25):e934–e935, 2006.
194. McElhinney DB, Cheatham JP, Jones TK, et al: Stent fracture, valve dysfunction, and right ventricular outflow tract reintervention after transcatheter pulmonary valve implantation: patient-related and procedural risk factors in the US Melody valve trial. *Circ Cardiovasc Interv* 4(6):602–614, 2011.
195. Nordmeyer J, Lurz P, Khambadkone S, et al: Pre-stenting with a bare metal stent before percutaneous pulmonary valve implantation: acute and 1-year outcomes. *Heart* 97(2):118–123, 2011.
196. Zahn EM, Hellenbrand WE, Lock JE, et al: Implantation of the Melody transcatheter pulmonary valve in patients with a dysfunctional right ventricular outflow tract conduit early results from the U.S. clinical trial. *J Am Coll Cardiol* 54(18):1722–1729, 2009.
197. McElhinney DB, Hellenbrand WE, Zahn EM, et al: Short- and medium-term outcomes after transcatheter pulmonary valve placement in the expanded multicenter US Melody valve trial. *Circulation* 122:507–516, 2010.
198. Batra AS, McElhinney DB, Wang W, et al: Cardiopulmonary exercise function among patients undergoing transcatheter pulmonary valve implantation in the US Melody valve investigational trial. *Am Heart J* 163(2):280–287, 2012.
199. Gillespie MJ, Rome JJ, Levi DS, et al: Melody valve implant within failed bioprosthetic valves in the pulmonary position: a multicenter experience. *Circ Cardiovasc Interv* 5(6):862–870, 2012.
200. Lurz P, Coats L, Khambadkone S, et al: Percutaneous pulmonary valve implantation: impact of evolving technology and learning curve on clinical outcome. *Circulation* 117(15):1964–1972, 2008.
201. Lurz P, Gaudin R, Taylor AM, et al: Percutaneous pulmonary valve implantation. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2009:112–117, 2009.
202. Morray BH, McElhinney DB, Cheatham JP, et al: Risk of coronary artery compression among patients referred for transcatheter pulmonary valve implantation: a multicenter experience. *Circ Cardiovasc Interv* 6(5):535–542, 2013.
203. Nordmeyer J, Coats L, Lurz P, et al: Percutaneous pulmonary valve-in-valve implantation: a successful treatment concept for early device failure. *Eur Heart J* 29(6):810–815, 2008.
204. Bonhoeffer P, Boudjemline Y, Qureshi SA, et al: Percutaneous insertion of the pulmonary valve. *J Am Coll Cardiol* 39(10):1664–1669, 2002.
205. McElhinney DB, Benson LN, Eicken A, et al: Infective endocarditis after transcatheter pulmonary valve replacement using the Melody valve: combined results of 3 prospective North American and European studies. *Circ Cardiovasc Interv* 6(3):292–300, 2013.
206. Villafane J, Baker GH, Austin EH, 3rd, et al: Melody pulmonary valve bacterial endocarditis: experience in four pediatric patients and a review of the literature. *Catheter Cardiovasc Interv* 84(2): 212–281, 2014.

Stem Cell Therapy for Ischemic Heart Disease

58

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KEY POINTS

- Advances in reperfusion therapy have produced a large population of patients with chronic heart failure who need new approaches such as stem cell therapy to improve outcomes.
- Large-scale clinical trials with meaningful outcomes are needed to determine efficacious cell populations and regenerative strategies. The time for small studies with multiple subgroups is past.
- Improvements in cardiac function with cell therapy do not necessarily imply improvements in electrical conduction or arrhythmogenic risk.
- Multiple delivery strategies and devices have entered the clinical realm.
- Advances in the generation of cardiomyocytes from induced pluripotent stem cells suggest autologous cardiac myocyte regeneration may be possible in the future.

The many efforts to maximize therapy for patients with acute myocardial infarction (AMI) have yielded significant benefits. Beginning with thrombolytic therapy for AMI and continuing with primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI), the mortality rates for this devastating ischemic event have decreased from almost 15% in clinical trials in the late 1980s[1] to less than 5% in recent primary PCI trials.[2] Before these innovations, ischemic heart disease was the leading cause of congestive heart failure (CHF). Although further improvements in reperfusion are needed, current efforts have produced growing numbers of patients with CHF who have survived what would have been fatal events in the past. The prevalence of CHF has increased dramatically over the preceding decade, and more than 10% of the U.S. population older than 65 years of age carry the diagnosis.

Although the mechanisms are still under investigation,[3,4] we understand that development of CHF after myocardial infarction is more than the loss of contractile tissue. The condition is partially determined by the ventricular remodeling that occurs in response to myocardial necrosis.[5] The inflammatory response to myocardial necrosis leads to infarct expansion, dilation of the left ventricular (LV) cavity, and replacement of cardiomyocytes with fibrous tissue.[3,5] The remodeling process results in an infarct border zone that is ischemic and may drive inflammation and further adverse remodeling.[6]

Treatment of the border zone is one target of cardiovascular regenerative therapies because increasing the contractile reserve of the border zone correlates with improved ventricular remodeling.[6,7] However, available therapies to alter the remodeling process and progression to CHF remain limited, and death rates for CHF continue to rise. Based on current trends, the problem is predicted to increase to more than 6 million cases by the year 2030.

The increasing burden of CHF has been addressed with pharmacologic therapy, which in some patients can improve and delay the morbidity and mortality of CHF; with electrical therapy, including cardiac resynchronization therapy; with LV remodeling surgery; and with mechanical therapy using the first LV assist device for destination therapy. During the past 15 years, cardiovascular medicine has taken great interest in the potential of regenerative therapies, particularly stem cell therapies, to prevent and treat cardiac dysfunction because this approach can address the underlying problem: loss of cardiomyocytes due to ischemic death. Although there was much excitement and fanfare in the beginning, the field has had to address many challenges. However, there has been progress, and there is hope for improving patient outcomes in the future.

APPROACHES TO CELL THERAPY

The field of cell transplantation for the treatment of LV dysfunction after ischemic injury continues to make significant progress. Dozens of completed studies and meta-analyses suggest overall benefit for patients treated compared with controls.[8-11] The goal has not changed: define a cell type that can incorporate into the recipient myocardium, survive, mature, and electromechanically couple to similar cells and to native cardiomyocytes.

The field began with differentiated cell transplantation (Fig. 58-1, *A*). The goal was to functionally achieve myoplasty through transplantation of autologous skeletal myoblasts (SKMBs) that would engraft into injured myocardium in patients with ischemic CHF.[12] Another strategy that has been implemented in clinical studies is stem cell mobilization (see Fig. 58-1, *B*), which involves the pharmacologic mobilization of a patient's own bone marrow cells into the bloodstream, homing of the stem cells to engraft in areas of myocardial damage, and directing the engrafted stem cells to differentiate into cardiomyocytes and vascular structures that fully integrate with the native myocardium.

Comprehensive studies have shown some patient benefit from stem cell transplantation (see Fig. 58-1, *C*). It involves removal of stem cells from the bone marrow of the patient (i.e., autologous graft) or a well-screened donor (i.e., allogeneic graft) and injection of whole bone marrow or a selected population of bone marrow–derived stem cells into the infarct zone.

Questions abound about how these strategies can lead to clinical benefit by preventing (for patients in the periinfarct period) or treating (for patients with CHF) cardiac dysfunction. In this chapter, we summarize the current state of knowledge, examine the findings of ongoing studies, and consider the future of stem cell therapy.

Differentiated Cell Transplantation

The goal of differentiated cell transplantation is substitution of scarred myocardium with viable cells, ultimately improving myocardial function. Several cell types, including smooth muscle cells and SKMBs, have been studied as candidates for differentiated cell transplantation. The value of these cell types is judged by their accessibility and their ability to be expanded in vitro before transplantation.

The first cell therapy for CHF was cardiomyoplasty. During this procedure, the heart was wrapped in skeletal muscle that was then paced to increase contractility of the weakened heart.[13-15] Skeletal muscle was engrafted in the epicardial layers of the heart,[16,17] a process now recognized as ingrowth and engraftment of SKMBs.[18]

Early preclinical and clinical studies with SKMBs set the stage for the benefits associated with the delivery and engraftment of exogenous cells into the heart to prevent and treat cardiac dysfunction. Studies found that exogenous cells could engraft into the heart and that the engraftment of SKMBs could produce clinical benefits, including

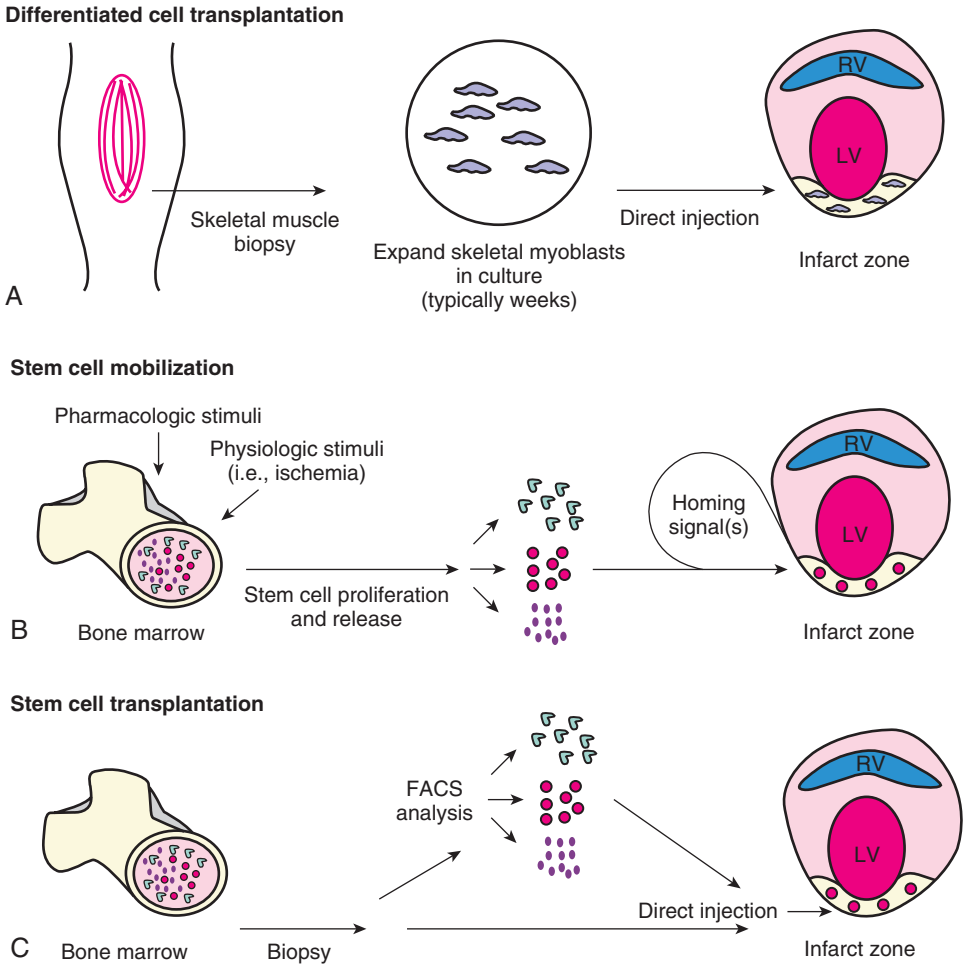

FIGURE 58-1 Schematic diagram of differentiated cell transplantation (**A**), stem cell mobilization (**B**), and stem cell transplantation strategies of cell therapy for the treatment of cardiac dysfunction (**C**). *FACS,* Fluorescence activated cell sorting.

inducing reverse remodeling of adverse LV remodeling.[19-21] Studies also demonstrated the importance of mechanical coupling of exogenous cells to the cellular milieu of the heart.[22] SKMBs do not integrate into the electrical syncytium of the myocardium and have been shown in animal studies to induce slow conduction,[23] increase the risk of reentrant rhythm,[24] and increase premature ventricular contractions and ventricular tachycardia in patients.[12]

Despite the arrhythmogenic risk of using SKMBs, the need for 2 to 3 weeks between skeletal muscle biopsy and production of sufficient SKMBs for transplantation in humans, and no viable vasculature grown in response to SKMB engraftment, SKMBs are still being developed as a strategy for the treatment of CHF.

Myocardial Regeneration

Since the turn of the century, a significant body of literature has corrected the once strongly held belief that the heart cannot repair itself. Studies have shown that after myocardial infarction in humans, there is a transient mobilization of stem cells and expression of stem cell homing factors that recruit these cells to the heart.[25,26]

Human female hearts transplanted into men were found to have cardiomyocytes and vascular structures that stained positive for the Y chromosome, suggesting that the cells originated from the transplant recipient's stem cells.[27] Unfortunately, studies also demonstrated that stem cell engraftment with differentiation into cardiomyocytes was an infrequent event (i.e., 0.02% of cardiomyocytes and 3.3% of endothelial cells). However, studies do suggest that the normal physiologic response to myocardial injury is mobilization of stem cells, homing of these cells to the damaged myocardium, and differentiation of some of the stem cells into cardiomyocytes. If this natural repair mechanism can be potentiated, clinically meaningful myocardial regeneration may be achievable.

Excitement surrounding the use of stem cells is based on their unique biologic properties and their capacity to self-renew and regenerate tissue and organ systems. Figure 58-2 groups stem cell populations of interest in myocardial regeneration based on their cardiogenic potential. It was once thought that all stem cell populations listed in Figure 58-2 could differentiate into cardiomyocytes.[28,29] Although many of these cell populations may lead to improved cardiac function,[28,30] most adult stem cells cannot differentiate into cardiomyocytes. The one unmanipulated adult cell population that may have the ability to differentiate into adult cardiomyocytes is cardiac stem cells.[31,32] All cells that have pluripotent to totipotent potential, such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), can generate adult cardiomyocytes.[33,34]

Bone Marrow–Derived Mononuclear Cells

Transplantation of adult stem cells by infusion into the infarct-related vessel or by endocardial injection has progressed to the point that data from randomized controlled trials are becoming available for patients with AMI (Table 58-1) and CHF (Table 58-2). The first randomized

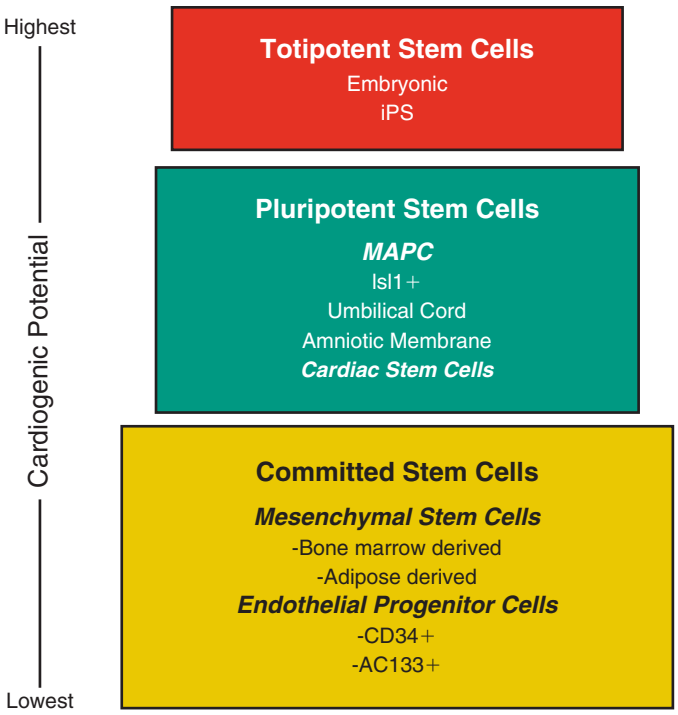

FIGURE 58-2 Stem cell populations of interest for myocardial repair are stratified by the differentiation capacity of the given populations. *iPS,* Induced pluripotent stem cells; *MAPC,* multipotent adult progenitor cells.

stem cell trial for patients with AMI was the Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration Trial (BOOST).[32] The trials of stem cell therapy for AMI can be summarized as follows:

- They have mostly focused on patients with a first STEMI and presumed normal LV function at baseline.
- All patients underwent primary PCI with restoration of antegrade flow.
- Bone marrow harvest was done on the day of stem cell infusion.
- Varied cell preparation approaches have been used, with cell dosing based on $CD34^+$ cell numbers.
- Cells were delivered down the infarct-related vessel by direct infusion or using a stop-flow technique that occludes coronary flow during infusion.
- Baseline and follow-up measurements of LV function consisted of an LV angiogram, cardiac magnetic resonance imaging (MRI), or echocardiography.

Although this strategy has not always improved cardiac function (see Table 58-1), most trials have demonstrated increased cardiac function ranging from 2% to 6%. In some trials, the early benefits seen with cell therapy were lost with subsequent follow-up, suggesting that infusion of bone marrow–derived mononuclear cells (BMMNCs) accelerates healing of the heart but may not further improve it.[50] In contrast, serial follow-up from the largest bone marrow infusion trial, the Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) study,[39] showed continued improvement in cardiac function and clinical parameters, including hospitalization for heart failure, reinfarction, and survival. After 4 months, the treated population had an increase in ejection fraction (EF) of 6% compared with baseline, and the control population exhibited only a 2.5% increase. In later follow-up studies, evidence of

TABLE 58-1 Stem Cell Transplantation in Acute Myocardial Infarction

Study	No. of Patients/ Placebo Control?	Cell Type	Delivery Method	Time After Infarction (days)	Baseline LV Function (%)	Comments
Chen et al[35]	69/yes	BM-derived MSCs	Intracoronary	18.4 ± 1.5	49-53	Improvement in perfusion, cardiac function, and decreased LV dilation; no increase in restenosis
BOOST[36,37]	60/yes	BMMNCs	Intracoronary	4.8	50-51	Six months after MI, increase in EF (6.7%) in patients who received BM cells compared with 0.6% in optimal medical management; controls caught up, benefit not lost at 18 mo
ASTAMI[38]	100/yes	BMMNCs	Intracoronary	5-8	46	Noted chest pain and/or ECG changes with infusion; no improvement 6 mo after cell stem cell infusion
REPAIR-AMI[39]	204/yes	BMMNCs	Intracoronary	4	47-48	Modest improvement in EF 4 mo after stem cell infusion, 5.5% with stem cells vs. 3.0% for placebo; for EF <49% at baseline, improvement of 7.5% with stem cells vs. 2.5% for placebo
Janssens et al[40]	66/yes	BMMNCs	Intracoronary	4	46-49	First randomized, placebo-controlled, blinded study for cell therapy at the time of AMI; no benefit seen
Yousef et al[41]	62/no	BMMNCs	Intracoronary	7	51	Registry control group; improved LV function and quality of life and mortality out to 5 yr
Hare et al[42]	53/yes	MSCs (allogeneic)	Intravenous	1-10	53	Trend toward improvement in LV function in AWMI; evidence of decreased arrhythmia in treated patients
Penn et al[43]	28	MAPCs (allogeneic)	Adventitial	2-5	43	Registry control; significant improvement at 50 M dose
TIME trial[44]	120/yes	BMMNCs	Intracoronary	3 or 7	36	No benefit of BMMNC delivery 3 or 7 days after AMI
LATETIME[45]	87/yes	BMMNCs	Intracoronary	14-21	36	No benefit of BMMNC delivery 2-3 wk after AMI

AMI, Acute myocardial infarction; *AWMI,* anterior wall myocardial infarction; *BM,* bone marrow; *BMMNCs,* bone marrow–derived mononuclear cells; *ECG,* electrocardiographic; *EF,* ejection fraction; *LV,* left ventricular; *MAPCs,* multipotent adult progenitor cells; *MSCs,* mesenchymal stem cells.

TABLE 58-2 Stem Cell Transplantation in Chronic Heart Failure

Study	No. of Patients/ Placebo Control?	Cell Type	Delivery Method	Etiology of Cardiomyopathy	Response of LV Function to Treatment	Comments
Tse et al[46]	8/no	BMMNCs	Stem cell transplantation (Noga catheter–guided intramyocardial injection	Severe ischemic heart disease	Unchanged	Despite no change in EF, improvement in target wall thickening and wall motion seen by MRI; no acute procedure-related complications seen
Seiler et al[47]	21/yes	Stem cells mobilized from the BM	GM-CSF, first dose intracoronary, then subcutaneous for 2 wk	Chronic ischemia	Unchanged but decreased ischemia	Stem cell mobilization to induce angiogenesis as assessed by improved coronary collateral blood flow after 2 wk of daily GM-CSF administration
Assmus et al[48]	75/yes with crossover	CPCs or BMMNCs	Intracoronary infusion	Ischemic cardiomyopathy	Improved with BMMNCs only	Baseline EF ≈ 40%; 2.9% improvement with BM-MNCs; 1.2% without therapy; 0.4% with CPCs
Perin et al[49]	21/yes, nonrandomized	BMMNCs	Noga catheter–guided intramyocardial injection	Severe ischemic cardiomyopathy	Improved	
Schaefer et al[50]	10/no	BMMNCs	Catheter-based intramyocardial delivery	Chronic ischemia	Unchanged but decreased ischemia	Decreased stress-induced ischemia and CCS angina score
FOCUS[51]	92/yes	BMMNCs	Noga catheter–guided intramyocardial injection	Ischemic cardiomyopathy	Unchanged	No benefit observed in LVESVI, MVO_2, or reversible defects
POSEIDON[52]	30/no	Allogeneic and autologous MSCs	Endocardial	Ischemic cardiomyopathy	Unchanged	Not placebo controlled and underpowered but equivalence of safety for allogeneic vs. autologous

BM, Bone marrow; *BMMNCs,* bone marrow–derived mononuclear cells; *CCS,* Canadian Cardiovascular Society; *CPCs,* circulating progenitor cells; *GM-CSF,* granulocyte-macrophage colony-stimulating factor; *LV,* left ventricular; *LVESVI,* left ventricular end-systolic volume index; *MRI,* magnetic resonance imaging; *MSCs,* mesenchymal stem cells; *MVO_2,* maximum oxygen consumption.

decreased clinical events has been maintained up to 2 and 5 years after treatment.[53]

The REPAIR-AMI study remains the benchmark against which all AMI studies are compared. Success of the REPAIR-AMI study led to the Effect of Intracoronary Reinfusion of Bone Marrow–Derived Mononuclear Cells on All-Cause Mortality in Acute Myocardial Infarction (BAMI) study (http://www.bami-fp7.eu). BAMI is the first study of stem cell treatment of patients with AMI that is powered to determine a mortality benefit. A planned total of 3000 patients will be enrolled, and the control group will receive standard of care without sham or placebo infusion.

Recently completed studies of BMMNCs for AMI were designed and executed by the Cardiovascular Cell Therapy Research Network. They attempted to address the important question of optimal timing for cell therapy. The Transplantation in Myocardial Infarction Evaluation (TIME) study randomized patients between bone marrow cells and placebo and to treatment 3 or 7 days after primary PCI. The subsequent LateTIME study was designed to explore whether delayed delivery of cells after AMI could improve global and regional LV function. Patients were randomized to receive cells or placebo at 2 to 3 weeks after primary PCI.

The TIME study results were negative and showed no benefit of BMMNC infusion at 3 or 7 days after AMI 4 or 12 months later.[54] The results of the LateTIME trial were predictably negative.[55] Whether the findings were negative because the cell preparation was devoid of functional benefit or because there are no signals for stem cell homing to the heart 2 to 3 weeks after AMI[25] is unknown because the same cell preparation failed in the TIME trial. This negative experience highlights the importance of validating the functional reparative potential of the cell processing protocol in animal studies and in proven human cell preparations such as those developed by Dimmeler and colleagues.[39]

NOVEL AUTOLOGOUS STEM CELL INDICATIONS AND TYPES

Several groups have used novel approaches to improve outcomes for patients with cardiovascular disease. In the placebo-controlled Granulocyte Colony-Stimulating Factor (G-CSF)–Mobilized Auto-$CD34^+$ Cells for Reduction of Angina Episodes in Patients With Refractory Chronic Myocardial Ischemia (ACT34) study, patients had G-CSF mobilization followed by apheresis and isolation of $CD34^+$ cells.[56,57] These cells were injected using an endoventricular approach with the Noga catheter. The 1-year follow-up data for this patient population revealed sustained benefit of the 6-month findings of a decrease of 5.6 angina events per week and a doubling of exercise treadmill time compared with baseline.

Disappointingly, phase III of the Controlled Study to Determine the Efficacy and Safety of Targeted Intramyocardial Delivery of Autologous $CD34^+$ Cells for Increasing Exercise Capacity During Standardized Exercise Testing in Subjects With Refractory Angina Pectoris and Chronic Myocardial Ischemia (RENEW) study (https://clinicaltrials.gov/ct2/show/NCT01508910) was stopped prematurely by the sponsor, leaving this population of patients to wait for future cell therapies.

Two trials focused on the utility of autologous myocardium-derived stem cells in patients with evolving ischemia-induced myocardial remodeling or ischemic cardiomyopathy. The Cardiosphere-Derived Autologous Stem Cells to Reverse Ventricular Dysfunction (CADUCEUS)[58] trial (https://clinicaltrials.gov/ct2/show/NCT00893360?term=CADUCEUS&rank=1) generated autologous cardiosphere-derived cells (CDCs). The Stem Cell Infusion in Patients with Ischemic Cardiomyopathy (SCIPOIO)[59] trial (https://clinicaltrials.gov/ct2/show/NCT00474461?term=NCT00474461&rank=1) isolated autologous cardiac stem cells (CSCs).

Based on the relative dosing of stem cells in preclinical trials, it appears that CDCs may be the most potent of all the adult stem cells.[60] If true, CSCs or CDCs may be the best cells to use for stem cell transplantation (see Fig. 58-1). The CADUCEUS trial delivered autologous CDCs through the infarct-related vessels in stable patients with a low EF within 1 year of an AMI. In the SCIPIO trial, CSCs were isolated from atrial tissue obtained at the time of coronary artery bypass surgery.

The CSCs were cultured, and after sufficient propagation, the cells were injected into injured myocardium using a percutaneous approach. The CSC population was infused into a coronary artery on average 3 to 4 months after open heart surgery.[59] Just as stem cells can be rapidly harvested from adipose tissue,[61,62] it may be possible to rapidly isolate CSCs from the left atrial appendage in the operating room or from endomyocardial biopsies in sufficient numbers to allow meaningful myocardial support.

The CADUCEUS team is studying allogeneic CDCs in the phase I/II Allogeneic Heart Stem Cells to Achieve Myocardial Regeneration (ALLSTAR) trial. Data from the Stem Cell Infusion in Patients with Ischemic Cardiomyopathy (SCIPIO) trial varied but on average showed an approximately 9% increase in cardiac function. In the CADUCEUS trial, the investigators demonstrated a significant decrease in myocardial scar by MRI and a trend toward improved LV volumes.[58] These preliminary trials are good examples of the novel approaches being undertaken to investigate and optimize adult stem cell therapy.

Mesenchymal Stem Cells and Multipotent Adult Progenitor Cells

Stromal progenitor cells account for less than 0.05% of the adult bone marrow. Mesenchymal stem cells (MSCs) and multipotent adult progenitor cells (MAPCs) form subpopulations of bone marrow stromal progenitor cells that maintain the ability to differentiate along multiple lineages.[29,63]

MSCs can be immunoselected by cell surface CD45 negativity and cultured through as many as 40 population doublings before attaining senescence. The benefits observed after MSC transplantation at the time of myocardial infarction may have little to do with the cells themselves, but rather reflect how the factors they secrete alter the tissue microenvironment. The so-called paracrine effect of MSCs has been demonstrated[64] by showing that injection of the supernatant of MSC cultures at the time of myocardial infarction results in benefits similar to those associated with MSC transplantation.

We have demonstrated that the CXC motif chemokine 12 (CXCL12), previously designated stromal cell–derived factor 1 (SDF-1), released by MSCs results in the recruitment of cardiac stem cells to the infarct border zone and inhibits cardiac myocyte death through the binding of CXCL12 to the CXCR4 receptor–expressing cardiomyocytes in the infarct border zone.[65,66] This is consistent with the work demonstrating that the relative benefit of a dose of CDCs (discussed earlier) correlates with the level of CXCL12 expression by the CDC preparation.[67]

Preclinical studies demonstrated that modulation of Wnt/β-catenin signaling through transforming growth factor-β1 (TGF-β1) pretreatment or, more precisely, by modulating disabled 2 (DAB2)–induced MSCs, increased expression of proteins in vitro that are normally expressed by cardiomyocytes, leading to an improved functional response.[68]

Two strategies are being studied to improve the function of MSCs for the treatment of CHF. They involve harvesting of bone marrow–derived MSCs and growing them under conditions that optimize their effects. The first effort has focused on inducing a cardiopoietic program within the MSC.[69,70] This elegant work has detailed pathways that optimize the cardiac potential of adult MSCs. The Cardiopoietic Stem Cell Therapy in Heart Failure (C-CURE) trial found that the cardiopoietic MSCs had the potential to improve cardiac function (e.g., EF increased 7% with cells but 0.2% with placebo), decrease end-systolic volume (16 mL relative to placebo), and improve the 6-minute walk distance.[71] This cell-processing protocol is being studied in the phase III Cardiopoietic Cells for Treatment of Ischemic Heart Failure. (CHART-1) trial (https://clinicaltrials.gov/ct2/show/NCT01768702) with a goal of enrolling 240 patients overseas.

The second approach in clinical development is a proprietary cell culturing system developed by Aastrom Biosciences in which adherent cells are propagated for 2 weeks in an enclosed system. The phase II Ixmyelocel-T Administered via Transendocardial Catheter-Based Injections to Subjects With Heart Failure Due to Ischemic Dilated Cardiomyopathy (IDCM) trial (https://clinicaltrials.gov/ct2/show/NCT01670981?term=ixCELL+DCM&rank=1) is delivering these cells by endocardial injection in patients with ischemic and nonischemic cardiomyopathy. This trial is estimated to enroll 108 patients.

MAPCs are stromal cells derived from the bone marrow. They can differentiate into endothelial, epithelial, and mesenchymal cell types.[72] They can be expanded in culture for more than 80 population doublings and still maintain their pluripotency by differentiating into most somatic cell types.[72] Whether these multipotent stem cells exist in vivo or are the result of serial cell passages in culture remains to be determined. However, the multipotent cells can be significantly expanded, and their reparative and immunomodulation properties hold the potential for benefit in cardiovascular disease,[73] stroke (https://clinicaltrials.gov/ct2/show/NCT01436487?term=NCT01436487&rank=1), graft-versus-host disease, and other pathologies.

MSCs and MAPCs can decrease cardiac myocyte cell death, decrease infarct size, and improve cardiac remodeling and function in rodent[74] and porcine models[75] of AMI. Each cell type has entered the clinical realm, with MSC clinical trials entering the phase III arena.

The MAPC phase I trial was a dose-ranging study in which 20, 50, and 100 million MAPCs were delivered to patients with a first-time STEMI and a postprimary PCI EF of 45% or less.[43] In contrast to BMMNC or MSC trials, the MAPC phase I trial used catheter-mediated adventitial delivery of the MAPCs with the Mercator MedSystems Cricket catheter 2 to 5 days after primary PCI. As the balloon is inflated on this catheter, a single needle is deployed that goes through the medial layer of the infarct-related artery and delivers the MAPCs to the adventitia (Fig. 58-3). Preclinical studies have demonstrated that the MAPCs in the adventitia distribute throughout the infarct zone.[75] MAPC delivery resulted on average in an absolute increase in EF of more than 12% in patients with a baseline EF of less than 45%.[43] As in other studies, no significant improvement was observed in patients with an EF greater than 45%.[76,40]

The ease of delivery of MAPCs with the Cricket catheter with respect to clinical workflow after PCI led to the development of a clinical study to investigate the utility of stem cell delivery in cases of non–ST-segment elevation myocardial infarction (NSTEMI). NSTEMI has a higher 1-year mortality rate than STEMI,[77] probably due to the fact that patients with NSTEMI have a greater likelihood of prior AMI and impaired EF. MAPCs in this setting have the potential to decrease infarct expansion and through immunomodulatory effects decrease adverse remodeling that may be initiated by an ischemic event in an impaired ventricle and to decrease the risk of additional plaque rupture along the coronary tree. This trial began active enrollment in 2015.

From an interventional perspective, it is interesting to compare the loss of efficacy in the translation of MSCs and MAPCs from preclinical studies to human studies. The efficacy of intravenous delivery of MSCs went from a relative increase of about 80% in rats to 10% at the high dose of MSCs used in the phase I trial.[65,42] For MAPCs, the improvement in EF found in a porcine AMI model was about 38%, compared with about 35% in the phase I trial.[75,43] Although the consistency in effect in the MAPC trial may reflect the cell type, it is more likely that the difference in translation resulted from the delivery method. In the MAPC trial, the cells were delivered to the adventitia, avoiding the atherosclerotic intima of the diseased coronaries. In contrast, the efficiency of MSC delivery to the myocardium in patients with coronary artery disease might have been inhibited compared with that observed in rodents, which had nondiseased arteries.

Studies are needed to define optimal strategies for stem cell delivery to the heart. The Cricket catheter offers one intriguing strategy for

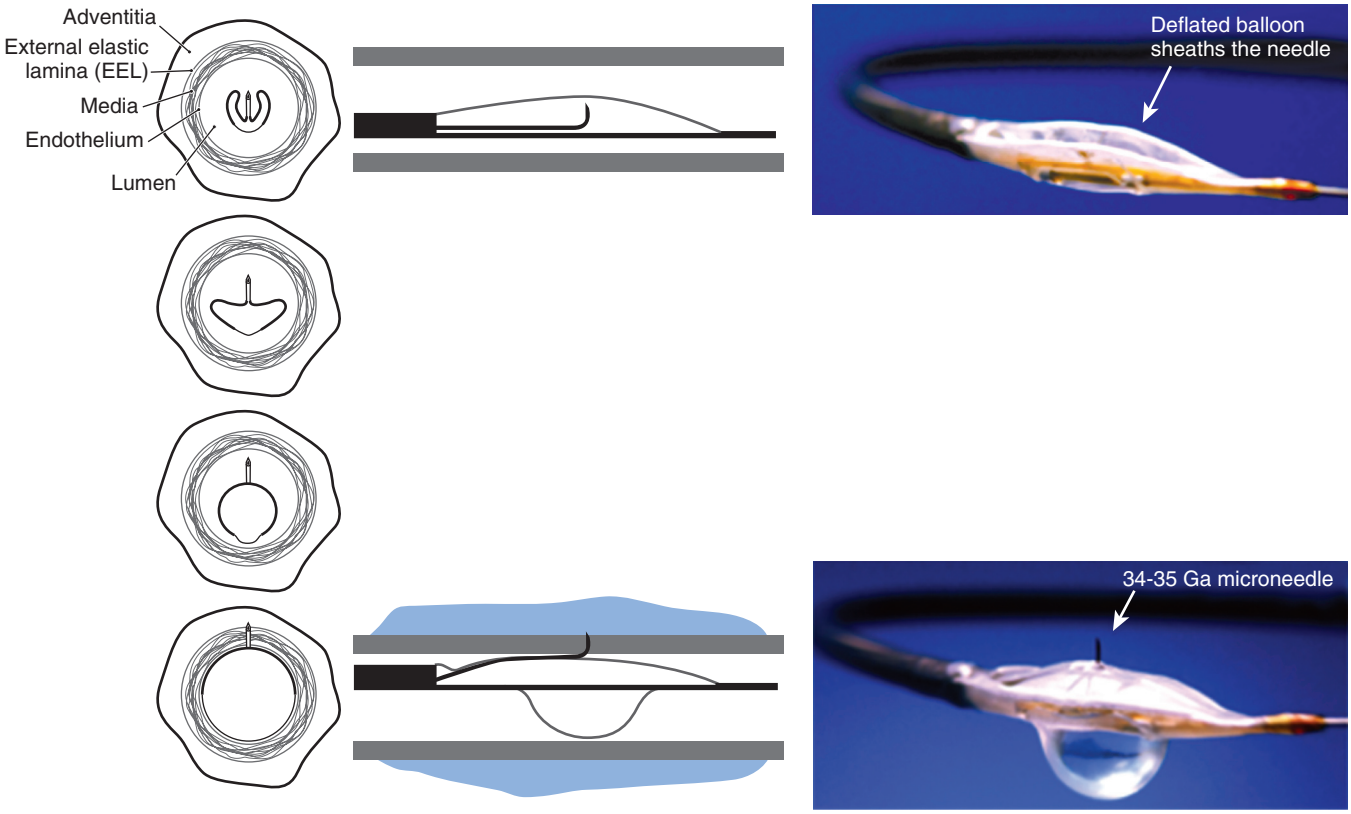

FIGURE 58-3 Schematic representation of microneedle catheter–mediated delivery to the coronary adventitia and photographs of deflated and inflated the Mercator Cricket catheter. *Ga,* Gauge.

delivery of stem cells to the infarct region immediately after primary PCI, obviating the need for complex delivery systems or additional procedures at a later date in the catheterization laboratory.

Cardiac Regeneration

There is little evidence that adult stem cells regenerate lost cardiomyocytes. Regeneration of cardiomyocytes and myocardial structures probably require ESCs, cardiomyocytes generated from iPSCs, or gene therapy to induce local directed differentiation.[78,79] ESCs continuously replicate cell lines derived from an embryonic origin isolated from the blastocyst's inner cell mass.[80] Properties of ESCs include derivation from the preimplantation or periimplantation embryo, prolonged undifferentiated proliferation with conditional constraints, and the ability to form tissues derived from all three germ layers. When they are properly cultured, ESCs expand at a rapid rate and group to form embryoid bodies that have the ability to differentiate into a wide variety of specialized cells, including cardiomyocytes.

Adult somatic cells can be differentiated into cardiomyocytes directly or through the intermediate step of generating iPSCs.[81,82] Transplantation of these cells leads to engraftment of cardiomyocytes in the infarct zone and improvement in cardiac function and remodeling. How these cells will ultimately translate into clinical use is unclear. Translation will require scaffolds and biologics to optimize the vascularization, integration, and workload of these contractile networks.

Published clinical data are not available for the delivery of significant numbers of cardiomyocytes to treat patients with CHF. There remains much excitement for the future of these cells, but for now, autologous iPSC-derived cardiomyocytes have shown significant utility for understanding the mechanisms associated with arrhythmias and cardiomyopathies.[83,84]

STEM CELL–BASED CHEMOKINE AND CYTOKINE STRATEGIES

An early focus of clinical trials for stem cell repair of the myocardium was based on cytokine-mediated mobilization of the marrow space using G-CSF and granulocyte-macrophage colony-stimulating factor (CM-CSF).[73] There is little evidence that stem cell mobilization of the marrow space in the periinfarct period with G-CSF leads to a significant change in cardiac function or remodeling.

One possible explanation for the failure of G-CSF mobilization in clinical trials is that mobilized hematopoietic stem cells are unable to home due to dysfunctional CXCR4 (the CXCL12 receptor) expression. G-CSF mobilizes stem cells by the degradation of CXCR4, releasing the stem cell from its anchor in the bone marrow. There is increasing evidence that the stem cell mobilizing agent AMD3100 (an antagonist to the CXCR4 receptor) induces stem cell mobilization that leads to improvement in cardiac function in preclinical models.[85] The early use of AMD3100 leads to stem cell mobilization but does not lead to persistent inhibition of CXCR4 binding in the myocardium,[85] whereas persistent AMD3100 administration leads to mobilization of stem cells but no improvement in cardiac function. These data suggest a potentially important role for cardiac CXCR4 expression in the myocardial response to stem cell–mediated repair.

The bone marrow naturally releases stem cells into the bloodstream on a daily basis. The idea of cytokine-based stem cell mobilization is to increase the number of circulating stem cells when the heart is signaling to recruit them. Although G-CSF and AMD3100 induce stem cells to enter the bloodstream, if the heart is not signaling to recruit them to the injured myocardium, no benefit can be realized.[25,86] We and others have taken the opposite approach: prolong the period that the heart signals to recruit stem cells to the injured myocardium and

take advantage of the fact that there are always circulating stem cells in the bloodstream.

In 2003, we defined CXCL12 as a stem cell homing factor to injured tissues.[25] We demonstrated that prolonging CXCL12 signaling in the myocardium by the delivery of mesenchymal stem cells, which express CXCL12 at baseline, or enhanced CXCL12-expressing mesenchymal stem cells produces significant preservation of cardiomyocytes and cardiac function.[65] We also demonstrated that reestablishment of CXCL12 expression through the delivery of a *CXCL12*-containing plasmid to a model of ischemic cardiomyopathy leads to remodeling of the scar and improvement in the EF.[87]

Based on these data and those from porcine models, *CXCL12* gene transfer is under clinical development. In a phase I, open-label, dose-escalation study, a plasmid *CXCL12* (JVS-100) was delivered by 15 endocardial injections using a helical injection catheter.[6] Fifteen injections of 1 mL per injection targeted the infarct and infarct border zone, delivering 5-, 15-, or 30-mg total. The trial demonstrated a dose-dependent improvement in the 6-minute walk distance and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, as well as neovascularization of the infarct border zone and stabilization of ventricular size and function at the higher two doses.[6]

The utility of transient CXCL12 overexpression in CHF was demonstrated in the randomized, double blind, placebo-controlled, 93 patient Sdf-1 Treatment Of Patients—Heart Failure (STOP-HF) trial. In STOP-HF, high-risk patients with ischemic cardiomyopathy who received 30 mg of JVS-100 demonstrated a statistically significant 11% increase ($p = 0.01$) in ejection fraction and a trend towards a 25 mL increase in stroke volume ($p = 0.09$) relative to placebo.[88]

CXCL12 overexpression is also being studied in ischemic cardiomyopathy using retrograde infusion through the coronary sinus in the JVS-100 Administered by Retrograde Delivery to Cohorts of Adults with Ischemic Heart Failure (RETRO-HF) trial (https://clinicaltrials.gov/ct2/show/NCT01961726?term=NCT01961726&rank=1). This is the first trial implementing retrograde infusion as a strategy for delivering a biologic, and it may open treatment options for patients with a LV wall thickness too thin for endocardial injection.

The direct overexpression of CXCL12 prepares and induces the myocardium to engraft circulating stem cells.[89] It has similarly been shown that preparing the heart before stem cell infusion increases the efficacy of the procedure. In the Cardiac Extracorporal Shock Wave Therapy for Induction of Therapeutic Neovascularization and Homing of Bone Marrow Progenitor Cells in Patients With Chronic Ischemic Heart Disease (CELLWAVE) study (https://clinicaltrials.gov/ct2/show/NCT00326989?term=NCT00326989&rank=1), the investigators used shock wave therapy directed at the heart to induce myocardial expression of CXCL12 and vascular endothelial growth factor (VEGF) in patients with chronic ischemic cardiomyopathy. Twenty-four hours later, patients underwent bone marrow harvest and intracoronary infusion of autologous bone marrow cells. This study found that only patients who received the combination of shock wave therapy with autologous bone marrow infusion had improvement in the EF, whereas shock wave or cell infusion alone had no effects.[89] This is an excellent example of the execution of a clinical trial to test an important hypothesis and increase our understanding of the factors associated with successful cell therapy.

ELECTRICAL EFFECTS OF CELL THERAPY

As the field of stem cell therapy identifies strategies that preserve or improve cardiac function in patients with AMI or CHF, it is becoming clear that the mechanical and electrical effects of therapy are independent.[20,24] We previously demonstrated that SKMBs or MSCs (1 million of each cell type) delivered in the periinfarct period to the myocardium results in similar improvements in cardiac function. However, when these hearts undergo an electrophysiology study with the introduction of extrasystoles, the rate at which ventricular tachycardia is induced depends on the cell type the animal received.[24] Hearts of animals that received SKMBs were always inducible for ventricular tachycardia.

Many studies have suggested an increased incidence of ventricular tachycardia in patients who received SKMBs (see Table 58-1). This may be a spurious result because all of the patients in these trials had a history of myocardial infarction. However, although SKMBs do express connexin 43 in culture, they do not express connexin 43 after transplantation, and SKMBs do not electrically couple with the native myocardium.[24] Establishment of connexin 43 expression in SKMBs decreases the arrhythmogenic risk of the cells.

These data coupled with clinical data demonstrating a decrease in clinical measures of arrhythmia in patients who received intravenous MSCs after AMI[42] suggest that the clinical indications for stem cell therapy could be expanded from improving cardiac function to decreasing reentry. A trial could be designed in which specific stem cells would be injected into the mapped circuit to reverse the area of slow conduction or remodel the size of the scar instead of inducing further LV injury to interrupt a reentrant circuit. The safety associated with cell therapy justifies expanding indications and using novel trial designs to address clinical populations with unmet needs.

FUTURE DIRECTIONS AND CONTROVERSIES

The field of stem cell therapy for the treatment of cardiovascular disease is continuing to make significant strides at the molecular level. Unfortunately, clinical progress, especially in the United States, has lagged. Critical issues in basic science and clinical science need to be addressed to advance stem cell therapy to prevent or treat cardiac dysfunction and improve outcomes for patients with heart disease.

Bench Investigation

The first issue in the area of basic science is delineating the molecular mechanisms associated with adult stem cell–based repair of the heart. As we have shown with CXCL12 over the past 15 years, defining the molecular mechanisms associated with stem cell–based repair can identify novel targets for therapy, provide insights into the biology of tissue healing,[90-92] and create agents for clinical investigation. Other molecules, such as stem cell factor[93] and thymosin β4 (TMSB4X),[94,95] may someday enter the clinical realm to further advance the concept of endogenous stem cell pool activation[96,97] and improve clinical outcomes.

The second issue is whether we can achieve cardiogenesis. Few data show that unmanipulated cardiomyocytes can divide and regenerate themselves after myocardial injury. However, genetic manipulation of cardiomyocytes in engineered murine models can induce cardiomyocytes to divide and the infarct size to regress.[98,99] Whether innovative pharmacologic strategies can activate these pathways after myocardial infarction remains to be seen.

Clinical Investigation

There have been limited advances in cell therapy trials over the past 4 years, especially in the academic arena. Perhaps the greatest advancement is the launch of the European BAMI trial, which is powered to detect a mortality benefit for cell therapy for AMI. In the United States, the National Institutes of Health (NIH)–sponsored Cardiovascular Cell Therapy Research Network (CCTRN) has contributed three trials with negative results to the literature in part due to poor trial design and possibly due to an ineffective cell preparation protocol. Unfortunately, the Sepax system for cell processing that was implemented by the CCTRN was never validated against an efficacious cell therapy protocol.

Other trials in the United States subdivided cohorts into underpowered groups that resulted in uninterpretable[52,100] and possibly inappropriately interpreted[101] findings, offering the field no real direction. It is also clear that the field can no longer advance on the execution of small, underpowered studies.[100] This contrasts with European clinical studies such as the CELLWAVE study (discussed earlier) and several industry-academic collaborations such as those being executed by

Caladrium, Inc. (CXCR4$^+$ progenitor cells), Capricor (cardiac cell–derived cardiospheres), Juventas Therapeutics (*CXCL12* gene transfer), and Celyad, Inc. (cardiopoietic mesenchymal stem cells) in which sufficiently sized trials are focusing on clinically relevant populations in collaboration with academic bench science groups investigating mechanisms of action before embarking on clinical trials. The bench to bedside to bench paradigm is alive and well in the field and is the most likely avenue to bring advances to clinical populations.[101]

An important issue is whether stem cell therapy can produce significant benefit for patients with NSTEMI. All trials have focused on patients with a first STEMI with normal cardiac function before the ischemic event. Although this study population has been essential for demonstrating proof of concept and biologic effect, it is not the one most at risk for adverse cardiac events, and the number of STEMI patients continues to decline. If adult stem cell therapy is going to have a significant impact on patient outcomes, it must be transitioned to patients with ischemic cardiomyopathy before their index event and who have NSTEMI.

CONCLUSIONS

Stem cell therapy for the prevention and treatment of cardiac dysfunction continues to make progress. The balance of data suggests that there is a therapeutic effect, and the bench science is coalescing around some common mechanisms of action. Given the growing prevalence of patients with CHF and myocardial infarction combined with the economic burden of CHF, the potential human and societal benefits are vast.

REFERENCES

1. Randomized factorial trial of high-dose intravenous streptokinase, of oral aspirin and of intravenous heparin in acute myocardial infarction. ISIS (International Studies of Infarct Survival) pilot study. *Eur Heart J* 8(6):634–642, 1987.
2. Stone GW, Grines CL, Cox DA, et al: Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 346(13):957–966, 2002.
3. Askari A, Brennan ML, Zhou X, et al: Myeloperoxidase and plasminogen activator inhibitor-1 play a central role in ventricular remodeling after myocardial infarction. *J Exp Med* 197(5): 615–624, 2003.
4. Heymans S, Luttun A, Nuyens D, et al: Inhibition of plasminogen activators or matrix metalloproteinases prevents cardiac rupture but impairs therapeutic angiogenesis and causes cardiac failure. *NatMed* 5(10):1135–1142, 1999.
5. Vasilyev N, Williams T, Brennan ML, et al: Myeloperoxidase-generated oxidants modulate left ventricular remodeling but not infarct size after myocardial infarction. *Circulation* 112(18): 2812–2820, 2005.
6. Penn MS, Mendelsohn FO, Schaer GL, et al: An open-label dose escalation study to evaluate the safety of administration of nonviral stromal cell-derived factor-1 plasmid to treat symptomatic ischemic heart failure. *Circ Res* 112(5):816–825, 2013.
7. Bian J, Popovic ZB, Benejam C, et al: Effect of cell-based intercellular delivery of transcription factor GATA4 on ischemic cardiomyopathy. *Circ Res* 100(11):1626–1633, 2007.
8. Kandala J, Upadhyay GA, Altman RK, et al: QRS morphology, left ventricular lead location, and clinical outcome in patients receiving cardiac resynchronization therapy. *Eur Heart J* 34(29): 2252–2262, 2013.
9. Li N, Yang YJ, Zhang Q, et al: Stem cell therapy is a promising tool for refractory angina: a meta-analysis of randomized controlled trials. *Can J Cardiol* 29(8):908–914, 2013.
10. Abdel-Latif A, Bolli R, Tleyjeh IM, et al: Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. *Arch Intern Med* 167(10):989–997, 2007.
11. Jiang M, He B, Zhang Q, et al: Randomized controlled trials on the therapeutic effects of adult progenitor cells for myocardial infarction: meta-analysis. *Expert Opin Biol Ther* 10(5):667–680, 2010.
12. Menasche P, Alfieri O, Janssens S, et al: The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation. *Circulation* 117(9):1189–1200, 2008.
13. Moreira LF, Bocchi EA, Stolf NA, et al: Dynamic cardiomyoplasty in the treatment of dilated cardiomyopathy: current results and perspectives. *J Card Surg* 11(3):207–216, 1996.
14. Bocchi EA, Moreira LF, de Moraes AV, et al: Effects of dynamic cardiomyoplasty on regional wall motion, ejection fraction, and geometry of left ventricle. *Circulation* 86(5 Suppl):II231–II235, 1992.
15. Jatene AD, Moreira LF, Stolf NA, et al: Left ventricular function changes after cardiomyoplasty in patients with dilated cardiomyopathy. *J Thorac Cardiovasc Surg* 102(1):132–138, 1991.
16. Chiu RC, Kochamba G, Walsh G, et al: Biochemical and functional correlates of myocardium-like transformed skeletal muscle as a power source for cardiac assist devices. *J Card Surg* 4(2):171–179, 1989.
17. Misawa Y, Mott BD, Lough JO, Chiu RC: Pathologic findings of latissimus dorsi muscle graft in dynamic cardiomyoplasty: clinical implications. *J Heart Lung Transplant* 16(6):585–595, 1997.
18. Menasche P, Hagege AA, Vilquin JT, et al: Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction. *J Am Coll Cardiol* 41(7):1078–1083, 2003.
19. Askari A, Unzek S, Goldman CK, et al: Cellular, but not direct adenoviral delivery of VEGF results in improved LV function and neovascularization in dilated ischemic cardiomyopathy. *J Am Coll Cardiol* 43(10):1908–1914, 2004.
20. Deglurkar I, Mal N, Mills WR, et al: Mechanical and electrical effects of cell-based gene therapy for ischemic cardiomyopathy are independent. *Hum Gene Ther* 17(11):1144–1151, 2006.
21. Dowell JD, Rubart M, Pasumarthi KB, et al: Myocyte and myogenic stem cell transplantation in the heart. *Cardiovasc Res* 58(2):336–350, 2003.
22. Reinecke H, MacDonald GH, Hauschka SD, Murry CE: Electromechanical coupling between skeletal and cardiac muscle: implications for infarct repair. *J Cell Biol* 149(3):731–740, 2000.
23. Fouts K, Fernandes B, Mal N, et al: Electrophysiological consequence of skeletal myoblast transplantation in normal and infarcted canine myocardium. *Heart Rhythm* 3(4):452–461, 2006.
24. Mills WR, Mal N, Kiedrowski M, et al: Stem cell therapy enhances electrical viability in myocardial infarction. *J Mol Cell Cardiol* 42(2):304–314, 2007.
25. Askari A, Unzek S, Popovic ZB, et al: Effect of stromal-cell-derived factor-1 on stem cell homing and tissue regeneration in ischemic cardiomyopathy. *Lancet* 362(9385):697–703, 2003.
26. Hofmann M, Wollert KC, Meyer GP, et al: Monitoring of bone marrow cell homing into the infarcted human myocardium. *Circulation* 111(17):2198–2202, 2005.
27. Muller P, Pfeiffer P, Koglin J, et al: Cardiomyocytes of noncardiac origin in myocardial biopsies of human transplanted hearts. *Circulation* 106(1):31–35, 2002.
28. Orlic D, Kajstura J, Chimenti S, et al: Bone marrow cells regenerate infarcted myocardium. *Nature* 410(6829):701–705, 2001.
29. Mangi AA, Noiseux N, Kong D, et al: Mesenchymal stem cells modified with Akt prevent remodeling and restore performance of infarcted hearts. *Nat Med* 9(9):1195–1201, 2003.
30. Kocher AA, Schuster MD, Szabolcs MJ, et al: Neovascularization of ischemic myocardium by human bone marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function. *Nat Med* 7(4):430–436, 2001.
31. Beltrami AP, Barlucchi L, Torella D, et al: Adult cardiac stem cells are multipotent and support myocardial regeneration. *Cell* 114(6):763–776, 2003.
32. Kajstura J, Urbanek K, Rota M, et al: Cardiac stem cells and myocardial disease. *J Mol Cell Cardiol* 45(4):505–513, 2008.
33. Dai B, Huang W, Xu M, et al: Reduced collagen deposition in infarcted myocardium facilitates induced pluripotent stem cells (iPSC) engraftment and angiomyogenesis for improvement of left ventricular function. *J Am Coll Cardiol* 58(20):2118–2127, 2011.
34. Kawamura M, Miyagawa S, Miki K, et al: Feasibility, safety, and therapeutic efficacy of human induced pluripotent stem cell-derived cardiomyocyte sheets in a porcine ischemic cardiomyopathy model. *Circulation* 126(11 Suppl 1):S29–S37, 2012.
35. Chen SL, Fang WW, Ye F, et al: Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. *Am J Cardiol* 94(1):92–95, 2004.
36. Meyer GP, Wollert KC, Lotz J, et al: Intracoronary bone marrow cell transfer after myocardial infarction: eighteen months' follow-up data from the randomized, controlled BOOST (BOne marrOw transfer to enhance ST-elevation infarct regeneration) trial. *Circulation* 113(10):1287–1294, 2006.
37. Wollert KC, Meyer GP, Lotz J, et al: Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *Lancet* 364(9429): 141–148, 2004.
38. Lunde K, Solheim S, Aakhus S, et al: Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. *N Engl J Med* 355(12):1199–1209, 2006.
39. Schachinger V, Erbs S, Elsasser A, et al: Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med* 355(12):1210–1221, 2006.
40. Janssens S, Dubois C, Bogaert J, et al: Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. *Lancet* 367(9505):113–121, 2006.
41. Yousef M, Schannwell CM, Kostering M, et al: The BALANCE Study: clinical benefit and long-term outcome after intracoronary autologous bone marrow cell transplantation in patients with acute myocardial infarction. *J Am Coll Cardiol* 53(24):2262–2269, 2009.
42. Hare J, Traverse J, Henry T, et al: A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (prochymal) following acute myocardial infarction. *J Am Coll Cardiol* 54(24):2277–2286, 2009.
43. Penn MS, Ellis S, Gandhi S, et al: Adventitial delivery of an allogeneic bone marrow-derived adherent stem cell in acute myocardial infarction: phase I clinical study. *Circ Res* 110(2): 304–311, 2012.
44. Traverse JH, Henry TD, Vaughn DE, et al: Rationale and design for TIME: a phase II, randomized, double-blind, placebo-controlled pilot trial evaluating the safety and effect of timing of administration of bone marrow mononuclear cells after acute myocardial infarction. *Am Heart J* 158(3):356–363, 2009.
45. Cohen ED, Wang Z, Lepore JJ, et al: Wnt/beta-catenin signaling promotes expansion of Isl-1-positive cardiac progenitor cells through regulation of FGF signaling. *J Clin Invest* 117(7):1794–1804, 2007.
46. Tse HF, Kwong YL, Chan JK, et al: Angiogenesis in ischaemic myocardium by intramyocardial autologous bone marrow mononuclear cell implantation. *Lancet* 361(9351):47–49, 2003.
47. Seiler C, Pohl T, Wustmann K, et al: Promotion of collateral growth by granulocyte-macrophage colony-stimulating factor in patients with coronary artery disease: a randomized, double-blind, placebo-controlled study. *Circulation* 104(17):2012–2017, 2001.
48. Assmus B, Honold J, Schachinger V, et al: Transcoronary transplantation of progenitor cells after myocardial infarction. *N Engl J Med* 355(12):1222–1232, 2006.
49. Perin EC, Dohmann HF, Borojevic R, et al: Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure. *Circulation* 107(18):2294–2302, 2003.
50. Schaefer A, Meyer GP, Fuchs M, et al: Impact of intracoronary bone marrow cell transfer on diastolic function in patients after acute myocardial infarction: results from the BOOST trial. *Eur Heart J* 27(8):929–935, 2006.
51. Willerson JT, Perin EC, Ellis SG, et al: Intramyocardial injection of autologous bone marrow mononuclear cells for patients with chronic ischemic heart disease and left ventricular dysfunction (First Mononuclear Cells injected in the US [FOCUS]): rationale and design. *Am Heart J* 160(2):215–223, 2010.
52. Hare JM, Fishman JE, Gerstenblith G, et al: Comparison of allogeneic vs autologous bone marrow-derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: the POSEIDON randomized trial. *JAMA* 308(22):2369–2379, 2012.
53. Assmus B, Rolf A, Erbs S, et al: Clinical outcome 2 years after intracoronary administration of bone marrow-derived progenitor cells in acute myocardial infarction. *Circ Heart Fail* 3(1):89–96, 2010.
54. Traverse JH, Henry TD, Pepine CJ, et al: Effect of the use and timing of bone marrow mononuclear cell delivery on left ventricular function after acute myocardial infarction: the TIME randomized trial. *JAMA* 308(22):2380–2389, 2012.
55. Traverse JH, Henry TD, Ellis SG, et al: Effect of intracoronary delivery of autologous bone marrow mononuclear cells 2 to 3 weeks following acute myocardial infarction on left ventricular function: the LateTIME randomized trial. *JAMA* 306(19):2110–2119, 2011.
56. Losordo DW, Schatz RA, White CJ, et al: Intramyocardial transplantation of autologous CD34+ stem cells for intractable angina: a phase I/IIa double-blind, randomized controlled trial. *Circulation* 115(25):3165–3172, 2007.
57. Losordo DW, Henry TD, Davidson C, et al: Intramyocardial, autologous CD34+ cell therapy for refractory angina. *Circ Res* 109(4):428–436, 2011.
58. Makkar RR, Smith RR, Cheng K, et al: Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. *Lancet* 379(9819):895–904, 2012.

59. Bolli R, Chugh AR, D'Amario D, et al: Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. *Lancet* 378(9806):1847–1857, 2011.
60. Bearzi C, Rota M, Hosoda T, et al: Human cardiac stem cells. *Proc Natl Acad Sci U S A* 104(35):14068–14073, 2007.
61. Cai L, Johnstone BH, Cook TG, et al: IFATS collection: Human adipose tissue-derived stem cells induce angiogenesis and nerve sprouting following myocardial infarction, in conjuncion with potent preservation of cardiac function. *Stem Cells* 27(1):230–237, 2009.
62. Hong SJ, Traktuev DO, March KL: Therapeutic potential of adipose-derived stem cells in vascular growth and tissue repair. *Curr Opin Organ Transplant* 15(1):86–91, 2010.
63. Toma C, Pittenger MF, Cahill KS, et al: Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. *Circulation* 105(1):93–98, 2002.
64. Gnecchi M, He H, Noiseux N, et al: Evidence supporting paracrine hypothesis for Akt-modified mesenchymal stem cell-mediated cardiac protection and functional improvement. *FASEB J* 20(6):661–669, 2006.
65. Zhang M, Mal N, Kiedrowski M, et al: SDF-1 expression by mesenchymal stem cells results in trophic support of cardiac myocytes after myocardial infarction. *FASEB J* 21(12):3197–3207, 2007.
66. Dong F, Harvey J, Finan A, et al: Myocardial CXCR4 expression is required for mesenchymal stem cell mediated repair following acute myocardial infarction. *Circulation* 126(3):314–324, 2012.
67. Cheng K, Malliaras K, Smith RR, et al: Human cardiosphere-derived cells from advanced heart failure patients exhibit augmented functional potency in myocardial repair. *JACC Heart Fail* 2(1):49–61, 2014.
68. Mayorga ME, Dong F, Sundararaman S, et al: Central role for disabled-2 in mesenchymal stem cell cardiac protein expression and functional consequences after engraftment in acute myocardial infarction. *Stem Cells Dev* 20(4):681–693, 2011.
69. Arrell DK, Niederlander NJ, Faustino RS, et al: Cardioinductive network guiding stem cell differentiation revealed by proteomic cartography of tumor necrosis factor alpha-primed endodermal secretome. *Stem Cells* 26(2):387–400, 2008.
70. Behfar A, Perez-Terzic C, Faustino RS, et al: Cardiopoietic programming of embryonic stem cells for tumor-free heart repair. *J Exp Med* 204(2):405–420, 2007.
71. Bartunek J, Behfar A, Dolatabadi D, et al: Cardiopoietic stem cell therapy in heart failure: the C-CURE (Cardiopoietic stem Cell therapy in heart failURE) multicenter randomized trial with lineage-specified biologics. *J Am Coll Cardiol* 61(23):2329–2338, 2013.
72. Jiang Y, Jahagirdar BN, Reinhardt RL, et al: Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature* 418(6893):41–49, 2002.
73. Yoon YS, Wecker A, Heyd L, et al: Clonally expanded novel multipotent stem cells from human bone marrow regenerate myocardium after myocardial infarction. *J Clin Invest* 115(2):326–338, 2005.
74. Van't HW, Mal N, Huang Y, et al: Direct delivery of syngeneic and allogeneic large-scale expanded multipotent adult progenitor cells improves cardiac function after myocardial infarct. *Cytotherapy* 9(5):477–487, 2007.
75. Medicetty S, Wiktor D, Lehman N, et al: Percutaneous adventitial delivery of allogeneic bone marrow derived stem cells via infarct related artery improves long-term ventricular function in acute myocardial infarction. *Cell Transplant* 21(6):1109–1120, 2012.
76. Penn MS: Stem-cell therapy after acute myocardial infarction: the focus should be on those at risk. *Lancet* 367(9505):87–88, 2006.
77. McManus DD, Gore J, Yarzebski J, et al: Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. *Am J Med* 124(1):40–47, 2011.
78. Qian L, Srivastava D: Direct cardiac reprogramming: from developmental biology to cardiac regeneration. *Circ Res* 113(7):915–921, 2013.
79. Qian L, Huang Y, Spencer CI, et al: In vivo reprogramming of murine cardiac fibroblasts into induced cardiomyocytes. *Nature* 485(7400):593–598, 2012.
80. Reubinoff BE, Pera MF, Fong CY, et al: Embryonic stem cell lines from human blastocysts: somatic differentiation in vitro. *Nat Biotechnol* 18(4):399–404, 2000.
81. Ieda M, Fu JD, Delgado-Olguin P, et al: Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors. *Cell* 142(3):375–386, 2010.
82. Nelson TJ, Martinez-Fernandez A, Yamada S, et al: Induced pluripotent reprogramming from promiscuous human stemness related factors. *Clin Transl Sci* 2(2):118–126, 2009.
83. Sinnecker D, Goedel A, Dorn T, et al: Modeling long-QT syndromes with iPSC cells. *J Cardiovasc Transl Res* 6(1):31–36, 2013.
84. Priori SG, Napolitano C, Di Pasquale E, Condorelli G: Induced pluripotent stem cell-derived cardiomyocytes in studies of inherited arrhythmias. *J Clin Invest* 123(1):84–91, 2013.
85. Jujo K, Hamada H, Iwakura A, et al: CXCR4 blockade augments bone marrow progenitor cell recruitment to the neovasculature and reduces mortality after myocardial infarction. *Proc Natl Acad Sci U S A* 107(24):11008–11013, 2010.
86. Schenk S, Mal N, Finan A, et al: Monocyte chemotactic protein-3 is a myocardial mesenchymal stem cell homing factor. *Stem Cells* 25(1):245–251, 2007.
87. Sundararaman S, Miller TJ, Pastore JM, et al: Plasmid-based transient human stromal cell-derived factor-1 gene transfer improves cardiac function in chronic heart failure. *Gene Ther* 18(9):867–873, 2011.
88. Chung ES, Miller L, Patel AN, et al: Changes in ventricular remodeling and clinical status during the year following a single administration of stromal cell-derived factor-1 non-viral gene therapy in chronic ischemic heart failure patients: the STOP-HF randomized Phase II trial. *Eur Heart J* 2015. [Epub ahead of print].
89. Assmus B, Walter DH, Seeger FH, et al: Effect of shock wave-facilitated intracoronary cell therapy on LVEF in patients with chronic heart failure: the CELLWAVE randomized clinical trial. *JAMA* 309(15):1622–1631, 2013.
90. Penn MS: Importance of the SDF-1:CXCR4 axis in myocardial repair. *Circ Res* 104(10):1133–1135, 2009.
91. Rabbany SY, Pastore J, Yamamoto M, et al: Continuous delivery of stromal cell-derived factor-1 from alginate scaffolds accelerates wound healing. *Cell Transplant* 19(4):399–408, 2010.
92. Penn MS: SDF-1:CXCR4 axis is fundamental for tissue preservation and repair. *Am J Pathol* 177(5):2166–2168, 2010.
93. Yaniz-Galende E, Chen J, Chemaly E, et al: Stem cell factor gene transfer promotes cardiac repair after myocardial infarction via in situ recruitment and expansion of c-kit+ cells. *Circ Res* 111(11):1434–1445, 2012.
94. Sopko N, Qin Y, Finan A, et al: Significance of thymosin beta4 and implication of PINCH-1-ILK-alpha-parvin (PIP) complex in human dilated cardiomyopathy. *PLoS One* 6(5):e20184, 2011.
95. Shrivastava S, Srivastava D, Olson EN, et al: Thymosin beta4 and cardiac repair. *Ann N Y Acad Sci* 1194:87–96, 2010.
96. Finan A, Sopko N, Dong F, et al: Bone marrow SSEA1+ cells support the myocardium in cardiac pressure overload. *PLoS One* 8(7):e68528, 2013.
97. Finan A, Kiedrowski M, Turturice BA, et al: Cardiac pressure overload initiates a systemic stem cell response. *Cytotherapy* 14(8):983–993, 2012.
98. Pasumarthi KB, Nakajima H, Nakajima HO, et al: Targeted expression of cyclin D2 results in cardiomyocyte DNA synthesis and infarct regression in transgenic mice. *Circ Res* 96(1):110–118, 2005.
99. Nakajima H, Nakajima HO, Tsai SC, Field LJ: Expression of mutant p193 and p53 permits cardiomyocyte cell cycle reentry after myocardial infarction in transgenic mice. *Circ Res* 94(12):1606–1614, 2004.
100. Karantalis V, DiFede DL, Gerstenblith G, et al: Autologous mesenchymal stem cells produce concordant improvements in regional function, tissue perfusion, and fibrotic burden when administered to patients undergoing coronary artery bypass grafting: the Prospective Randomized Study of Mesenchymal Stem Cell Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) trial. *Circ Res* 114(8):1302–1310, 2014.
101. Nowbar AN, Mielewczik M, Karavassilis M, et al: Discrepancies in autologous bone marrow stem cell trials and enhancement of ejection fraction (DAMASCENE): weighted regression and meta-analysis. *BMJ* 348:g2688, 2014.

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Qualitative and Quantitative Coronary Angiography

59

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KEY POINTS

- Although clinical outcomes after percutaneous coronary intervention (PCI) have continued to improve over the past 2 decades, precise assessment of coronary lesion complexity remains valuable in estimating early and late procedural risk.
- Aggregate scores that consider the vessel patency and underlying lesion morphology provide the most predictive information for estimating outcome. The SYNTAX trial score, a quantitative assessment of the extent of coronary artery disease, has provided valuable insights into the selection of patients for multivessel PCI or coronary artery bypass grafting.
- Longer lesions, thrombus-containing lesions, degenerated saphenous vein grafts, severe tortuosity and angulation, and total coronary occlusions hold the highest risk for failure with PCI.
- Assessment of myocardial blood flow and myocardial perfusion is useful in predicting prognosis for patients with ST-segment elevation myocardial infarction (STEMI) and may be valuable in predicting events in patients with non–ST-segment elevation myocardial infarction as well. More quantitative than qualitative indices are preferred to assess the value of new drugs and devices STEMI patients.
- Coronary angiography is standard for assessing lesion severity before and after PCI, but physiologically intermediate (40% to 70%) lesions require assessment using adjunct modalities, such as fractional flow reserve.
- For research, reliable and reproducible methods of severity assessment using quantitative angiography have provided important insights into the mechanisms of benefit of new drugs and devices in patients undergoing coronary intervention. Use of novel quantitative programs has yielded three-dimensional imaging methods for precise characterization of total occlusions and bifurcation disease.
- Late clinical restenosis can be predicted by the quantitative measurement of percent diameter stenosis and late lumen loss in patients undergoing drug-eluting and bare-metal stent placement.
- Quantitative angiographic methods remain an essential tool for assessing the outcome after new device and drug therapy in patients undergoing intervention for ischemic heart disease.

Percutaneous coronary intervention (PCI) has evolved dramatically over the past 3 decades, fundamentally altering the management of ischemic coronary artery disease (CAD). Bare-metal stents (BMSs) and drug-eluting coronary stents (DESs) are used in more than 90% of PCI procedures. Coronary arteriography is a fundamental component of PCI, providing prognostic information about the baseline lesion morphology and severity, quantification of anterograde perfusion, and adequacy of the final result. Although conventional visual angiography has formed the cornerstone of clinical decision making for patients undergoing cardiovascular interventions, quantitative analyses of procedural and late angiograms have elucidated the therapeutic mechanisms of new devices and drugs and identified the factors predisposing to procedural complications, thrombosis, and restenosis, improving patient selection for these procedures.

The standard criteria used to stratify the baseline procedural risk of patients undergoing PCI are reviewed in this chapter. These criteria have been modified since the availability of DESs, and several predictive scores (e.g., SYNTAX trial score) have provided useful tools for deciding between multivessel PCI and coronary artery bypass grafting (CABG) in patients with complex CAD. Newer methods to assess myocardial perfusion beyond coronary flow that provide important prognostic information for patients with acute myocardial infarction (AMI) are discussed. The quantitative angiographic methods used for evaluating early and late procedural outcome after PCI are outlined, including the value of these indices as surrogates for clinical outcome in novel stent studies.

QUALITATIVE ANGIOGRAPHY

Calculation of the procedural risk for PCI begins with accurate assessment of the complexity of the baseline coronary anatomy. Predictors for an adverse procedural outcome after balloon angioplasty were identified in early series, but a standardized approach to the assessment of lesion morphology in patients undergoing PCI was lacking until the late 1980s. Refinement of these criteria was necessary after the introduction of coronary stents to estimate procedural risk, particularly with the continued availability of the alternative of CABG.

ACC/AHA Task Force Criteria for Lesion Morphology

A joint task force of the American College of Cardiology (ACC) and American Heart Association (AHA) established criteria to estimate procedural success and complication rates after balloon angioplasty based on the presence or absence of specific high-risk lesion characteristics more than 2 decades ago.[1] Although these criteria were developed based solely on the task force's clinical impressions (Table 59-1), their estimates of procedural success and complications closely correlated with the procedural outcomes demonstrated in patients undergoing multivessel balloon angioplasty.[2] Chronic total occlusion, high-grade stenosis, stenosis on a bend of 60 degrees or more, and occlusion location in vessels with proximal tortuosity were associated with adverse outcomes.[2] The most complex lesion morphologies (i.e., type C lesions) were associated with less satisfactory procedural outcomes.[3,4] Definitions for these variables are provided (Table 59-2).

With the improved outcomes associated with the use of coronary stents, contemporary composite risk scores were proposed.[5,6] The Society for Cardiac Angiography and Interventions (SCAI) Registry evaluated 61,926 patients (74.5% received stents) from the ACC

TABLE 59-1 American College of Cardiology/American Heart Association Characteristics of Type A, B, and C Coronary Lesions

Type A lesions: high success rate (≈85%), low risk
- Discrete (<10 mm)
- Concentric
- Readily accessible
- Nonangulated segment (<45 degrees)
- Absence of thrombus
- Little or no calcium
- Less than totally occlusive
- Not ostial in location
- Smooth contour, no major side branch
- No side branch involvement

Type B lesions: moderate success rate (60%-85%), moderate risk
- Tubular (10-20 mm long)
- Eccentric
- Moderate tortuosity of proximal segment
- Bifurcation lesion requiring double guidewire
- Some thrombus
- Moderate to heavy calcification
- Total occlusion <3 mo old
- Moderately angulated (45-90 degrees)
- Irregular contour

Type C lesions: low success rate (≈60%), high risk
- Diffuse (>20 mm long)
- Excessive tortuosity of proximal segment
- Extremely angulated segment (>90 degrees)
- Total occlusion >3 mo old
- Inability to protect major side branches
- Degenerated vein grafts with friable lesions

Modified from Ryan TJ, Faxon DP, Gunnar RP, et al: Guidelines for percutaneous transluminal coronary angioplasty: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). *J Am Coll Cardiol* 12:529-545, 1988.

TABLE 59-2 Definitions of Preprocedural Lesion Morphology

Variable	Definition
Eccentricity	Stenosis with one of its luminal edges in the outer one fourth of the apparently normal lumen
Irregularity	Lesion ulceration, intimal flap, aneurysm, or sawtooth pattern
Ulceration	Small crater consisting of a discrete luminal widening in the area of the stenosis but does not extend beyond the normal arterial lumen
Aneurysmal dilation	Segment of arterial dilation larger than the dimensions of the normal arterial segment
Sawtooth pattern	Multiple, sequential stenotic irregularities
Lesion length	Measured shoulder to shoulder in an unforeshortened view
Discrete	Lesion length <10 mm
Tubular	Lesion length 10-20 mm
Diffuse	Lesion length >20 mm
Ostial location	Origin of the lesion within 3 mm of the vessel origin
Lesion angulation	Vessel angle formed by the centerline through the lumen proximal to the stenosis and extending beyond it and a second centerline in the straight portion of the artery distal to the stenosis
Moderate	Lesion angulation >45 to 90 degrees
Severe	Lesion angulation >90 degrees
Bifurcation	Medium or large branch (>1.5 mm) originates within the stenosis, and the side branch is completely surrounded by stenotic portions of the lesion to be dilated
Lesion accessibility	
Moderate tortuosity	Lesion is distal to two bends ≥75 degrees
Severe tortuosity	Lesion is distal to three bends ≥75 degrees
Degenerated SVG	Graft characterized by luminal irregularities or ectasia comprising >50% of the graft length
Calcification	Readily apparent densities within the apparent vascular wall at the site of stenosis
Moderate	Densities seen only with cardiac motion before contrast injection
Severe	Radiopacities seen without cardiac motion before contrast injection
Total occlusion	TIMI grade 0 or 1 flow
Thrombus	Discrete, intraluminal filling defect with defined borders that is largely separated from the adjacent wall; contrast staining may or may not be seen

SVG, Saphenous vein graft; *TIMI,* Thrombolysis in Myocardial Infarction.

National Cardiovascular Data Registry and classified their lesions in four groups: non–type C, type C, non–type C occluded, and type C occluded (Table 59-3).[5] These simplified criteria provided better discrimination for success or complications than the ACC/AHA original classification with a c statistic of 0.69 for success using the ACC/AHA original classification system, 0.71 using the modified ACC/AHA system, and 0.75 for the SCAI classification.[5]

The Mayo Clinic risk score was constructed by adding integer scores for eight morphologic variables, and it was compared with the ACC/AHA risk score for 5064 patients undergoing PCI, of whom 183 (4%) experienced an adverse event (e.g., death, Q-wave myocardial infarction, stroke, emergency CABG).[6] The Mayo Clinic risk score offered significantly better risk stratification than the ACC/AHA lesion classification for the development of cardiovascular complications, whereas the ACC/AHA lesion classification was a better system for determining angiographic success.[6]

SYNTAX Score

The SYNTAX score was developed during the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial to classify patients according to the complexity and extent of CAD.[7,8] A lesion is defined as significant when it causes a greater than 50% reduction in luminal diameter by visual assessment in a vessel that is more than 1.5 mm in diameter.[8] A multiplication factor of 2 is used for nonocclusive lesions, and 5 is used for occlusive lesions, reflecting the difficulty of the percutaneous treatment.[8] Up to 12 lesions are identified within the coronary tree, and each lesion is assessed for its severity, including total occlusion (with appropriate characterization) and side branches and their size.[8]

Each lesion is also weighted by its contribution to the myocardial bed that it supplies.[8] In a right-dominant system, the right coronary artery supplies approximately 16% and the left coronary artery supplies 84% of the flow to the left ventricle, of which 66% is supplied by the left anterior descending artery and 33% is supplied by the left circumflex coronary artery. These factors have been included in the weight given to each segment.

Lesions are further graded by their complexity, including multiple tandem lesions, morphology of total occlusions, bifurcation and trifurcation involvement, aortoostial location, diffuse disease and small vessels, severe tortuosity, length greater than 20 mm, heavy calcification, and thrombus.[8,9] An online algorithm (http://www.syntaxscore.com) automatically sums each of these features to calculate the total score.

The SYNTAX score is an important prognostic tool for risk stratifying patients with multivessel disease who are being considered for coronary revascularization. Its predictive value was assessed for 1292

TABLE 59-3 SCAI Classification of Class I Through IV Lesions

Type I Lesion*

1. Does not meet ACC/AHA criteria for type C lesion
2. Patent

Type II Lesion

1. Meets any of the following criteria for type C lesion:
   - Diffuse (>2 cm long)
   - Excessive tortuosity of proximal segment
   - Extremely angulated segments >90 degrees
   - Inability to protect major side branches
   - Degenerated vein grafts with friable lesions
2. Patent

Type III Lesion

1. Does not meet ACC/AHA criteria for type C lesion
2. Occluded

Type IV Lesion

1. Meets any of the following criteria for type C lesion:
   - Diffuse (>2 cm long)
   - Excessive tortuosity of proximal segment
   - Extremely angulated segments (>90 degrees)
   - Inability to protect major side branches
   - Degenerated vein grafts with friable lesions
2. Occluded

Modified from Krone R, Shaw R, Klein L, et al: Evaluation of the American College of Cardiology/American Heart Association and the Society for Coronary Angiography and Interventions lesion classification system in the current "stent era" of coronary interventions (from the ACC National Cardiovascular Data Registry). *Am J Cardiol* 92:389-394, 2003. *ACC/AHA,* American College of Cardiology/American Heart Association; *SCAI,* Society for Cardiac Angiography and Interventions.
*Highest success rate expected, lowest risk.

lesions in 306 patients who underwent PCI for three-vessel disease in the Arterial Revascularization Therapies Study Part II.[10] The rate of major adverse cardiac and cerebrovascular events at 370 days was 27.9% in the highest SYNTAX score tertile and 8.7% in the lowest SYNTAX tertile (hazard ratio = 3.5, $P = .001$).[10] By multivariable analyses, the SYNTAX score independently predicted outcome and the risk of major adverse cardiac and cerebrovascular events. Compared with the modified ACC/AHA lesion classification scheme, SYNTAX score showed a better discrimination ability and goodness of fit.[10]

The SYNTAX score has been used to predict outcomes for patients enrolled in DES studies.[11,12] In an analysis of 819 patients with left main CAD who underwent revascularization in two Italian centers, the outcomes of patients undergoing PCI and CABG were studied. In patients with a SYNTAX score of 34 or less, the 2-year mortality rates were similar for CABG and PCI (6.2% vs. 8.1%, $P = .461$).[11] Among patients with a SYNTAX score greater than 34, those treated with CABG had lower mortality rates than those treated with PCI (8.5% vs. 32.7%, $P < .001$).[11] A similar correlation of the SYNTAX score and surgical outcome was not found for patients undergoing CABG.[13,14]

The value of the SYNTAX score in predicting clinical outcomes has been investigated and validated in other clinical settings, including patients who underwent primary PCI for ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation myocardial infarction (NSTEMI).[15] The SYNTAX score is advocated in European and U.S. revascularization guidelines to risk-stratify patients with complex CAD to the most appropriate revascularization modality.[16,17]

Determining risk based purely on anatomic descriptions without the addition of clinical variables is an important limitation of the SYNTAX score. Patients with equivalent scores may have very different outcomes because of different comorbidities. To address this limitation, attempts have been made to combine clinically based scores with the SYNTAX score. The SYNTAX score II was developed to optimize decisions about the revascularization strategy.[18] It was developed and validated on the basis of a core model consisting of the anatomic SYNTAX score, age, creatinine clearance value, left ventricular ejection fraction, unprotected left main disease, peripheral vascular disease, female sex, and chronic obstructive pulmonary disease. The combination of clinical variables and the SYNTAX score has the best discriminatory value for patients undergoing multivessel PCI.[19,20]

In a effort to further integrate clinical and angiographic variables into a combined risk score, the Acute Catheterization and Urgent Intervention Triage Strategy–Percutaneous Coronary Intervention (ACUITY-PCI) trial included six: insulin-treated diabetes, renal insufficiency, baseline cardiac biomarker elevation or ST-segment deviation, bifurcation lesion, small vessel or diffuse CAD, and extent of CAD.[21] The ACUITY-PCI score had the best discrimination, calibration, and index of separation compared with other risk scores.[21] In a comparative analysis of 2094 patients enrolled in the ACUITY Study, the SYNTAX score; combined clinical variables plus SYNTAX score (CSS); new risk stratification (NERS) score; age, creatinine, and ejection fraction (ACEF) score; Global Registry for Acute Coronary Events (GRACE) score; and Thrombolysis in Myocardial Infarction (TIMI) study score were compared for their risk assessment of 1-year mortality, cardiac mortality, myocardial infarction, target-vessel revascularization (TLR), and stent thrombosis for patients with non–ST-segment elevation acute coronary syndromes undergoing PCI.[22] In this analysis, scores incorporating clinical and angiographic variables (i.e., CSS and NERS) showed the best balance between discrimination and calibration.[22]

Risk Assessment Using Specific Lesion Morphologic Criteria

Despite the value of risk scores in estimating aggregate procedural risk, they have several limitations when applied to individual patients. Identification of lesion characteristics, such as eccentricity, irregularity, angulation, and tortuosity, is limited by substantial interobserver variability. Agreement with ACC/AHA classification was found for only 58% of lesions in one series, with disagreement by two classification grades identified for almost 10% of lesions.[2] Similarly, the SYNTAX score suffers from the interobserver variability inherent in visual estimation of disease severity. The weighted κ value for the interobserver reproducibility of the SYNTAX score was 0.45, whereas the intraobserver weighted κ value was 0.59.[9]

Rather than a composite score, the description of individual morphologic features may be more predictive of early and late outcomes after PCI. Some ACC/AHA morphologic features are associated with complicated procedures (e.g., thrombus, saphenous vein graft [SVG] degeneration, angulated segments), whereas others are associated with unsuccessful but uncomplicated procedures (e.g., chronic total occlusions, diffuse disease).

Irregular Lesions

With the advent of coronary stents, the prognostic importance of irregular lesions has been diminished substantially, although identification of an irregular plaque on angiography suggests an acute coronary syndrome and intracoronary thrombus. Semiquantitative and quantitative measurements of lesion irregularity were developed in the early 1990s to better characterize lesion morphology in patients with acute coronary syndromes, but these methods have not found clinical utility independent of other clinical risk factors.

A novel technique of identifying plaque rupture defined any irregular lesion with ulceration, flap, or aneurysm on a qualitative angiogram as suspicious for plaque rupture. Intravascular ultrasound (IVUS)–detected lesions with or without plaque rupture were compared with the corresponding angiograms.[23] Proximal coronary location, a wide cavity, and counterflow rupture were strong predictors of correct angiographic diagnoses, enabling four specific angiographic patterns to be identified using three-dimensional (3-D) IVUS plaque rupture reconstruction.[23] An aneurysmal or ulcerated lesion was one of several components of a stent thrombosis risk score.[24]

Angulated Lesions

Vessel curvature at the site of maximum stenosis should be measured in the most unforeshortened projection using a length of curvature that

approximates the balloon length used for coronary dilation. Although balloon angioplasty of highly angulated lesions is associated with an increased risk of coronary dissection, in the era of coronary stenting, the greatest impediment of angulated lesions is the inability to deliver the stent to the stenosis and straighten the arterial contour after stent placement, which may predispose to late stent fracture. One of the advantages of bioresorbable scaffolds has been less vessel straightening than conventional metallic stents, particularly as the scaffold is resorbed over time.[25]

Lesion Calcification

Coronary artery calcium remains an important marker for coronary atherosclerosis. Conventional coronary angiography has limited sensitivity for the detection of smaller amounts of calcium and is only moderately sensitive for the detection of extensive lesion calcium (60% and 85% sensitivity for three- and four-quadrant calcium, respectively).[26] Coronary calcification reduces the compliance of the vessel and may predispose to dissection at the interface between calcified plaque and normal wall after balloon angioplasty.[27] Coronary calcification also reduces the ability to cross chronic total occlusions, and in severely calcified lesions, stent strut expansion is inversely correlated with the circumferential arc of calcium.[26] Patients treated with sirolimus-eluting stents who had lesion calcification had higher TLR rates than those who did not.[28,29] A pooled analysis of seven trials of first- and second-generation DESs identified severe calcification as an independent predictor of poor outcome after PCI.[30]

Rotational atherectomy is the preferred pretreatment method in patients with severe lesion calcification, particularly ostial lesions, and it facilitates the delivery and expansion of coronary stents by creating microdissection planes within the fibrocalcific plaque. Even with these contemporary methods, moderate or severe coronary calcification is associated with reduced procedural success and higher complication rates, including stent dislodgment. A novel device, the Diamondback 360 Orbital Atherectomy System (Cardiovascular Systems, St. Paul, MN), used centrifugal action of a diamond-coated crown to modify calcified lesions in a series of 443 patients with severe calcification to facilitate stent placement; stent delivery was successful in 97.7% of cases.[31] In less severely calcified lesions, no difference in the restenosis rate was found after paclitaxel-eluting stent implantation in calcified or noncalcified vessels.[32] Calcification in SVGs usually occurs within the reference vessel wall rather than the lesion and is associated with older graft age, insulin-dependent diabetes, and a history of smoking.[33] Calcified lesions were an independent predictor of stent thrombosis in one series.[34]

Degenerated Saphenous Vein Grafts

SVGs degenerate over time, with 25% occluding within the first year after coronary bypass surgery[35] and 50% developing occlusion within 10 years after surgery, often necessitating repeat revascularization. SVGs are the most common site for a culprit lesion in patients with acute coronary syndromes after CABG[36] and account for 6% of all PCIs.[37] PCIs for SVG lesions have been associated with a worse late outcome compared with native vessel interventions.[4,38,39] The SVG plaques are particularly prone to distal embolization.[38] The risk of embolic complications appears to be related to the degree of overall graft degeneration and the length and bulkiness of the lesion.[40] The risk of embolization may be reduced with the use of excimer laser atherectomy[41,42] and with the use of undersized balloons.[43]

Embolic protection devices (EPDs) have been associated with improved angiographic and clinical outcomes in percutaneous SVG interventions.[40] In the landmark Saphenous Vein Graft Angioplasty Free of Emboli Randomized (SAFER) trial, use of a distal balloon occlusion EPD was associated with a decrease (9.6% vs. 16.5%) in the 30-day composite outcome of death, myocardial infarction, emergency CABG, or TLR compared with no embolic protection.[44] Subsequent noninferiority comparisons have demonstrated similar benefit with proximal occlusion and distal filter EPD, with the benefit limited to reduction in periprocedural myocardial infarction.[45,46] When feasible, the use of EPDs during SVG PCI has been given a class I recommendation in the ACC/AHA PCI guidelines.[16] One exception may be in patients treated for in-stent restenosis (ISR), for which embolic protection may not be required.

Restenosis and TLR rates are lower with DESs compared with BMSs in SVG interventions, even though mortality and stent thrombosis rates are similar.[47] Self-expanding stents made with expanded polytetrafluoroethylene (ePTFE) provide no additional advantage over noncovered balloon-expandable stents in the development of early complications or late restenosis.[48,49]

Thrombus

Conventional angiography is relatively insensitive for the detection of coronary thrombus but may be useful in up to 15% of patients undergoing PCI for an acute coronary syndrome.[50] Angiographic thrombus is usually identified by the appearance of discrete, intraluminal filling defects within the arterial lumen, and it is associated with a 6% to 73% incidence of ischemic complications after PCI.[50] A large thrombus burden is an independent predictor of stent thrombosis in patients with STEMI treated with DESs,[51] and it may be managed with intensive anticoagulation therapy before PCI to reduce periprocedural complications.[52]

The primary PCI-related complications of thrombus-containing lesions are distal embolization and thrombotic occlusion, and the risk of angiographic thrombus complications is related to the size of the coronary thrombus. Routine rheolytic thrombectomy provides no benefit in patients with AMI,[53] although it may be useful for patients with a large thrombus burden. Several aspiration catheters have been used in patients with AMI and large thrombus burden, but large-scale studies are lacking.[54]

Traditionally, the extent of coronary thrombus has been determined using the semiquantitative TIMI thrombus grade (TTG). A novel method to assess intracoronary thrombus burden uses the discrepancy of luminal areas assessed with edge detection and video densitometry and measured with the Cardiovascular Angiography Analysis System II.[55] Thrombus remains an important predictor of outcome after PCI.[3]

Ostial Location

Ostial lesions begin within 3 mm of the origin of the coronary artery, and they are classified as aortoostial or nonaortoostial lesions. Balloon angioplasty of ostial lesions is limited by suboptimal procedural outcome, primarily due to technical factors such as difficulties with guide catheter support, lesion inelasticity precluding maximal balloon expansion, and early vascular recoil limiting the acute angiographic result. Debulking techniques such as directional and rotational atherectomy improve compliance of the aortoostial lesion but have had limited effect on preventing late restenosis. Ostial lesions have been associated with higher rates of TLR after DES placement.[29,56]

Coronary stenting, recently performed with DESs, has become the default therapy for most aortoostial lesions, although there are unique challenges of stent placement in the aortoostial location, such as protrusion of the stent into the aorta precluding subsequent injection catheter engagement, compression, and avulsion of the stent struts into the aorta when new devices such as cutting balloon angioplasty are used to treat ISR.

Aortoostial lesions remain associated with higher failure rates than nonaortoostial lesions.[54] Isolated nonaortoostial stenoses of the left circumflex and left anterior descending coronary arteries[57] and ostial side branch bifurcation lesions are also effectively treated with DESs,[54,58] but they pose unique challenges regarding vessel wall geometry, adequate ostial branch coverage (particularly for a narrow angle with the adjacent branch), and plaque shifting causing compromise of the parent or adjacent branch vessels. Whereas stent protrusion into the parent vessel of less than 1 mm is usually well tolerated, greater stent protrusion precludes treatment of the parent branches.[58] Stent fractures have been reported with more advanced stenting techniques used to treat the parent vessel and ostial side branch stenoses.

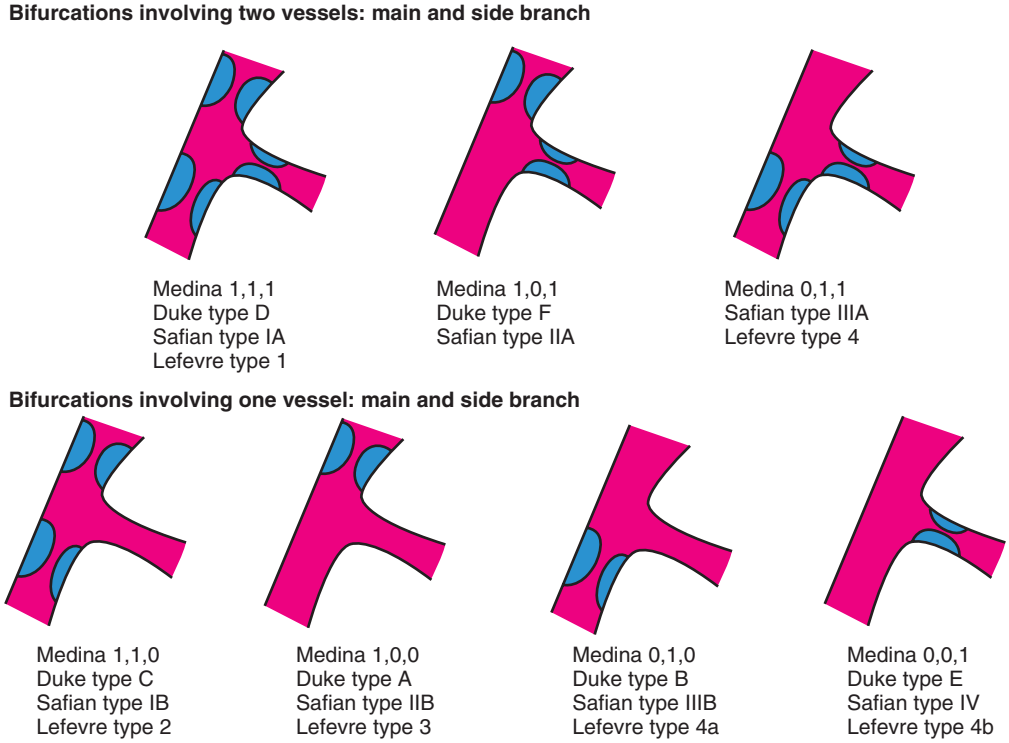

FIGURE 59-1 Schematic classification systems for types of bifurcation stenoses.

Long Lesions

Lesion length may be estimated quantitatively as the shoulder-to-shoulder extent of atherosclerotic narrowing greater than 20%, although many clinicians estimate lesion length based on the identification of a normal-to-normal segment, which is usually longer than the length obtained with quantitative methods. Conventional balloon angioplasty of long lesions has been associated with reduced procedural success, particularly when the segment is diffusely diseased (e.g., >20 mm long), primarily because of the more extensive plaque burden in long lesions.

Stents improve late outcomes compared with balloon angioplasty, but stent and lesion length remain the most important predictors of restenosis in the stent era.[59] Coronary stents have been used to treat suboptimal angiographic results (i.e., spot stenting) and dissections after balloon angioplasty of longer lesions, although the "full metal jacket" stent approach to diffuse disease is associated with a higher recurrence rate in the absence of complete stent expansion, particularly in smaller vessels. Overlapping sirolimus-eluting stents provide safe and effective treatment for long coronary lesions.[60] However, stent length greater than 35 mm remains a risk factor for restenosis and the need for revascularization.[61] Longer stented lesions were associated with stent thrombosis in one series.[34]

In a contemporary analysis of 10,004 patients undergoing surveillance, binary restenosis was detected in 2643 (26.4%) patients.[62] Use of a first-generation DES or BMS (odds ratio [OR] = 0.35) and use of a second-generation DES or first-generation DES (OR = 0.67) were independent predictors of lower rates of restenosis. On multivariate analysis, smaller vessel size (OR = 1.59 for each 0.5-mm decrease), total stented length (OR = 1.27 for each 10-mm increase), complex lesion morphology (OR = 1.35), diabetes mellitus (OR = 1.32), and history of bypass surgery (OR = 1.38) were independently associated with restenosis and were similar across the spectrum of stent devices.[62]

Bifurcation Lesions

Bifurcation lesions are common (up to 20% of all PCIs), and their percutaneous management is associated with higher rates of restenosis and thrombosis compared with nonbifurcation lesions.[63] The risk of side branch occlusion in bifurcation lesions is related to the extent of atherosclerotic involvement of the side branch and geometry of the carina.[64]

Several classification systems have been proposed (Fig. 59-1).[65-68] The Medina classification is the most commonly used and characterizes stenoses in the proximal parent vessel (0 = no disease; 1 = disease), distal vessel (0 = no disease; 1 = disease), and side branch (0 = no disease; 1 = disease). For example, a bifurcation lesion that involves the proximal and distal parent vessel and a side branch with a greater than 50% diameter stenosis is designated Medina 1,1,1, whereas a bifurcation lesion involving only the proximal parent vessel is designated Medina 1,0,0.[66]

One stent usually is preferable to two stents in the parent vessel and side branch.[69,70] If two stents are planned for the parent vessel and side branch due to complex bifurcation disease, several stenting techniques are possible, including simultaneous kissing stents, crush and double-kissing (DK) crush, culotte, T, and T plus protrusion (TAP) stenting. Common to all of these strategies is a final kissing balloon inflation in the parent vessel and side branch,[71,72] although a sequential two-step dilation of the branch vessel followed by the parent vessel may also be suitable.[73] There is no consensus on which techniques are the optimal treatment strategy for bifurcation lesions.[74,75]

The origin of the side branch rather than the parent vessel is the most common location of failure (recurrence) after bifurcation stenting,[76] and one study of Medina 0,0,1 bifurcation lesions suggested that a two-stent strategy was associated with lower rates of clinical restenosis than a single-stent strategy.[77] Other studies have suggested that the DK crush technique is superior to culotte stenting for left main CAD[78] and native vessel bifurcations.[79]

Dedicated bifurcation stents were developed to provide adequate vessel coverage and side branch access,[67,80-86] but they have been challenged with their higher profile and difficult delivery. A specifically designed side-branch stent has also shown favorable results.[87-90] Drug-eluting balloons have been used in bifurcation lesions with mixed results.[91]

The angiographic analysis of bifurcation lesions is a challenging task. Although the visual assessment of these lesions is inaccurate, the

standard quantitative coronary angiography (QCA) packages designed for single lesions cannot overcome the complexities of the bifurcation lesions.[92,93] In an effort to address this shortcoming, dedicated bifurcation QCA algorithms have been developed, such as the Cardiovascular Angiography Analysis System (Pie Medical Imaging, Maastricht, The Netherlands) and QAngio XA (Medis, Leiden, The Netherlands).[93-95] In a survey of experts in the field of bifurcation PCI, accuracy and precision of visual estimates of stenosis severity in phantom bifurcation lesions varied greatly and was less precise compared with the dedicated QCA algorithms, justifying the use of these software packages in clinical and research practice.[96]

Total Occlusion

Total coronary occlusion is identified as an abrupt termination of the epicardial vessel; anterograde and retrograde collaterals may be helpful in quantifying the length of the totally occluded segment. Coronary occlusions are common findings[97] and often lead to the decision to perform coronary bypass surgery rather than PCI in the setting of multivessel disease.[98,99]

The success rate for recanalization depends on the occlusion duration and on certain lesion morphologic features, such as bridging collaterals, occlusion length greater than 15 mm, and absence of a nipple to guide wire advancement. Although newer technologies and techniques have been used to recanalize refractory occlusions,[100,101] better guidewires and wire techniques have accounted for much of the improvement in crossing success.[102] Simultaneous coronary injections are sometimes useful for identifying the length of the total occlusion (Fig. 59-2). After the occlusion has been crossed, coronary stents have been used to provide the best long-term outcomes.[103] DESs usually are preferred to BMSs.[104]

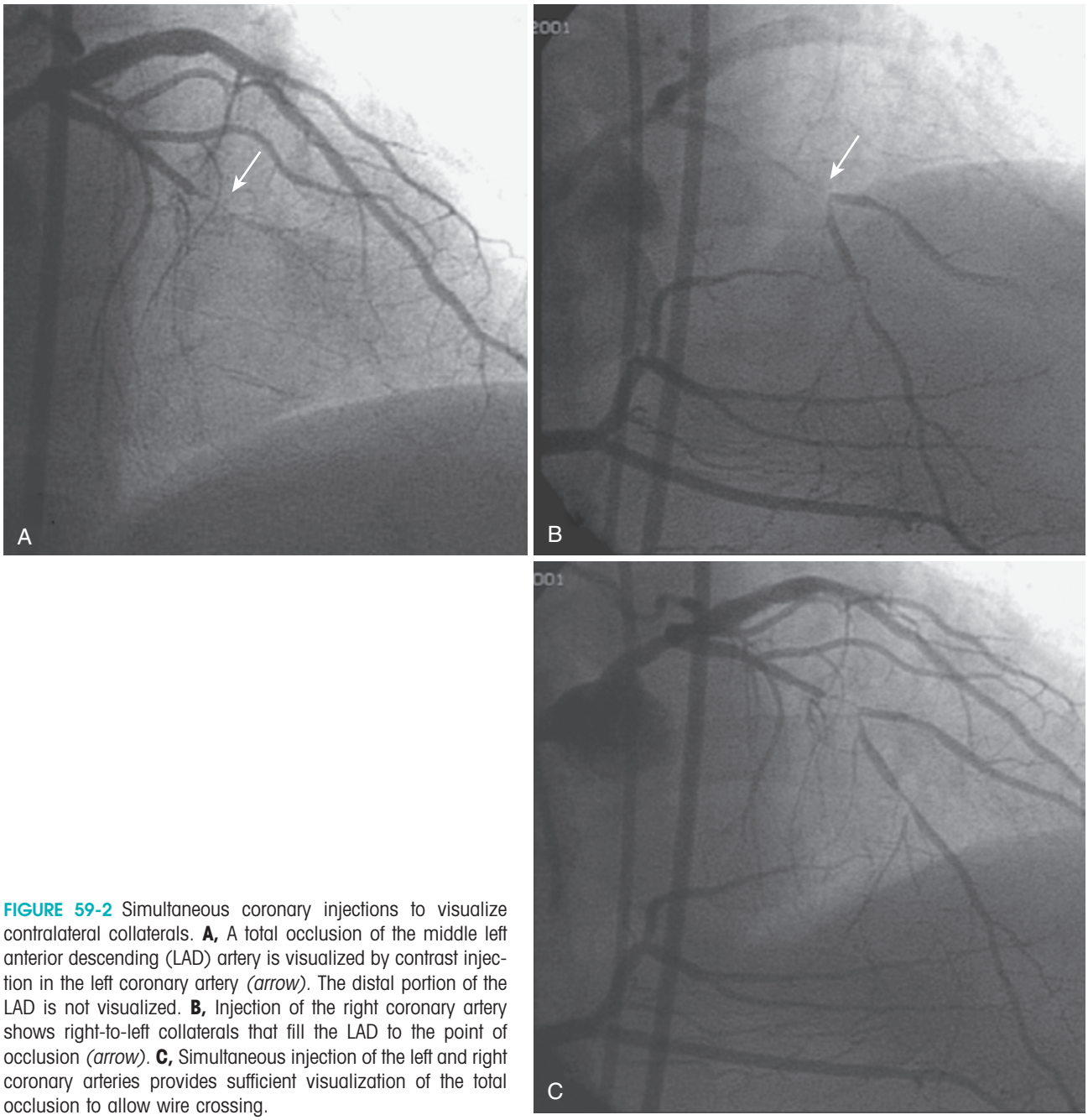

FIGURE 59-2 Simultaneous coronary injections to visualize contralateral collaterals. **A,** A total occlusion of the middle left anterior descending (LAD) artery is visualized by contrast injection in the left coronary artery *(arrow)*. The distal portion of the LAD is not visualized. **B,** Injection of the right coronary artery shows right-to-left collaterals that fill the LAD to the point of occlusion *(arrow)*. **C,** Simultaneous injection of the left and right coronary arteries provides sufficient visualization of the total occlusion to allow wire crossing.

The optimal technique for coronary revascularization is determined using four angiographic parameters: location of the proximal cap, occlusion length, existence of branches and size and quality of the target vessel at the distal cap, and suitability of collaterals for retrograde techniques.[105] On the basis of these four characteristics, there has been a substantial improvement in the ability of the operator to secure access to the coronary vessel.[105]

A key component to the assessment of total occlusion is definition of the collateral grades that provide blood flow to the jeopardized myocardium.[106] The Rentrop classification system includes Rentrop grade 0 (no filling), grade 1 (small side branches filled), grade 2 (partial epicardial filling of the occluded artery), and grade 3 (complete epicardial filling of the occluded artery). Anatomic collaterals summarized by the 26 potential pathways were consolidated into four groups: septal, intraarterial (bridging), epicardial with proximal takeoff (atrial branches), and epicardial with distal takeoff.[107] The size of the collateral connection can be quantified as group 0 (no continuous connection between donor and recipient artery), group 1 (continuous threadlike connection ≤0.3 mm), or group 2 (continuous small, branchlike collateral through its course ≥0.4 mm).[107]

Angiographic Complications After Percutaneous Coronary Intervention

Although the frequency of angiographic complications during PCI has been reduced substantially with the use of coronary stents, untoward effects resulting from disruption of the atherosclerotic plaque and embolization of atherosclerotic debris, thrombus, and vasoactive mediators still occur during 5% to 10% of PCIs (Table 59-4).

Coronary Dissection

Plaque fracture is an integral component of balloon angioplasty, although significant vessel wall disruption resulting in reduced anterograde flow and lumen compromise is a relatively uncommon occurrence (≈3%).[108]

The National Heart, Lung, and Blood Institute (NHLBI) coronary dissection criteria categorize the severity of coronary dissection after PCI (see Table 59-4), with the prognostic implications of the coronary dissection depending on extension into the media and adventitia, axial length, existence of contrast staining, and effect on anterograde coronary perfusion. It is sometimes difficult to assess the angiographic residual lumen in the setting of coronary dissection because of the frame-to-frame lumen diameter changes seen with two-dimensional (2-D) imaging. IVUS or optimal coherence tomography may provide a more accurate reflection of the lumen's circumference.[109-111] Dissections resulting in a residual stenosis area of 60% or greater by IVUS[109] and those extending to more than 5 to 10 mm in axial length are associated with a worse prognosis. A residual coronary dissection is an independent predictor of stent thrombosis.[63]

No-Reflow Phenomenon

Reduced flow during PCI, also known as the no-reflow phenomenon, is defined as a reduction in anterograde flow despite a patent lumen at the site of PCI.[112] It occurs during 1% to 5% of PCIs. The no-reflow phenomenon is a strong predictor of mortality after PCI.[113] It is more common (15%) during primary angioplasty for AMI.[114] Predictors include a higher plaque burden, thrombus, lipid pools seen by IVUS, higher lesion elastic membrane cross-sectional area, preinfarction angina, and TIMI flow grade 0 on the initial coronary angiogram.[115-118]

Compared with aspirates obtained from patients without the no-reflow phenomenon, aspirates obtained from patients who developed it contained more atheromatous plaque and significantly more platelet and fibrin complex, macrophages, and cholesterol crystals.[119] The 30-day mortality rate was significantly higher (27.5%) for patients with combined slow-flow and no-reflow phenomenon than for patients with normal coronary blood flow after PCI (5.3%; $P < .001$).[114] Intracoronary or intragraft nitroprusside,[120] adenosine,[121] verapamil,[122,123] and nicardipine[124] and aspiration of atherosclerotic debris have each been used to correct the no-reflow episode.

TABLE 59-4 Complications After Percutaneous Coronary Intervention

Variable	Definition
Abrupt closure	Obstruction of contrast flow (TIMI grade 0 or 1) in a dilated segment with previously documented anterograde flow
Ectasia	Lesion diameter greater than the reference diameter in one or more areas
Luminal irregularities	Arterial contour that has a sawtooth pattern consisting of opacification but not fulfilling the criteria for dissection or intracoronary thrombus
Intimal flap	Discrete filling defect in apparent continuity with the arterial wall
Thrombus	Discrete, mobile angiographic filling defect with or without contrast staining
Dissection*	
A	Small radiolucent area within the lumen of the vessel
B	Linear, nonpersistent extravasation of contrast
C	Extraluminal, persisting extravasation of contrast
D	Spiral-shaped filling defect
E	Persistent lumen defect with delayed anterograde flow
F	Filling defect accompanied by total coronary occlusion
Length	Measured end to end for type B through F dissections
Staining	Persistence of contrast within the dissection after washout of contrast from the remaining portion of the vessel
Perforation	
Localized	Extravasation of contrast confined to the pericardial space immediately surrounding the artery and not associated with clinical tamponade
Nonlocalized	Extravasation of contrast with a jet not localized to the pericardial space, potentially associated with clinical tamponade
Side branch loss	TIMI grade 0, 1, or 2 flow in a side branch >1.5 mm in diameter that previously had TIMI 3 flow
Coronary spasm	Transient or permanent narrowing >50% when a <25% stenosis was previously identified

TIMI, Thrombolysis in Myocardial Infarction.
*National Heart, Lung, and Blood Institute classification system for coronary dissection.

Distal Embolization

Periprocedural myonecrosis provides clinical evidence of distal particulate embolization during PCI. Angiographic distal embolization is migration of a filling defect or thrombus that distally occludes the target vessel or one of its branches.[125] It occurs in approximately 10% of patients with AMI undergoing PCI. Embolic complications occur more often in patients with AMI and in patients undergoing balloon angioplasty of SVG lesions, particularly those with a recent occlusion.

Coronary Perforation

Coronary perforation is an uncommon (<1%) complication of PCI that is associated with significant morbidity and mortality.[126-130] Coronary perforations are uncommon in patients undergoing balloon angioplasty (0.1%) compared with patients undergoing atheroablative therapy (1.3%, $P < .001$).[127,131] Perforation due to coronary guidewires may manifest late after the procedure.[132] Initial management strategies include prolonged balloon inflation, reversal of anticoagulation, and in refractory cases, use of PTFE-covered stents.[133-135]

Prognosis after coronary perforation depends on the extent of extravasation into the pericardium.[131] A classification scheme has been developed based on the angiographic appearance of the

perforation. Type I perforations have an extraluminal crater without extravasation, type II perforations contain pericardial or myocardial blushing, and type III perforations have a diameter equal to or greater than 1 mm with contrast streaming and cavity spilling.[131] Type I perforations were associated with no deaths and cardiac tamponade in 8% of patients; type II perforations were associated with no deaths and cardiac tamponade in 13% of cases; and type III perforations were associated with a higher mortality risk and other adverse events.[131,136,137]

Coronary Spasm

Coronary spasm is a transient or sustained reduction in the diameter stenosis by more than 50% in an arterial segment with insignificant (<25%) baseline narrowing. Although coronary spasm may occur in approximately 5% of cases, its frequency has been reduced with the routine use of coronary vasodilators such as nitroglycerin and calcium channel blockers. Wire straightening of the vessel can mimic coronary spasm.

Abrupt Closure

Abrupt closure during coronary intervention is defined as an abrupt cessation of coronary flow to TIMI grade 0 or 1. It occurs during 3% to 5% of balloon angioplasty procedures. Abrupt closure may be caused by coronary dissection, embolization, or thrombus formation within the vessel. Its incidence has been markedly reduced with the availability of coronary stents.[138]

Stent Thrombosis

The Academic Research Consortium has proposed criteria for the timing and definitions used to document stent thrombosis in clinical studies. Timing of stent thrombosis is defined as acute (<24 hours), subacute (24 hours to 30 days), late (30 days to 1 year), and very late (after 1 year).[139] The categories of definite stent thrombosis, probable stent thrombosis, and possible stent thrombosis have been proposed as a more inclusive and standardized way to characterize the occurrence of this event in patients undergoing stent implantation (Table 59-5).

The incidence of BMS thrombosis within 30 days of the procedure is less than 1%. Predictive factors for stent thrombosis include persistent dissection of NHLBI grade B or higher after stenting, greater total stent length, and a smaller final minimal lumen diameter within the stent.[140] DESs administered with longer durations (3 to 6 months) of dual antiplatelet therapy have similar stent thrombosis rates similar to those found with BMSs,[141,142] although premature discontinuation of dual antiplatelet therapy has been associated with higher stent thrombosis rates (6% to 29%) with the use of first-generation DESs.[143,144]

Other factors that predispose to stent thrombosis are diabetes, prior brachytherapy, bifurcation lesions with two stents, AMI, renal failure, lower ejection fraction, and longer stent length.[143,144] One concern is the occurrence of very late (>1 year) stent thrombosis with the use of a DES[145] due to inflammation from the stent.[146,147] The likelihood has been substantially reduced with the use of second- and third-generation DESs. The estimated incidence of very late stent thrombosis ranges from 0.2% to 0.6% per year up to 3 years after stent placement. Long-term dual antiplatelet therapy may not completely prevent stent thrombosis.[142] A lower stent thrombosis rate has been found for second-generation DESs,[148-150] and a shorter duration of dual antiplatelet therapy has been recommended.

TABLE 59-5 Academic Research Consortium (ARC) Stent Thrombosis Definitions

Event	Definition
Definite	
Angiographic confirmation	TIMI flow grade 0 with occlusion originating in or within 5 mm of the stent in the presence of a thrombus *or* TIMI flow grade 1, 2, or 3 originating in or within 5 mm of the stent in the presence of a thrombus Plus at least one of the following criteria within the last 48 hr: • New acute onset of ischemic symptoms at rest (typical chest pain lasting >20 min) • New ischemic ECG changes suggesting acute ischemia • Typical rise and fall in cardiac biomarkers
Pathologic confirmation	Evidence of recent thrombus within the stent determined at autopsy or by examination of tissue retrieved after thrombectomy
Probable	Unexplained death within the first 30 days, irrespective of the time after the index procedure MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of another cause
Possible	Unexplained death >30 days after intracoronary stenting

ECG, Electrocardiographic; *MI,* myocardial infarction; *TIMI,* Thrombolysis in Myocardial Infarction.

Restenosis Pattern

When ISR occurs after BMS implantation, the risk of recurrence can be predicted by the pattern of restenosis.[151,152] Using the Mehran classification system, pattern I includes focal (<10 mm long) lesions, pattern II is defined as an ISR greater than 10 mm within the stent, pattern III includes an ISR greater than 10 mm extending outside the stent, and pattern IV is a totally occluded ISR.[151] Pattern I can be classified further by the location of the restenosis: Ia, at the articulation or gap; Ib, at the edge of the stent; Ic, within the stent; and Id, multifocal.[151]

The need for recurrent TLR increased with increasing ISR class, from 19% to 35%, 50%, and 83% in classes I through IV, respectively ($P < .001$).[151] Restenosis after DES implantation usually is more focal than after BMS placement,[153] and with the sirolimus-eluting stent, it is more commonly seen at the margin of the stent due to balloon injury that is not covered with the stent.[154]

Late Aneurysm Formation

Late vessel wall expansion of greater than 20% after PCI is called a coronary artery aneurysm or, more precisely, a pseudoaneurysm. Aneurysms are rare findings after balloon angioplasty, atheroablation, and coronary stenting.

Coronary artery aneurysms most likely arise from tears or dissection and incomplete healing that compromises vessel wall integrity and results in vessel wall expansion. Coronary artery aneurysms are seen after less than 1% of DES placements, and their cause in this setting may be related to expansion of all three layers of the arterial wall due to inflammation, the effects of cytostatic or cytotoxic drugs, and malapposition of the stent struts.[155,156] Rarely, coronary artery aneurysms can become infected, requiring surgical intervention.[157,158]

Coronary Perfusion

Evaluation of pharmacologic and mechanical methods to reperfuse coronary occlusions in patients with STEMI is supported by the development of a reproducible angiographic method to assess the degree of coronary recanalization achieved with these therapies. The TIMI flow grade classification characterizes the extent of coronary recanalization in patients with STEMI treated with systemic thrombolytic agents and in patients with NSTEMI and unstable angina (Table 59-6).[159] The TIMI frame count[160] and the TIMI myocardial perfusion grade were developed to further quantify anterograde flow and assess distal microvascular perfusion.[161]

TIMI Flow Grade Classification

The TIMI flow grade system is a valuable tool for assessing the efficacy of reperfusion strategies in patients with STEMI and for identifying patients at higher risk for an adverse outcome with acute coronary

syndromes or undergoing PCI. Several thrombolytic trials have identified an important relationship between the 90-minute TIMI flow grade after thrombolysis and clinical outcome.[162] In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) angiographic substudy, the mortality rate for patients with TIMI grade 2 flow (7.4%) was similar to the mortality rate for those with TIMI grade 0 or 1 flow (8.9%). In contrast, the mortality rate was lowest (4.4%) for patients with TIMI grade 3 flow.[162]

Despite these important associations, the TIMI classification system has several limitations. Substantial observer variability has been seen for the TIMI flow grade, with the best agreement between the angiographic core laboratory and clinical centers occurring when the artery is graded as open or closed (TIMI grade 0 or 1 flow; $\kappa = 0.84$).[160] Observer agreement is only moderate when assessing TIMI grade 3 flow ($\kappa = 0.55$) and is poor in the assessment of TIMI grade 2 flow ($\kappa = 0.38$). The lack of concordance for determining TIMI flow grade was also shown between experienced angiographic core laboratories.

Another limitation of the TIMI flow grade is that it provides ordinal values rather than continuous values, limiting its statistical power in clinical trials. Although the TIMI flow grade has classically compared flow in the infarct-related vessel to flow in the normal, nonculprit artery, flow in the non–infarct-related artery in patients with STEMI is not truly normal compared with flow in patients without STEMI.[163] Difficulties in reproducibly assessing myocardial flow relative to other vessels (e.g., right coronary artery, total occlusions of the contralateral vessel) led some investigators to modify the definition of TIMI grade 3 flow to include opacification of the distal coronary artery within three cardiac cycles.[164] The three cardiac cycle definition of TIMI grade 3 flow results in an absolute rate increase of approximately 10% compared with the original definition.[165] Accordingly, more quantitative measures of anterograde flow were developed.

TIMI Frame Count

The TIMI frame count (TFC) provides a quantitative assessment of the number of frames required for dye to reach standardized distal landmarks, and it may provide a more objective and precise method of estimating coronary blood flow than the TIMI flow grade.[160] The first frame used for TIMI frame counting is the cineframe in which a column of dye touches both borders of the coronary artery and moves forward, and the last frame is the cineframe in which dye begins to enter (but does not necessarily fill) a standard distal landmark in the artery. The standard distal landmarks for epicardial vessels are the first branch of the posterolateral artery for the right coronary artery, the most distal branch of the obtuse marginal branch in the dye path through the culprit lesion in the circumflex system, and the distal bifurcation, which is also known as the *moustache*, *pitch fork*, or *whale's tail*, in the left anterior descending coronary artery. These frame counts are corrected for the longer length of the left anterior descending coronary artery by dividing the TFC by 1.7 to arrive at the corrected TIMI frame count (CTFC).

The CTFC provides several advantages over TIMI flow grades. The CTFC is quantitative rather than qualitative, objective rather than subjective, and a continuous rather than a categorical variable. Observer variability is substantially less with TFC measurements compared with TIMI flow grades.[160] Although it was traditionally assumed that basal flow in nonculprit arteries in the setting of AMI after thrombolysis was normal, use of the CTFC has shown that basal flow in the uninvolved artery is abnormal.[163]

TIMI Myocardial Perfusion Grade

Epicardial flow does not necessarily imply tissue-level or microvascular perfusion. These findings led to the development of the TIMI myocardial perfusion grade (TMPG) (Table 59-7 and Fig. 59-3), which is a multivariate predictor of mortality in AMI.[161] The TMPG permits risk stratification even within epicardial TIMI grade 3 flow. Despite achieving normal TIMI grade 3 flow after reperfusion therapy, patients with diminished microvasculature perfusion (TMPG 0 or 1) have a persistently elevated mortality rate of 5.4% compared with patients with both TIMI grade 3 flow and TMPG 3, who have a mortality rate less than 1%.[161]

The TIMI flow grades and TMPGs can be combined to identify a group of patients with very low or very high mortality risks after STEMI. Patients with both TIMI grade 3 flow and TMPG 3 flow had a mortality rate of 0.7%, whereas patients with both TIMI grade 0 or 1 and TMPG 0 or 1 flow had a mortality rate of 10.9%.

Another approach to assess myocardial perfusion is to use digital subtraction angiography (DSA) to quantitatively characterize the kinetics of dye entering the myocardium during contrast angiography. DSA is performed at end-diastole by aligning cineframe images taken

TABLE 59-6 Thrombolysis in Myocardial Infarction (TIMI) Flow Grade Classification

Grade	Definition
3 (complete reperfusion)	Anterograde flow into the terminal coronary artery segment through a stenosis is as prompt as anterograde flow into a comparable segment proximal to the stenosis. Contrast material clears as rapidly from the distal segment as from an uninvolved, more proximal segment.
2 (partial reperfusion)	Contrast material flows through the stenosis to opacify the terminal artery segment, but contrast enters the terminal segment perceptibly more slowly than more proximal segments. Alternatively, contrast material clears from a segment distal to a stenosis noticeably more slowly than from a comparable segment not preceded by a significant stenosis.
1 (penetration with minimal perfusion)	A small amount of contrast flows through the stenosis but fails to fully opacify the artery beyond.
0 (no perfusion)	No contrast flow through the stenosis

Modified from Sheehan FH, Braunwald E, Canner P, et al: The effect of intravenous thrombolytic therapy on left ventricular function: a report on tissue-type plasminogen activator and streptokinase from the Thrombolysis in Myocardial Infarction (TIMI) Phase I Trial. *Circulation* 72:817-829, 1987.

TABLE 59-7 Thrombolysis in Myocardial Infarction (TIMI) Myocardial Perfusion Grades

Grade	Definition
3	Normal entry and exit of dye from the microvasculature. There is a ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that clears normally and is gone or is mildly or moderately persistent at the end of the washout phase (approximately three cardiac cycles), similar to an uninvolved artery. Blush that has only mild intensity throughout the washout phase but fades normally is also classified as grade 3.
2	Delayed entry and exit of dye from the microvasculature. There is a ground-glass appearance or opacification of the myocardium in the distribution of the culprit lesion that is strongly persistent at the end of the washout phase (i.e., dye is strongly persistent after three cardiac cycles of the washout phase and does not diminish or only minimally diminishes in intensity during washout).
1	Slow entry of dye into, but failure to exit the microvasculature. There is a ground-glass appearance or opacification of the myocardium in the distribution of the culprit lesion that fails to clear from the microvasculature, and dye staining is seen on the next injection (≈30 sec between injections).
0	Failure of the dye to enter the microvasculature. There is minimal or no ground-glass appearance or opacification of the myocardium in the distribution of the culprit artery, indicating lack of tissue-level perfusion.

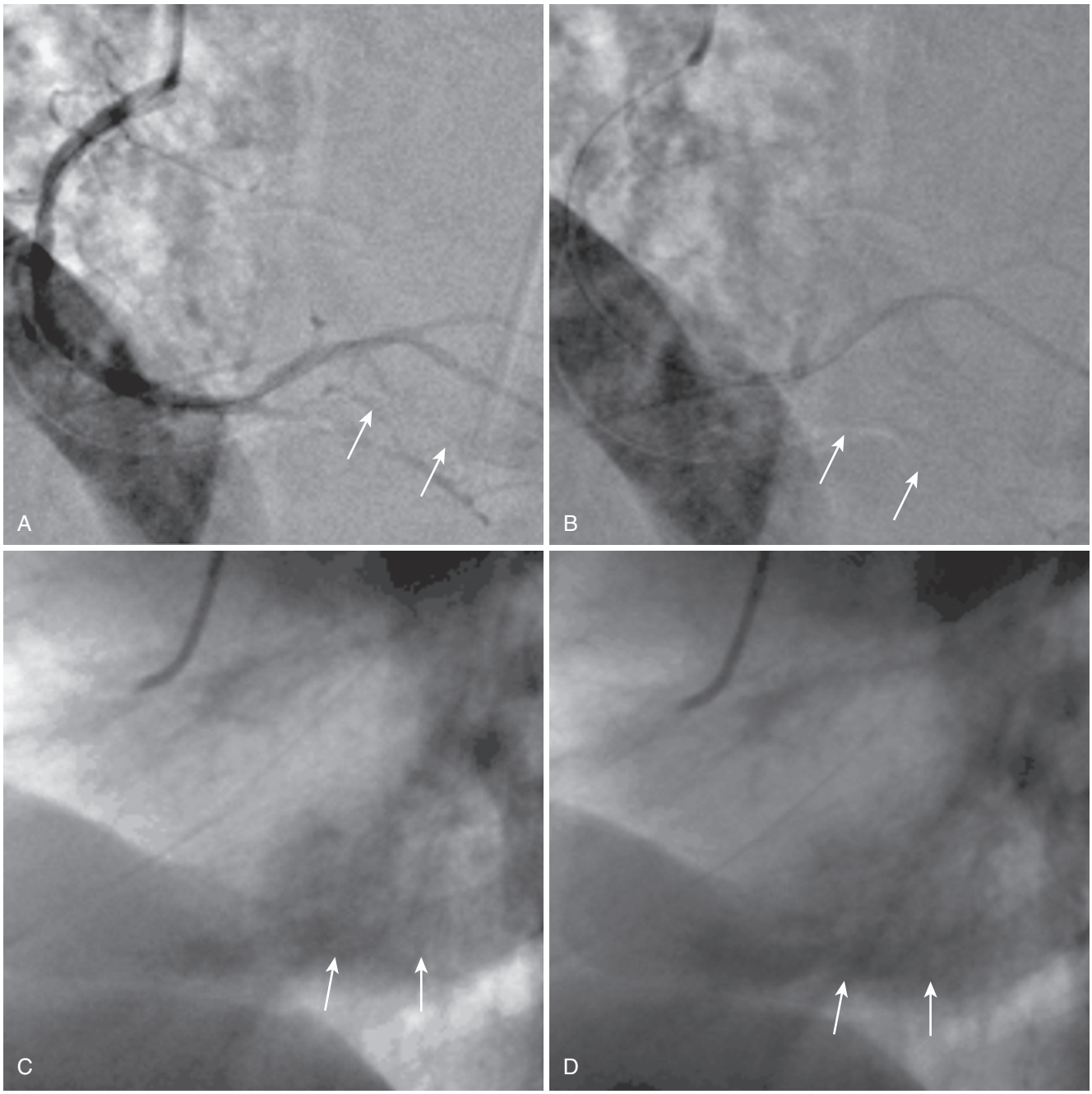

FIGURE 59-3 Thrombolysis in Myocardial Infarction (TIMI) myocardial perfusion grade using digital subtraction angiography. Perfusion grade 0 is characterized by the absence of the typical ground-glass filling *(arrows)* of the distal vascular bed during coronary injection (**A**) and washout (**B**). Perfusion grade 1 is demonstrated by persistent contrast staining *(arrows)* at the beginning (**C**) and end (**D**) of the coronary injection.

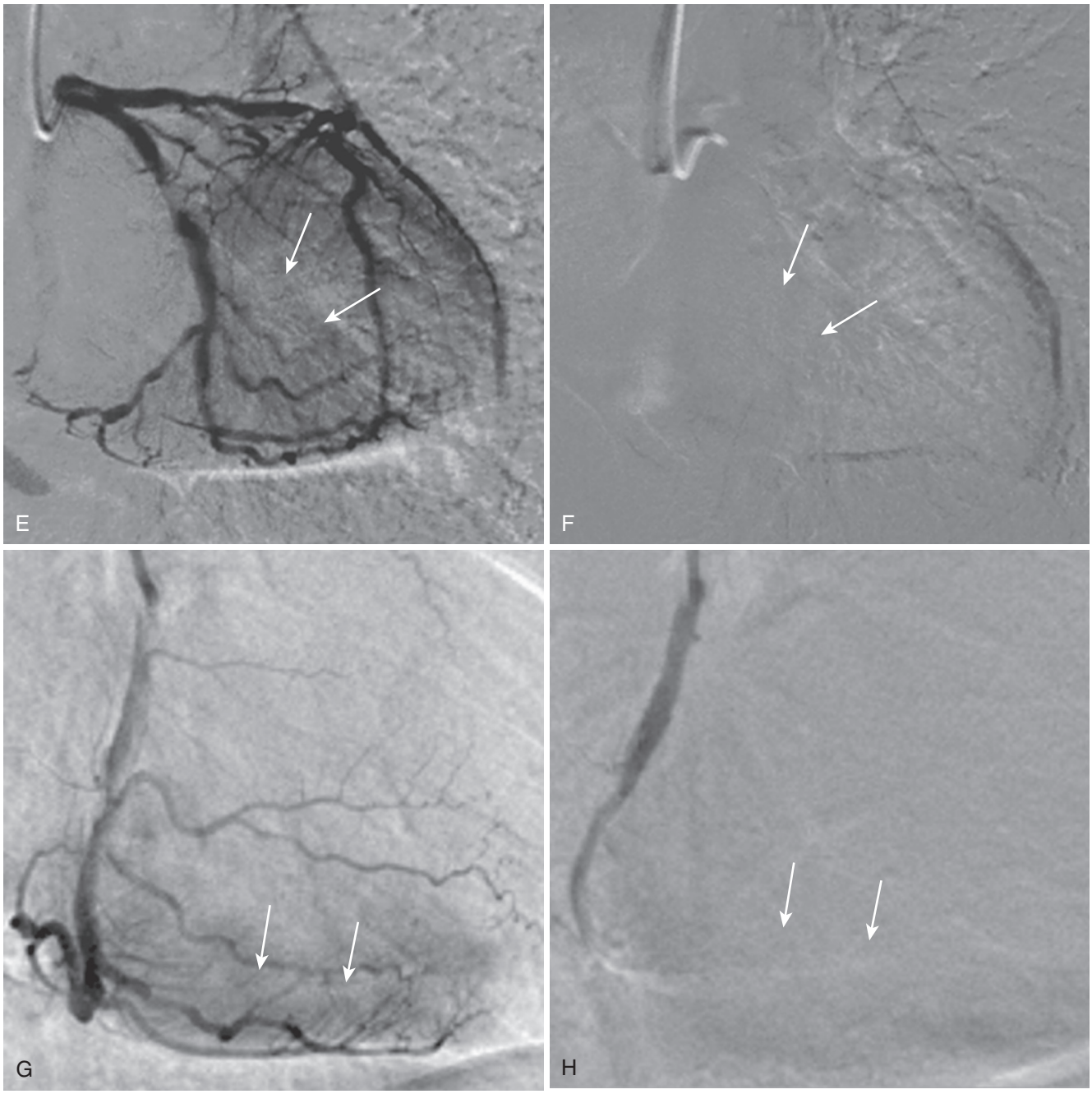

FIGURE 59-3, cont'd Perfusion grade 2 is manifested by a very prominent contrast appearance *(arrows)* at the end of coronary injection (**E**) that washes out at the end of the contrast injection (**F**). Perfusion grade 3 is shown as a normal ground-glass appearance *(arrows)* of the distal vascular bed at the end of the contrast injection (**G**) that washes out at the end of the injection (**H**).

before dye fills the myocardium with those taken at the peak of myocardial filling to subtract the spine, ribs, diaphragm, and epicardial artery. A representative region of the myocardium that is free of overlap by epicardial arterial branches is sampled to determine the increase in the gray-scale brightness of the myocardium when it first reached its peak intensity. The circumference of the myocardial blush is measured using a hand-held planimeter.

The number of frames required for the myocardium to first reach its peak brightness is converted into time (seconds) by dividing the frame count by 30 (for images acquired at 30 frames per second). The rate of rise in brightness (gray-scale change per second) and the rate of growth of blush in circumference (centimeters per second) can then be calculated. Using DSA, microvascular perfusion was reduced in AMI patients compared with normal patients, as demonstrated by a reduction in peak brightness (gray-scale peak), the rate of rise in brightness, the blush circumference, and the rate of growth of the blush circumference.[165]

Coronary Flow Velocity

Absolute flow velocity can be measured using PCI guidewire velocity.[166] With this technique, the guidewire tip is placed at the coronary landmark after PCI, and a Kelly clamp is placed on the guidewire at the point at which it exits the Y-adapter. The guidewire tip is then withdrawn to the catheter tip, and a second Kelly clamp is placed on the wire where it exits the Y-adapter. The distance between the two Kelly clamps outside the body is measured as the distance between the catheter tip and the anatomic landmark inside the body. Velocity (centimeters per second) may be calculated as this distance (centimeters) divided by the product of the TFC (frames) and the film frame speed (frames per second). Flow (milliliters per second) may be calculated by multiplying velocity and the mean cross-sectional lumen area (square centimeters) along the length of the artery to the TIMI landmark.

QUANTITATIVE ANGIOGRAPHY

QCA is most commonly performed using automated arterial contour detection, although video densitometry and digital parametric imaging have also been tried with limited success. Whereas online QCA is somewhat cumbersome to use in the catheterization laboratory, offline QCA has proved to be valuable for research investigation in determining the effect of new drugs and devices on lumen dimensions early and late after PCI. For clinical decision making about intermediate lesions, neither trained visual estimates nor online quantitative angiography is a substitute for precise physiologic measurements of stenosis severity, such as fractional flow reserve or coronary Doppler measurements.[167]

Nonquantitative Estimates of Lesion Severity

Virtually every interventionalist visually estimates angiographic stenosis severity, although the estimations are of limited value for research studies because of substantial interobserver variability. Blinded review of cineangiograms by experienced cardiologists found that the average visual estimate of percent diameter stenosis was 85% before PCI (versus 68% using quantitative methods) and 30% after PCI (versus 49% using quantitative methods); these differences correspond to a 200% error in the estimation of percent diameter stenosis.[168] Visual estimates of stenosis severity also result in some values (e.g., 90% to 99% diameter stenosis) that are physiologically untenable for anterograde flow. Inherent visual overestimation and underestimation of stenosis severity can be overcome by retraining the clinician's eye.

A more quantitative approach to the assessment of lesion severity uses hand-held or digital calipers to estimate quantitative diameters and percent diameter stenosis. Angiographic images are magnified, and calibration is performed by measuring the known dimensions of the diagnostic or guiding catheter using digital calipers. The observer then visually identifies the lumen border using the calipers, and a calibration factor is obtained to determine absolute coronary dimensions. Properly applied, this method appears to correlate weakly with automated edge-detection algorithms. If caliper measurements are obtained from nonmagnified images, the correlation with automated edge-detection algorithms is less accurate.

Computer-Assisted Quantitative Coronary Angiography

QCA was initiated almost 30 years ago by Brown and colleagues,[168a] who magnified 35-mm cineangiograms obtained from orthogonal projections and hand-traced the arterial edges on a large screen. After computer-assisted correction for pincushion distortion, the tracings were digitized, and the orthogonal projections were combined to form a 3-D representation of the arterial segment, assuming an elliptical geometry. Although the accuracy and precision were enhanced compared with visual methods, the time needed for image processing limited clinical use of this method.

Several automated edge-detection algorithms were then developed and applied to directly acquired digital images or to 35-mm cinefilm digitized images using a cine-video converter. Subsequent iterations of these first-generation devices used enhanced microprocessing speed and digital image acquisition to render the end-user interface more flexible, and they substantially shortened the time required for image analysis.

QCA is divided into several distinct processes, including film digitization (when applicable), image calibration, and arterial contour detection (Fig. 59-4). For processing 35-mm cinefilm, a cine-video converter is used to digitize images into a 512×512 (or larger) $\times$ 8-bit pixel matrix. Optical (preferably) or digital magnification results in an effective pixel matrix up to 2458×2458.[169]

For estimation of absolute coronary dimensions, the diagnostic or guiding catheter usually serves as the scaling device. A nontapered segment of the catheter is selected, and a centerline through the catheter is drawn. Linear density profiles are then constructed perpendicular to the catheter centerline, and a weighted average of the first and second derivative functions is used to define the catheter edge points. Individual edge points are then connected using an automated algorithm, outliers are discarded, and the edges are smoothed. The diameter of the catheter is used to obtain a calibration factor, which is expressed in millimeters per pixel. The injection catheter dimensions may be influenced by whether contrast or saline is imaged within the catheter tip and by the type of material used in catheter construction. As high-flow injection catheters have been developed, more quantitative angiographic systems have been using contrast-filled injection catheters for image calibration.

The automated algorithm is then applied to a selected arterial segment. Absolute coronary dimensions are obtained from the minimal lumen diameter (MLD) reference diameter, and from these, the percent diameter stenoses are derived. For most angiographic systems, interobserver variabilities are 3.1% for percent diameter stenosis and 0.10 to 0.18 mm for MLD for cineangiographic readings. Interobserver variabilities are slightly higher (<0.25 mm) for repeated analyses of the digital angiograms due to the slightly lower resolution compared with cineangiography. The two most commonly used QCA systems are described in the following sections.

Cardiovascular Angiography Analysis System

The Cardiovascular Angiography Analysis System (Pie Data Medical B.V., Maastricht, The Netherlands) is a QCA system developed for offline cineangiographic analysis (see Fig. 59-2). The edge-detection algorithm incorporates an optional correction for pincushion distortion. Its edge detection uses a weighted (50%) sum of the first and second derivatives of the mean pixel density, and it applies minimal-cost criteria for smoothing of the arterial edge contours.

In addition to reporting an interpolated reference diameter and an MLD, subsegment analysis provides mean, minimum, and maximum subsegment diameters. Specific reporting algorithms have been developed for DESs, for patients undergoing radiation brachytherapy, and for those undergoing peripheral intervention.

FIGURE 59-4 Quantitative coronary angiography. **A,** Image calibration is performed using the nontapered portion of the injection catheter as the calibration source. **B,** The automated edge detection algorithm (Coronary Measurement System, Medis, Leiden, The Netherlands) is applied to the arterial contour, and the minimal lumen diameter is identified. A diameter function profile curve *(insert)* shows the diameters of the vessel along the length of the analysis segment. **C,** After coronary stent placement, the identical length of artery is analyzed to assess lumen improvement. **D,** At the time of angiographic follow-up, the location of late lumen loss along the length of the analysis segment is identified.

Coronary Measurement System

Specific features of the Coronary Measurement System (CMS, Medis, Leiden, The Netherlands) include two-point, user-defined centerline identification; arterial edge detection using a weighted (50%) sum of the first and second derivatives of the mean pixel density; arterial contour detection using a minimal-cost matrix algorithm; and an interpolated reference vessel diameter. One limitation of the minimal-cost algorithm used with the first-generation CMS system (and the Cardiovascular Angiography Analysis System II system) has been its inability to precisely quantify arterial lumen contours characterized by abrupt changes.

The CMS-GFT algorithm (Medis, Leiden, The Netherlands) is not restricted in its search directions, incorporating multidirectional information about the arterial boundaries for construction of the arterial edge that is suitable for the analysis of complex coronary artery lesions. Specific reporting algorithms have been developed for bifurcation lesions (Fig. 59-5), for DESs (Fig. 59-6), for patients undergoing radiation brachytherapy (Fig. 59-7), and for those undergoing peripheral intervention.

Factors Contributing to Variability Using Quantitative Coronary Angiography

Variability associated with measurements of MLD and reference diameter is affected by several factors, including the biologic differences among lumen diameters (e.g., reference vessel size, vasomotor tone, thrombus), inconsistencies in radiographic image acquisition parameters (e.g., quantum mottling, out-of-plane magnification, foreshortening), and variations in angiographic measurement (e.g., frame selection, factors affecting the edge-detection algorithm) (Table 59-8). These factors should be controlled to improve the overall diagnostic accuracy of QCA.

Biologic Variability

Studies that include a wide range of vessel sizes have more biologic variability in vessel diameter (reflected in the standard deviation of the measurements) than those that are more restrictive in their inclusion criteria. Vasomotor tone may also affect the reference vessel size, resulting in distal vasoconstriction and vasospasm that dynamically affect the arterial diameter in paired measurements. Transient

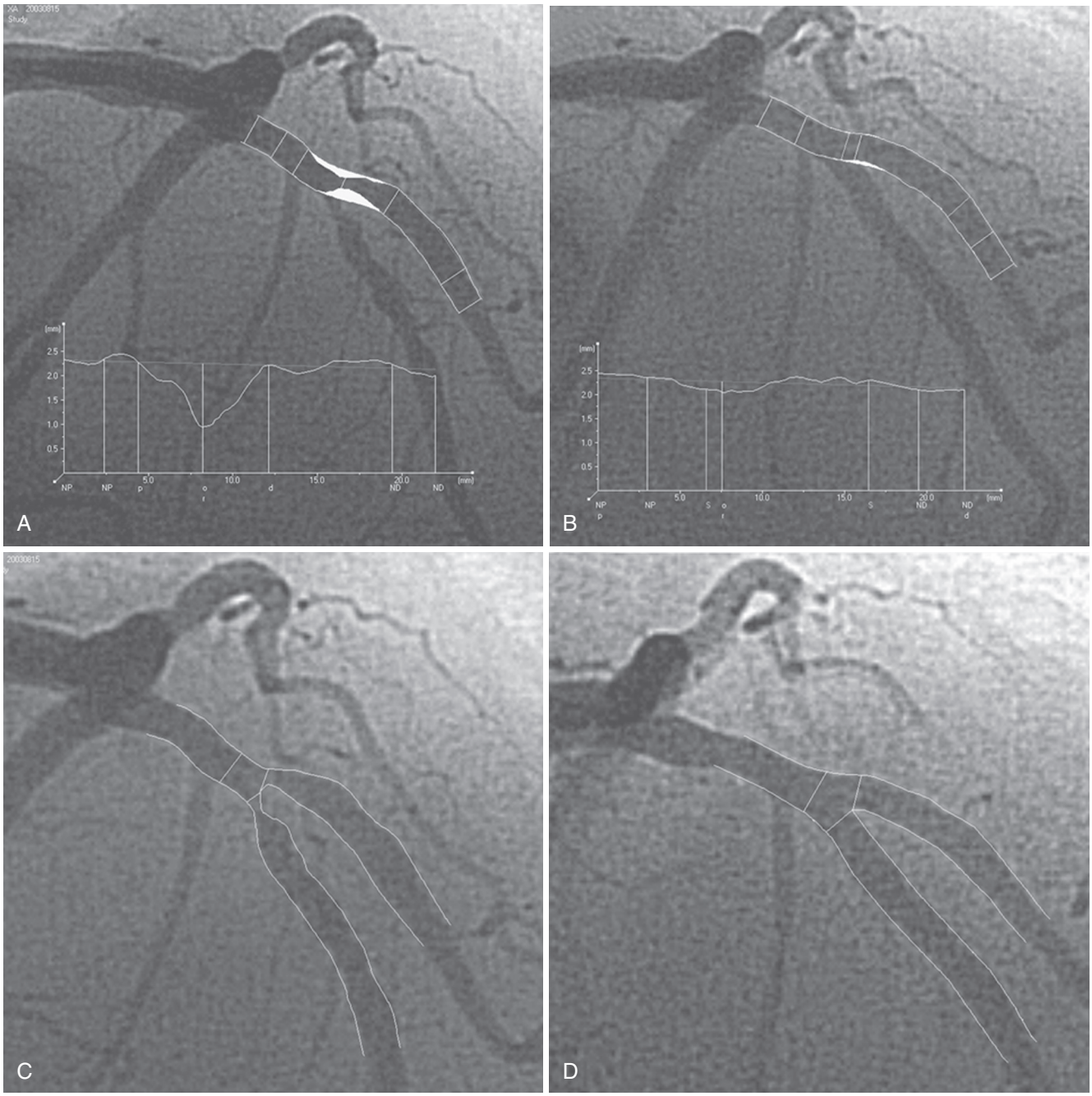

FIGURE 59-5 Bifurcation quantitative analysis. Quantitative angiographic analysis of bifurcation lesions is complicated by the difficulty in identifying the minimal lumen diameter at the site of vessel branching. Three methods of bifurcation analysis have been employed. The first is conventional quantitative angiography separately applied to each branch (**A,** before intervention; **B,** after intervention). The second method is application of the edge algorithm to both branches (**C,** before intervention; **D,** after intervention).

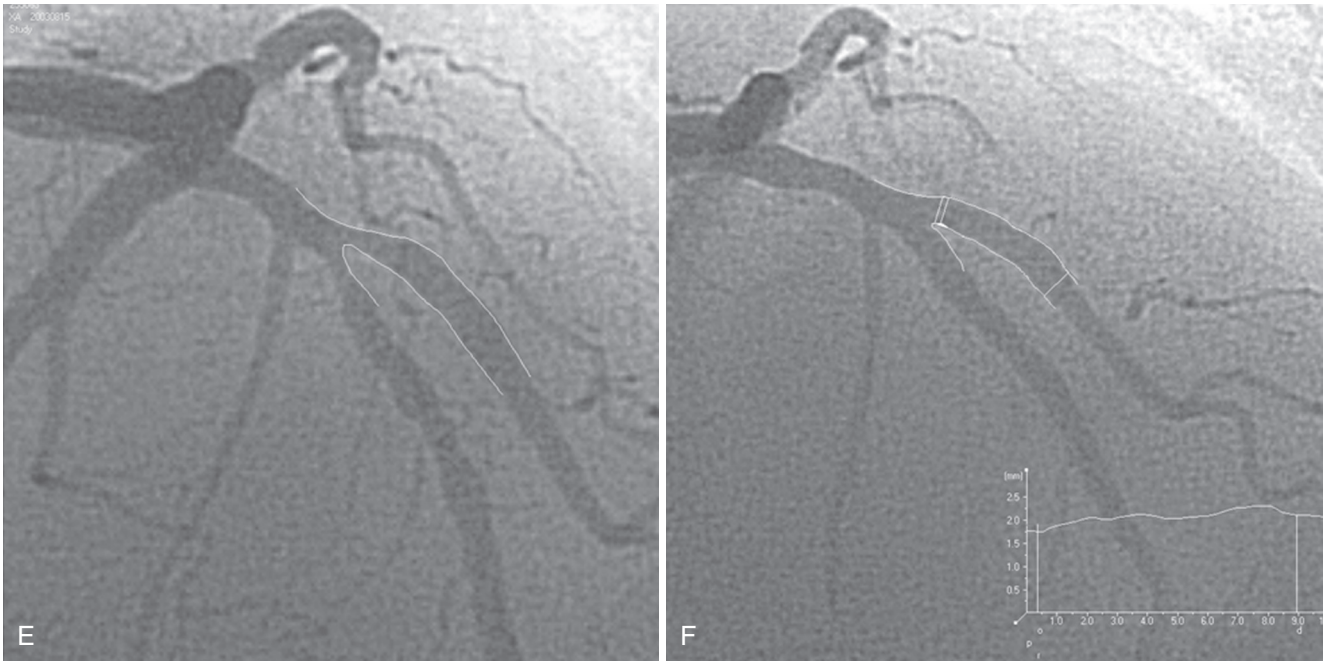

FIGURE 59-5, cont'd The third method is beginning analysis at the ostium of the branch (**E,** before intervention; **F,** after intervention).

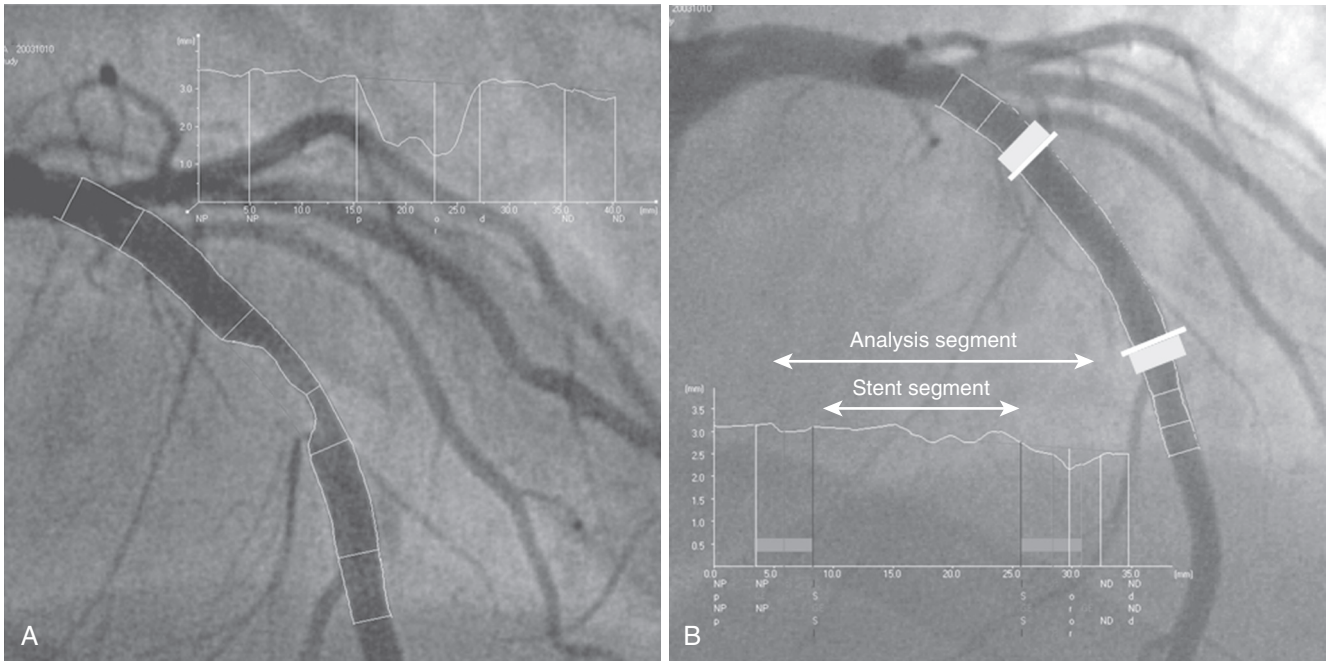

FIGURE 59-6 Drug-eluting stent quantitative angiographic analysis. **A,** Quantitative angiography is performed on a focal stenosis in the midportion of the left anterior descending coronary artery. **B,** After placement of a drug-eluting stent, the proximal and distal portions of the stent are identified *(solid bars)*. A 5-mm proximal and distal edge is also analyzed *(shaded boxes)*. From these measurements, the minimal lumen diameters within the stent (stent segment) and within the region of analysis (analysis segment) are identified.

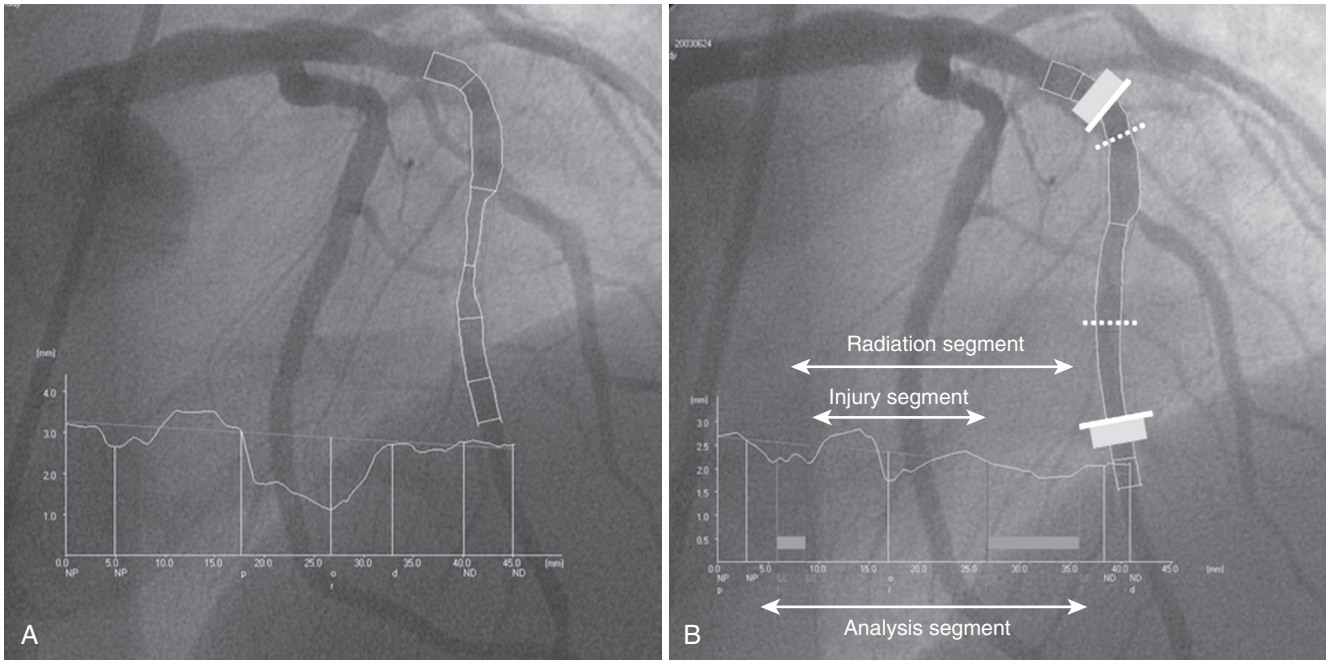

FIGURE 59-7 Brachytherapy analysis. **A,** Quantitative angiography is performed on a focal stenosis in the midportion of the left anterior descending coronary artery. **B,** After balloon angioplasty, the proximal and distal portions of the balloon injury are identified *(dotted lines)*. After radiation brachytherapy, the proximal and distal portion of the radiation injury are identified *(solid lines)*. A 5-mm proximal and distal edge of the radiation zone is also analyzed *(shaded boxes)* to identify the edge effect. From these measurements, the minimal lumen diameters within the segment of balloon injury (injury segment), the segment of radiation injury (radiation segment), and the region of analysis (analysis segment) are identified. The *shaded portion* in the diameter function profile curve *(insert)* represents the region of the artery that was treated with radiation but was not injured with the balloon.

TABLE 59-8 Correctable Sources of Imaging Error During Acquisition

Source of Error	Potential Corrections
Biologic Variation in Lumen Diameter	
Vasomotor tone	Nitroglycerin, 100-200 μg intracoronary every 10 min
Variations in Image Acquisition	
Single Studies	
Vessel motion	
Cardiac	End-diastolic/end-systolic cine frame
Respiratory	Breath hold
Vessel foreshortening	Obtain multiple angiographic projections
Insufficient contrast injection	Use 7- or 8-Fr, large, high-flow catheters
Branch vessel overlap	Obtain multiple angiographic projections
Pincushion distortion	Image objects in center of image
Sequential Studies	
X-ray generator (pulse width/beam)	Repeat study in same imaging
X-ray tube (focal spot/shape/tube current)	Repeat study in same imaging
Image intensifier (magnification/resolution)	Repeat study in same imaging
Differences in angles and gantry height	Record gantry height/angle/skew on worksheet
Image calibration	Use measured catheter diameter
Errors in Image Analysis	
Electronic noise	Recursive digitization and frame averaging
Quantum noise	Spatial filtering of digital image data
Automated edge-detection algorithm	Minimize observer interaction
Selection of reference positions	Interpolated or averaged normal segment
Identification of lesion length	Use of side branches, other landmarks
Frame selection	End-diastolic frame showing worst view

maximum coronary vasodilation may be achieved with intracoronary (50 to 200 μg), intravenous (>10 μg/min), or sublingual (0.4 to 0.8 mg) nitroglycerin.

Acquisition Variability

Acquisition factors that affect variability include cardiac and respiratory motion artifact, vessel foreshortening, inadequate filling of the coronary artery (i.e., streaming), overfilling of the aortic cusp with contrast, and failure to separate overlapping branch vessels from the stenosis.[170] These factors may lead to overestimation or underestimation of lesion severity. Out-of-plane magnification and pincushion distortion may also contribute to small errors in angiographic imaging.

For sequential studies, use of the identical angiographic imaging laboratory allows replication of the x-ray generator, tube, and image intensifier parameters. With the introduction of digital imaging and archiving, image compression has raised potential problems with the quality of image quality for analysis. The Digital Imaging and Communications in Medicine (DICOM) 2:1 Joint Photographic Experts Group (JPEG) lossless compression has become the industry standard for image storage and transfer. It requires approximately 500 megabytes of storage for each imaging study.

The effect of image compression and decompression on image quality was evaluated by a joint task force of the American College of Cardiology and European Society of Cardiology using JPEG) images at compression ratios of 1:1 (uncompressed), 6:1, 10:1, and 16:1.[171] Intraobserver analysis showed significant systematic and random errors in the calibration factor at JPEG compression ratios of 10:1 and higher, and they should not be used in QCA clinical research studies.[171] Similar issues exist for the analysis of S-VHS video tapes, which have substantial loss of image resolution. Flat-panel image acquisition does not affect the quality of QCA.[172]

Measurement Variability

Analysis of two or more orthogonal projections permits a more accurate assessment of the physiologic significance of lesion severity, although a second, technically suitable projection in many cases is unavailable due to vessel foreshortening, overlap, and poor image quality. If orthogonal projections are not available, analyses of the worst-view projection may provide sufficiently accurate information for clinical studies.

Herrington and colleagues[173] used a components-of-variance model to show that the process of acquiring and performing QCA on selected cineframes accounted for 57% of the total measurement variability, whereas day-to-day variations in the patient, procedure, and equipment accounted for 30% of total variability. Frame selection accounted for the remaining 13% of total variability. When direct digital angiography is performed and random errors associated with noise in the cine-video pathway are eliminated, frame selection may be a much more important contributor to overall measurement variability. Frame selection has been associated with substantial interobserver variability, and the frame demonstrating the sharpest and tightest view of the stenosis should be used.

Core laboratory reproducibility of various angiographic parameters may affect sample size calculations for various studies.[174] In a repeated (over 1 year) comparisons of five quantitative parameters (e.g., MLD, ejection fraction) and six qualitative parameters (e.g., TMPG, TTG), MLD and ejection fraction were the most reproducible, yielding the smallest sample size calculations, whereas percent diameter stenosis and centerline wall motion require substantially larger trials.[174] Of the qualitative parameters, all except TIMI flow grade gave reproducibility characteristics yielding sample sizes of many hundreds of patients. Reproducibility of TMPG and TTG was only moderately good within and between core laboratories, underscoring an intrinsic difficulty in assessing them.[174]

Automated QCA systems have differences in the preferred method of calibration, location of the arterial border, construction of its contour; use of minimal-cost or smoothing algorithms, and selection of normal reference segments. Edge-detection algorithms that identify the arterial edge using a 50% weighted threshold of the first- and second-derivative extrema may produce systematically larger reference and obstruction diameters than those using a 75% weighted value (weighted toward the first-derivative extremum) or the first-derivative extremum itself. These systematic differences may also affect the accuracy and reproducibility of the absolute and relative angiographic measurements. Each angiographic core laboratory should independently determine its own variabilities during the performance of QCA studies, potentially permitting standardization of techniques among different core laboratories.

Quantitative Angiographic Indices

Lumen Improvements After Percutaneous Coronary Intervention

Early and late angiographic results after PCI have been described using a number of QCA criteria. Coronary stents provide a superior residual lumen compared with balloon angioplasty, but they may result in higher amounts of late intimal hyperplasia and late lumen loss than is seen after balloon angioplasty. The net balance is that stents provide a larger late angiographic result.

Angiographic Success

The change in MLD that occurs immediately after PCI is called the acute gain (in millimeters), and the loss of MLD that occurs during the follow-up period is the late loss (in millimeters). Relative changes that occur in the percent diameter stenosis are provided by the following relationship: % diameter stenosis = (1 − [MLD/reference vessel diameter]) × 100.

Traditionally, angiographic success after PCI has been defined as achievement of a less than 50% residual diameter stenosis,[1] which is most often associated with at least 20% improvement from the baseline diameter stenosis and symptom improvement. With the advent of coronary stents and the determination that stent thrombosis is associated with a suboptimal initial angiographic result, a more contemporary definition of angiographic stenting success is attainment of a less than 20% residual diameter stenosis within the stent, although higher (up to 30%) inflow or outflow diameter stenosis may exist due to residual plaque at the stent margins. Although the documented disparity between visual and quantitative estimates of angiographic success remains a challenge for self-reporting registries that describe procedural outcomes, there has been documented improvement in angiographic success rates over the past decade with the widespread use of coronary stents.[175]

Binary Angiographic Restenosis

Several binary criteria have been used to describe angiographic restenosis after PCI. Binary angiographic restenosis is best defined as a 50% or greater diameter stenosis at follow-up, although other dichotomous criteria have been used (e.g., loss of <50% of the initial gain, MLD loss of ≥0.72 mm). Binary angiographic restenosis after DES placement may occur within the stent (i.e., ISR), within the 5-mm margins of the stent (i.e., edge restenosis), or within the segment between the proximal and distal reference segments (i.e., in-segment or in-lesion restenosis).

Late Lumen Loss

The long-term success of PCI can be measured by several QCA parameters. Serial QCA studies have shown that there is an approximately 0.50-mm reduction in lumen diameter that develops within 3 to 6 months after balloon angioplasty, although angiography cannot differentiate whether this reduction in lumen diameter results from intimal hyperplasia or arterial remodeling or constriction.

Lumen loss after balloon angioplasty follows a near-gaussian distribution. Because there is little or no arterial remodeling after BMS placement, late lumen loss after stent placement primarily results from intimal hyperplasia, and angiographic estimates of volumetric percent volume obstruction correlate well with intravascular ultrasound measurements of intimal hyperplasia.[176] Several technical factors may compromise the ability of late lumen loss to characterize overall reductions

in lumen diameters, including calibration errors at the time of postprocedural or follow-up assessments and the relocation of the MLD between the postprocedural and follow-up examinations.[177] The distribution of late lumen loss after placement of DES is unlike the distribution of late lumen loss after BMS placement, with a narrowing variance (i.e., standard deviation) due to the reduced tissue growth and a rightward skew of the late lumen loss histogram.[178]

The patient-based relationship between late lumen loss and TLR was examined in 1314 patients with de novo lesions who were treated with BMSs or paclitaxel-eluting stents.[179] Analysis found that the relationship between late lumen loss and TLR was monotonic and curvilinear, with the likelihood of TLR not exceeding 5% until the analysis segment late loss was greater than 0.5 mm, and did not exceed 10% until late loss was greater than 0.65 mm.[179] At lower magnitudes of late lumen loss, there was a very small incremental increase in the occurrence of TLR. With higher degrees of late lumen loss, the relationship of late loss and TLR was steep and almost linear.[179] The rate of TLR was related to median late loss and measures of its statistical distribution. TLR increased with the lack of homogeneous biologic response, manifested by greater variance (i.e., higher standard deviations) and a greater right skew of the late lumen loss histogram.[179]

To correct for the rightward skew and to develop better predictive models of restenosis, an optimized power transformation was applied to data from patients enrolled in two sirolimus-eluting stent trials to predict binary angiographic restenosis rates and compare them with observed restenosis rates.[178] The mean in-stent late loss was 0.17 ± 0.45 mm after sirolimus-eluting stent placement and 1.00 ± 0.70 mm after BMS placement. If a normal distribution was assumed, late loss accurately estimated in-stent binary angiographic restenosis for the BMS (predicted 35.4% vs. observed 35.4%) but underestimated the binary restenosis rate in the sirolimus-eluting stent arm (predicted 0.6% vs. observed 3.2%). Power transformation improved the reliability of the estimate in the sirolimus arm (predicted 3.2% vs. observed 3.2%). Another study did not confirm the value of the power transformation as a predictor of binary angiographic restenosis.[180]

To formally evaluate four potential angiographic surrogate markers for TLR by applying well-defined criteria of surrogacy to an extensive database of randomized DES trials, Pocock and colleagues analyzed 11 multicenter, prospective, randomized stent trials enrolling 5381 patients with a single treated lesion and follow-up angiography.[181] Based on four surrogate criteria, late loss and percent diameter stenosis strongly predicted the risk of TLR, with in-segment percent diameter stenosis being the most highly predictive (c statistic = 0.95). Whereas late loss as a surrogate was dependent on vessel size, percent diameter stenosis was independent of vessel size. Differences in TLR rates for BMSs and DESs were fully explained statistically by their differences in late loss and percent diameter stenosis. However, because of the curvilinearity of the logistic model, trials comparing two effective DESs can have significant differences in mean late losses and percent diameter stenosis but negligible expected differences in TLR risk. Others have suggested a stronger relationship between late loss and TLR for comparative DES trials,[182] but whether late lumen loss will serve as a meaningful surrogate end point in DES comparative trials remains controversial.

Limitations of Quantitative Coronary Angiography

The ability of QCA to accurately detect the presence and severity of coronary atherosclerosis is limited by several factors. Compensatory arterial dilation occurs during the early stages of coronary atherosclerosis, resulting in a preserved coronary lumen despite significant coronary atherosclerosis. Routine coronary angiography can accurately measure the arterial lumen but is relatively insensitive for the detection of arterial wall atherosclerosis, circumferential plaque distribution, vessel wall calcification, and lumen dimensions after stent implantation.

Coronary angiography is limited to a lesser extent by radiographic factors, such as cardiac motion, pincushion distortion, and quantum mottling. Most analytic systems have difficulty discriminating values less than 1.0 mm due to the limitations of radiographic imaging of small objects (e.g., veiling glare, point spread function). Newer methods incorporating adaptive simultaneous coronary border detection have been developed to more accurately assess smaller vessel dimensions. Interpretation of 2-D angiographic views can be affected by foreshortening and overlapping of vessels, leading to inaccurate measurements, particularly in tortuous vessels.[183]

Three-Dimensional Imaging

Some commercial software systems have developed 3-D reconstruction of a coronary artery by fusing two or more orthogonal angiographic images to address some of the limitations associated with 2-D QCA.[184,185] The 3-D QCA yields a more accurate depiction than standard 2-D QCA of intermediate lesions using fractional flow reserve as the reference standard.[186] Validation of 3-D QCA against IVUS in small studies has shown good correlation between the two in assessing vessel geometry, especially assessment of segment length.[187,188] In an analysis of patients with left main stenosis, 3-D QCA was better than 2-D QCA in identifying a significant left main stenosis when using IVUS as the gold standard.[189] Given these results, 3-D QCA reconstruction is proving to be a promising tool for clinical and research applications in interventional cardiology.

REFERENCES

1. Smith S, Feldman T, Hirshfeld J, et al: ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation* 113:156–175, 2006.
2. Ellis SG, Roubin GS, King SB, III, et al: Importance of stenosis morphology in the estimation of restenosis risk after elective percutaneous transluminal coronary angioplasty. *Am J Cardiol* 63:30–34, 1989.
3. Madan P, Elayda MA, Lee VV, Wilson JM: Predicting major adverse cardiac events after percutaneous coronary intervention: the Texas Heart Institute risk score. *Am Heart J* 155:1068–1074, 2008.
4. Waksman R, Buch AN, Torguson R, et al: Long-term clinical outcomes and thrombosis rates of sirolimus-eluting versus paclitaxel-eluting stents in an unselected population with coronary artery disease (REWARDS registry). *Am J Cardiol* 100:45–51, 2007.
5. Krone R, Shaw R, Klein L, et al: Evaluation of the American College of Cardiology/American Heart Association and the Society for Coronary Angiography and Interventions lesion classification system in the current "stent era" of coronary interventions (from the ACC-National Cardiovascular Data Registry). *Am J Cardiol* 92:389–394, 2003.
6. Singh M, Rihal CS, Lennon RJ, et al: Comparison of Mayo Clinic risk score and American College of Cardiology/American Heart Association lesion classification in the prediction of adverse cardiovascular outcome following percutaneous coronary interventions. *J Am Coll Cardiol* 44:357–361, 2004.
7. Serruys PW, Morice MC, Kappetein AP, et al: Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 360:961–972, 2009.
8. Sianos G, Morel MA, Kappetein AP, et al: The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 1:219–227, 2005.
9. Serruys PW, Onuma Y, Garg S, et al: Assessment of the SYNTAX score in the Syntax study. *EuroIntervention* 5:50–56, 2009.
10. Valgimigli M, Serruys PW, Tsuchida K, et al: Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. *Am J Cardiol* 99:1072–1081, 2007.
11. Capodanno D, Capranzano P, Di Salvo ME, et al: Usefulness of SYNTAX score to select patients with left main coronary artery disease to be treated with coronary artery bypass graft. *JACC Cardiovasc Interv* 2:731–738, 2009.
12. Wykrzykowska JJ, Garg S, Girasis C, et al: Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. *J Am Coll Cardiol* 56:272–277, 2010.
13. Holzhey DM, Luduena MM, Rastan A, et al: Is the SYNTAX score a predictor of long-term outcome after coronary artery bypass surgery? *Heart Surg Forum* 13:E143–E148, 2010.
14. Lemesle G, Bonello L, de Labriolle A, et al: Prognostic value of the Syntax score in patients undergoing coronary artery bypass grafting for three-vessel coronary artery disease. *Catheter Cardiovasc Interv* 73:612–617, 2009.
15. Yadav M, Palmerini T, Caixeta A, et al: Prediction of coronary risk by SYNTAX and derived scores: synergy between percutaneous coronary intervention with taxus and cardiac surgery. *J Am Coll Cardiol* 62:1219–1230, 2013.
16. Levine GN, Bates ER, Blankenship JC, et al: 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 124:e574–e651, 2011.
17. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS), European Association for Percutaneous Cardiovascular Interventions (EACP), et al: Guidelines on myocardial revascularization. *Eur J Cardiothorac Surg* 38(Suppl):S1–S52, 2010.

18. Farooq V, van Klaveren D, Steyerberg EW, et al: Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 381:639–650, 2013.
19. Sinning JM, Asdonk T, Erlhofer C, et al: Combination of angiographic and clinical characteristics for the prediction of clinical outcomes in elderly patients undergoing multivessel PCI. *Clin Res Cardiol* 102:865–873, 2013.
20. Sinning C, Lillpopp L, Appelbaum S, et al: Angiographic score assessment improves cardiovascular risk prediction: the clinical value of SYNTAX and Gensini application. *Clin Res Cardiol* 102:495–503, 2013.
21. Palmerini T, Genereux P, Caixeta A, et al: A new score for risk stratification of patients with acute coronary syndromes undergoing percutaneous coronary intervention: the ACUITY-PCI (Acute Catheterization and Urgent Intervention Triage Strategy–Percutaneous Coronary Intervention) risk score. *JACC Cardiovasc Interv* 5(11):1108–1116, 2012.
22. Palmerini T, Caixeta A, Genereux P, et al: Comparison of clinical and angiographic prognostic risk scores in patients with acute coronary syndromes: Analysis from the Acute Catheterization and Urgent Intervention Triage StrategY (ACUITY) trial. *Am Heart J* 163:383–391, 2012.
23. Gilard M, Rioufol G, Zeller M, et al: Reliability and limitations of angiography in the diagnosis of coronary plaque rupture: an intravascular ultrasound study. *Arch Cardiovasc Dis* 101:114–120, 2008.
24. Dangas GD, Claessen BE, Mehran R, et al: Development and validation of a stent thrombosis risk score in patients with acute coronary syndromes. *JACC Cardiovasc Interv* 5:1097–1105, 2012.
25. Gomez-Lara J, Brugaletta S, Farooq V, et al: Angiographic geometric changes of the lumen arterial wall after bioresorbable vascular scaffolds and metallic platform stents at 1-year follow-up. *JACC Cardiovasc Interv* 4:789–799, 2011.
26. Mintz GS, Popma JJ, Pichard AD, et al: Patterns of calcification in coronary artery disease. A statistical analysis of intravascular ultrasound and coronary angiography in 1155 lesions. *Circulation* 91:1959–1965, 1995.
27. Vavuranakis M, Toutouzas K, Stefanadis C, et al: Stent deployment in calcified lesions: can we overcome calcific restraint with high-pressure balloon inflations? *Catheter Cardiovasc Interv* 52:164–172, 2001.
28. Kawaguchi R, Tsurugaya H, Hoshizaki H, et al: Impact of lesion calcification on clinical and angiographic outcome after sirolimus-eluting stent implantation in real-world patients. *Cardiovasc Revasc Med* 9:2–8, 2008.
29. Mutoh M, Ishikawa T, Hasuda T, et al: Predictors of target lesion revascularization and documented stent thrombosis beyond 30 days after sirolimus-eluting stent implantation: retrospective analysis in consecutive 1,070 angiographic follow-up lesions. *Circ J* 71:1328–13231, 2007.
30. Bourantas CV, Zhang YJ, Garg S, et al: Prognostic implications of coronary calcification in patients with obstructive coronary artery disease treated by percutaneous coronary intervention: a patient-level pooled analysis of 7 contemporary stent trials. *Heart* 100:1158–1164, 2014.
31. Chambers JW, Feldman RL, Himmelstein SI, et al: Pivotal trial to evaluate the safety and efficacy of the orbital atherectomy system in treating de novo, severely calcified coronary lesions (ORBIT II). *JACC Cardiovasc Interv* 7:510–518, 2014.
32. Moussa I, Ellis SG, Jones M, et al: Impact of coronary culprit lesion calcium in patients undergoing paclitaxel-eluting stent implantation (a TAXUS-IV substudy). *Am J Cardiol* 96:1242–1247, 2005.
33. Castagna MT, Mintz GS, Ohlmann P, et al: Incidence, location, magnitude, and clinical correlates of saphenous vein graft calcification: an intravascular ultrasound and angiographic study. *Circulation* 111:1148–1152, 2005.
34. Machecourt J, Danchin N, Lablanche JM, et al: Risk factors for stent thrombosis after implantation of sirolimus-eluting stents in diabetic and nondiabetic patients: the EVASTENT Matched-Cohort Registry. *J Am Coll Cardiol* 50:501–508, 2007.
35. Alexander JH, Hafley G, Harrington RA, et al: Efficacy and safety of edifoligide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery: PREVENT IV: a randomized controlled trial. *JAMA* 294:2446–2454, 2005.
36. Chen L, Theroux P, Lesperance J, et al: Angiographic features of vein grafts versus ungrafted coronary arteries in patients with unstable angina and previous bypass surgery. *J Am Coll Cardiol* 28(6):1493–1499, 1996.
37. Brilakis ES, Lee M, Mehilli J, et al: Saphenous vein graft interventions. *Curr Treat Options Cardiovasc Med* 16:301, 2014.
38. Hindnavis V, Cho SH, Goldberg S: Saphenous vein graft intervention: a review. *J Invasive Cardiol* 24:64–71, 2012.
39. Lee MS, Park SJ, Kandzari DE, et al: Saphenous vein graft intervention. *JACC Cardiovasc Interv* 4:831–843, 2011.
40. Giugliano GR, Kuntz RE, Popma JJ, et al: Determinants of 30-day adverse events following saphenous vein graft intervention with and without a distal occlusion embolic protection device. *Am J Cardiol* 95:173–177, 2005.
41. Giugliano GR, Falcone MW, Mego D, et al: A prospective multicenter registry of laser therapy for degenerated saphenous vein graft stenosis: the COronary graft Results following Atherectomy with Laser (CORAL) trial. *Cardiovasc Revasc Med* 13:84–89, 2012.
42. Niccoli G, Belloni F, Cosentino N, et al: Case-control registry of excimer laser coronary angioplasty versus distal protection devices in patients with acute coronary syndromes due to saphenous vein graft disease. *Am J Cardiol* 112:1586–1591, 2013.
43. Maluenda G, Alfonso F, Pichard AD: Percutaneous intervention of a thrombotic-occluded saphenous vein graft successfully treated using the undersized stent approach to prevent distal embolization. *Catheter Cardiovasc Interv* 78:65–69, 2011.
44. Baim D, Wahr D, George B, et al: Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. *Circulation* 105:1285–1290, 2002.
45. Mauri L, Cox D, Hermiller J, et al: The PROXIMAL trial: proximal protection during saphenous vein graft intervention using the Proxis Embolic Protection System: a randomized, prospective, multicenter clinical trial. *J Am Coll Cardiol* 50:1442–1449, 2007.
46. Stone GW, Rogers C, Hermiller J, et al: Randomized comparison of distal protection with a filter-based catheter and a balloon occlusion and aspiration system during percutaneous intervention of diseased saphenous vein aorto-coronary bypass grafts. *Circulation* 108:548–553, 2003.
47. Lee MS, Yang T, Kandzari DE, et al: Comparison by meta-analysis of drug-eluting stents and bare metal stents for saphenous vein graft intervention. *Am J Cardiol* 105:1076–1082, 2010.
48. Turco MA, Buchbinder M, Popma JJ, et al: Pivotal, randomized U.S. study of the Symbiottrade mark covered stent system in patients with saphenous vein graft disease: eight-month angiographic and clinical results from the Symbiot III trial. *Catheter Cardiovasc Interv* 68:379–388, 2006.
49. Bennett J, Dens J, Stammen F, et al: Long-term follow-up after percutaneous coronary intervention with polytetrafluoroethylene-covered Symbiot stents compared to bare metal stents, with and without FilterWire embolic protection, in diseased saphenous vein grafts. *Acta Cardiol* 68:1–9, 2013.
50. Goto K, Lansky AJ, Nikolsky E, et al: Prognostic significance of coronary thrombus in patients undergoing percutaneous coronary intervention for acute coronary syndromes: a subanalysis of the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. *JACC Cardiovasc Interv* 4:769–777, 2011.
51. Sianos G, Papafaklis MI, Daemen J, et al: Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. *J Am Coll Cardiol* 50:573–583, 2007.
52. Echavarria-Pinto M, Lopes R, Gorgadze T, et al: Safety and efficacy of intense antithrombotic treatment and percutaneous coronary intervention deferral in patients with large intracoronary thrombus. *Am J Cardiol* 111:1745–1750, 2013.
53. Ali A, Cox D, Dib N, et al: Rheolytic thrombectomy with percutaneous coronary intervention for infarct size reduction in acute myocardial infarction: 30-day results from a multicenter randomized study. *J Am Coll Cardiol* 48:244–252, 2006.
54. Frobert O, Lagerqvist B, Olivecrona GK, et al: Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 369:1587–1597, 2013.
55. Aleong G, Vaqueriza D, Del Valle R, et al: Dual quantitative coronary angiography: a novel approach to quantify intracoronary thrombotic burden. *EuroIntervention* 4:475–480, 2009.
56. Taniwaki M, Stefanini GG, Silber S, et al: 4-Year clinical outcomes and predictors of repeat revascularization in patients treated with new-generation drug-eluting stents: a report from the RESOLUTE All-Comers trial (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention). *J Am Coll Cardiol* 63:1617–1625, 2014.
57. Tsagalou E, Stancovic G, Iakovou I, et al: Early outcome of treatment of ostial de novo left anterior descending coronary artery lesions with drug-eluting stents. *Am J Cardiol* 97:187–191, 2006.
58. Kini AS, Moreno PR, Steinheimer AM, et al: Effectiveness of the stent pull-back technique for nonaorto ostial coronary narrowings. *Am J Cardiol* 96:1123–1128, 2005.
59. Popma JJ, Leon MB, Moses JW, et al: Quantitative assessment of angiographic restenosis after sirolimus-eluting stent implantation in native coronary arteries. *Circulation* 110:3773–3780, 2004.
60. Kereiakes DJ, Wang H, Popma JJ, et al: Periprocedural and late consequences of overlapping Cypher sirolimus-eluting stents: pooled analysis of five clinical trials. *J Am Coll Cardiol* 48:21–31, 2006.
61. Lemos PA, Hoye A, Goedhart D, et al: Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. *Circulation* 109:1366–1370, 2004.
62. Cassese S, Byrne RA, Tada T, et al: Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography. *Heart* 100:153–159, 2014.
63. van Werkum JW, Heestermans AA, Zomer AC, et al: Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. *J Am Coll Cardiol* 53:1399–1409, 2009.
64. Vassilev D, Gil RJ, Koo BK, et al: The determinants of side branch compromise after main vessel stenting in coronary bifurcation lesions. *Kardiol Pol* 70:989–997, 2012.
65. Gobeil F, Lefevre T, Guyon P, et al: Stenting of bifurcation lesions using the Bestent: a prospective dual-center study. *Catheter Cardiovasc Interv* 55:427–433, 2002.
66. Medina A, de Lezo J: A new classification of coronary bifurcation lesions. *Rev Esp Cardiol* 59(2):183–184, 2006.
67. Lefevre T, Louvard Y, Morice MC, et al: Stenting of bifurcation lesions: classification, treatments, and results. *Catheter Cardiovasc Interv* 49:274–283, 2000.
68. Movahed MR: Quantitative angiographic methods for bifurcation lesions: a consensus statement from the European Bifurcation Group. Shortcoming of the Medina classification as a preferred classification for coronary artery bifurcation lesions in comparison to the Movahed classification. *Catheter Cardiovasc Interv* 74:817–818, 2009.
69. Maeng M, Holm NR, Erglis A, et al: Long-term results after simple versus complex stenting of coronary artery bifurcation lesions: Nordic Bifurcation Study 5-year follow-up results. *J Am Coll Cardiol* 62:30–34, 2013.
70. Iakovou I, Schmidt T, Bonizzoni E, et al: Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 293:2126–2130, 2005.
71. Rahman S, Leesar T, Cilingiroglu M, et al: Impact of kissing balloon inflation on the main vessel stent volume, area, and symmetry after side-branch dilation in patients with coronary bifurcation lesions: a serial volumetric intravascular ultrasound study. *JACC Cardiovasc Interv* 6:923–931, 2013.
72. Niemela M, Kervinen K, Erglis A, et al: Randomized comparison of final kissing balloon dilatation versus no final kissing balloon dilatation in patients with coronary bifurcation lesions treated with main vessel stenting: the Nordic-Baltic Bifurcation Study III. *Circulation* 123:79–86, 2011.
73. Foin N, Torii R, Mortier P, et al: Kissing balloon or sequential dilation of the side branch and main vessel for provisional stenting of bifurcations: lessons from micro-computed tomography and computational simulations. *JACC Cardiovasc Interv* 5:47–56, 2012.
74. Kornowski R: The complexity of stenting in bifurcation coronary lesions. *JACC Cardiovasc Interv* 6:696–697, 2013.
75. Sirker A, Sohal M, Oldroyd K, et al: The impact of coronary bifurcation stenting strategy on health-related functional status: a quality-of-life analysis from the BBC One (British Bifurcation Coronary; Old, New, and Evolving Strategies) study. *JACC Cardiovasc Interv* 6:139–145, 2013.
76. Colombo A, Moses JW, Morice MC, et al: Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation* 109:1244–1249, 2004.
77. Jang WJ, Song YB, Hahn JY, et al: Impact of bifurcation stent technique on clinical outcomes in patients with a medina 0,0,1 coronary bifurcation lesion: results from the COBIS (COronary BIfurcation Stenting) II registry. *Catheter Cardiovasc Interv* 84:E43–E50, 2014.
78. Chen SL, Xu B, Han YL, et al: Comparison of double kissing crush versus Culotte stenting for unprotected distal left main bifurcation lesions: results from a multicenter, randomized, prospective DKCRUSH-III study. *J Am Coll Cardiol* 61:1482–1488, 2013.
79. Chen SL, Mintz G, Santoso T, et al: Comparison of paclitaxal vs. sirolimus eluting stents with bio-degradable polymer for the treatment of coronary bifurcation lesions: subgroup analysis from DKCRUSH-I and DKCRUSH-II studies. *Chin Med J (Engl)* 125:3382–3387, 2012.
80. Ikeno F, Kim YH, Luna J, et al: Acute and long-term outcomes of the novel side access (SLK-View) stent for bifurcation coronary lesions: a multicenter nonrandomized feasibility study. *Catheter Cardiovasc Interv* 67:198–206, 2006.
81. Buysschaert I, Dubois CL, Dens J, et al: Three-year clinical results of the Axxess Biolimus A9 eluting bifurcation stent system: the DIVERGE study. *EuroIntervention* 9:573–581, 2013.
82. Mamas MA, Farooq V, Latib A, et al: Use of the Sideguard (Cappella) stent in bifurcation lesions: a real-world experience. *EuroIntervention* 7:1170–1180, 2012.
83. Gil RJ, Vassilev D, Michalek A, et al: Dedicated paclitaxel-eluting bifurcation stent BiOSS(R) (bifurcation optimisation stent system): 12-month results from a prospective registry of consecutive all-comers population. *EuroIntervention* 8:316–324, 2012.
84. Gil RJ, Vassiliev D, Michalek A, et al: First-in-man study of paclitaxel-eluting stent BiOSS (Bifurcation Optimisation Stent System) dedicated for coronary bifurcation stenoses: three month results. *Kardiol Pol* 70:45–52, 2012.
85. Verheye S, Ramcharitar S, Grube E, et al: Six-month clinical and angiographic results of the STENTYS® self-apposing stent in bifurcation lesions. *EuroIntervention* 7:580–587, 2011.
86. Amoroso G, van Geuns RJ, Spaulding C, et al: Assessment of the safety and performance of the STENTYS self-expanding coronary stent in acute myocardial infarction: results from the APPOSITION I study. *EuroIntervention* 7:428–436, 2011.
87. Grundeken MJ, Garcia-Garcia HM, Kraak RP, et al: Side branch healing patterns of the Tryton dedicated bifurcation stent: a 1-year optical coherence tomography follow-up study. *Int J Cardiovasc Imaging* 30:1445–1456, 2014.
88. Grundeken MJ, Lesiak M, Asgedom S, et al: Clinical outcomes after final kissing balloon inflation compared with no final kissing balloon inflation in bifurcation lesions treated with a dedicated coronary bifurcation stent. *Heart* 100:479–486, 2014.
89. Grundeken MJ, Hassell ME, Kraak RP, et al: Treatment of coronary bifurcation lesions with the Absorb bioresorbable vascular

scaffold in combination with the Tryton dedicated coronary bifurcation stent: evaluation using two- and three-dimensional optical coherence tomography. *EuroIntervention* 2014. doi: 10.4244/EIJY14M08_15.
90. Dubois C, Adriaenssens T, Ughi G, et al: Healing responses after bifurcation stenting with the dedicated TRYTON Side-Branch Stent in combination with XIENCE-V stents: a clinical, angiography, fractional flow reserve, and optical coherence tomography study: the PYTON (Prospective evaluation of the TRYTON Side-Branch Stent with an additional XIENCE-v everolimus-eluting stent in coronary bifurcation lesions) study. *Catheter Cardiovasc Interv* 81:E155–E164, 2013.
91. Stella PR, Belkacemi A, Dubois C, et al: A multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug-eluting stent in bifurcation lesions treated with a single-stenting technique: six-month angiographic and 12-month clinical results of the drug-eluting balloon in bifurcations trial. *Catheter Cardiovasc Interv* 80:1138–1146, 2012.
92. Lansky A, Tuinenburg J, Costa M, et al: Quantitative angiographic methods for bifurcation lesions: a consensus statement from the European Bifurcation Group. *Catheter Cardiovasc Interv* 73:258–266, 2009.
93. Ishibashi Y, Grundeken MJ, Nakatani S, et al: In vitro validation and comparison of different software packages or algorithms for coronary bifurcation analysis using calibrated phantoms: implications for clinical practice and research of bifurcation stenting. *Catheter Cardiovasc Interv* 2014. doi: 10.1002/ccd.25618.
94. Holm NR, Hojdahl H, Lassen JF, et al: Quantitative coronary analysis in the Nordic Bifurcation studies. *Int J Cardiovasc Imaging* 27:175–180, 2011.
95. Ramcharitar S, Onuma Y, Aben JP, et al: A novel dedicated quantitative coronary analysis methodology for bifurcation lesions. *EuroIntervention* 3:553–557, 2008.
96. Girasis C, Onuma Y, Schuurbiers JC, et al: Validity and variability in visual assessment of stenosis severity in phantom bifurcation lesions: a survey in experts during the fifth meeting of the European Bifurcation Club. *Catheter Cardiovasc Interv* 79:361–368, 2012.
97. Christofferson RD, Lehmann KG, Martin GV, et al: Effect of chronic total coronary occlusion on treatment strategy. *Am J Cardiol* 95:1088–1091, 2005.
98. Stone GW, Kandzari DE, Mehran R, et al: Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: Part I. *Circulation* 112:2364–2372, 2005.
99. Stone GW, Reifart NJ, Moussa I, et al: Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part II. *Circulation* 112:2530–2537, 2005.
100. Baim DS, Braden G, Heuser R, et al: Utility of the Safe-Cross-guided radiofrequency total occlusion crossing system in chronic coronary total occlusions (results from the Guided Radio Frequency Energy Ablation of Total Occlusions Registry Study). *Am J Cardiol* 94:853–858, 2004.
101. Orlic D, Stankovic G, Sangiorgi G, et al: Preliminary experience with the Frontrunner coronary catheter: novel device dedicated to mechanical revascularization of chronic total occlusions. *Catheter Cardiovasc Interv* 64:146–152, 2005.
102. Saito S, Tanaka S, Hiroe Y, et al: Angioplasty for chronic total occlusion by using tapered-tip guidewires. *Catheter Cardiovasc Interv* 59:305–311, 2003.
103. Golemati S, Sanidas EA, Dangas GD: Long-term clinical outcomes after percutaneous coronary intervention for chronic total occlusions. *Curr Cardiol Rep* 16:450, 2014.
104. Patel MR, Marso SP, Dai D, et al: Comparative effectiveness of drug-eluting versus bare-metal stents in elderly patients undergoing revascularization of chronic total coronary occlusions: results from the National Cardiovascular Data Registry, 2005-2008. *JACC Cardiovasc Interv* 5:1054–1061, 2012.
105. Kandzari DE, Grantham JA, Lombardi W, Thompson C: Not all subintimal chronic total occlusion revascularization is alike. *J Am Coll Cardiol* 61:2570, 2013.
106. Seiler C: The human coronary collateral *Circulation*. *Heart* 89: 1352–1357, 2003.
107. Werner GS, Ferrari M, Heinke S, et al: Angiographic assessment of collateral connections in comparison with invasively determined collateral function in chronic coronary occlusions. *Circulation* 107:1972–1977, 2003.
108. Laskey WK, Williams DO, Vlachos HA, et al: Changes in the practice of percutaneous coronary intervention: a comparison of enrollment waves in the National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry. *Am J Cardiol* 87:964–969, A3–A4, 2001.
109. Nishida T, Colombo A, Briguori C, et al: Outcome of nonobstructive residual dissections detected by intravascular ultrasound following percutaneous coronary intervention. *Am J Cardiol* 89:1257–1262, 2002.
110. Chamie D, Bezerra HG, Attizzani GF, et al: Incidence, predictors, morphological characteristics, and clinical outcomes of stent edge dissections detected by optical coherence tomography. *JACC Cardiovasc Interv* 6:800–813, 2013.
111. Radu M, Jorgensen E, Kelbaek H, et al: Optical coherence tomography at follow-up after percutaneous coronary intervention: relationship between procedural dissections, stent strut malapposition and stent healing. *EuroIntervention* 7:353–361, 2011.
112. Feher A, Chen SY, Bagi Z, Arora V: Prevention and treatment of no-reflow phenomenon by targeting the coronary microcirculation. *Rev Cardiovasc Med* 15:38–51, 2014.
113. Resnic FS, Wainstein M, Lee MK, et al: No-reflow is an independent predictor of death and myocardial infarction after percutaneous coronary intervention. *Am Heart J* 145:42–46, 2003.
114. Yip HK, Chen MC, Chang HW, et al: Angiographic morphologic features of infarct-related arteries and timely reperfusion in acute myocardial infarction: predictors of slow-flow and no-reflow phenomenon. *Chest* 122:1322–1332, 2002.
115. Iijima R, Shinji H, Ikeda N, et al: Comparison of coronary arterial finding by intravascular ultrasound in patients with "transient no-reflow" versus "reflow" during percutaneous coronary intervention in acute coronary syndrome. *Am J Cardiol* 97:29–33, 2006.
116. Iwakura K, Ito H, Kawano S, et al: Predictive factors for development of the no-reflow phenomenon in patients with reperfused anterior wall acute myocardial infarction. *J Am Coll Cardiol* 38:472–477, 2001.
117. Tanaka A, Kawarabayashi T, Nishibori Y, et al: No-reflow phenomenon and lesion morphology in patients with acute myocardial infarction. *Circulation* 105:2148–2152, 2002.
118. Wu X, Mintz GS, Xu K, et al: The relationship between attenuated plaque identified by intravascular ultrasound and no-reflow after stenting in acute myocardial infarction: the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. *JACC Cardiovasc Interv* 4:495–502, 2011.
119. Kotani J, Nanto S, Mintz GS, et al: Plaque gruel of atheromatous coronary lesion may contribute to the no-reflow phenomenon in patients with acute coronary syndrome. *Circulation* 106:1672–1677, 2002.
120. Hillegass WB, Dean NA, Liao L, et al: Treatment of no-reflow and impaired flow with the nitric oxide donor nitroprusside following percutaneous coronary interventions: initial human clinical experience. *J Am Coll Cardiol* 37:1335–1343, 2001.
121. Barcin C, Denktas AE, Lennon RJ, et al: Comparison of combination therapy of adenosine and nitroprusside with adenosine alone in the treatment of angiographic no-reflow phenomenon. *Catheter Cardiovasc Interv* 61:484–491, 2004.
122. Michaels AD, Appleby M, Otten MH, et al: Pretreatment with intragraft verapamil prior to percutaneous coronary intervention of saphenous vein graft lesions: results of the randomized, controlled vasodilator prevention on no-reflow (VAPOR) trial. *J Invasive Cardiol* 14:299–302, 2002.
123. Su Q, Li L, Liu Y: Short-term effect of verapamil on coronary no-reflow associated with percutaneous coronary intervention in patients with acute coronary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Clin Cardiol* 36:E11–E16, 2013.
124. Huang RI, Patel P, Walinsky P, et al: Efficacy of intracoronary nicardipine in the treatment of no-reflow during percutaneous coronary intervention. *Catheter Cardiovasc Interv* 68:671–676, 2006.
125. Ishizaka N, Issiki T, Saeki F, et al: Angiographic follow-up after successful percutaneous coronary angioplasty for chronic total coronary occlusion: experience in 110 consecutive patients. *Am Heart J* 127:8–12, 1994.
126. Fasseas P, Orford JL, Panetta CJ, et al: Incidence, correlates, management, and clinical outcome of coronary perforation: analysis of 16,298 procedures. *Am Heart J* 147:140–145, 2004.
127. Dippel EJ, Kereiakes DJ, Tramuta DA, et al: Coronary perforation during percutaneous coronary intervention in the era of abciximab platelet glycoprotein IIb/IIIa blockade: an algorithm for percutaneous management. *Catheter Cardiovasc Interv* 52: 279–286, 2001.
128. Klein LW: Coronary artery perforation during interventional procedures. *Catheter Cardiovasc Interv* 68:713–717, 2006.
129. Javaid A, Buch AN, Satler LF, et al: Management and outcomes of coronary artery perforation during percutaneous coronary intervention. *Am J Cardiol* 98:911–914, 2006.
130. Stankovic G, Orlic D, Corvaja N, et al: Incidence, predictors, in-hospital, and late outcomes of coronary artery perforations. *Am J Cardiol* 93:213–216, 2004.
131. Ellis SG, Ajluni S, Arnold AZ, et al: Increased coronary perforation in the new device era. Incidence, classification, management, and outcome. *Circulation* 90:2725–2730, 1994.
132. Stathopoulos IA, Kossidas K, Garratt KN: Delayed perforation after percutaneous coronary intervention: rare and potentially lethal. *Catheter Cardiovasc Interv* 83:E45–E50, 2014.
133. Ly H, Awaida JP, Lesperance J, Bilodeau L: Angiographic and clinical outcomes of polytetrafluoroethylene-covered stent use in significant coronary perforations. *Am J Cardiol* 95:244–246, 2005.
134. Gercken U, Lansky AJ, Buellesfeld L, et al: Results of the Jostent coronary stent graft implantation in various clinical settings: procedural and follow-up results. *Catheter Cardiovasc Interv* 56:353–360, 2002.
135. Lansky AJ, Yang YM, Khan Y, et al: Treatment of coronary artery perforations complicating percutaneous coronary intervention with a polytetrafluoroethylene-covered stent graft. *Am J Cardiol* 98:370–374, 2006.
136. Al-Lamee R, Ielasi A, Latib A, et al: Incidence, predictors, management, immediate and long-term outcomes following grade III coronary perforation. *JACC Cardiovasc Interv* 4:87–95, 2011.
137. Stathopoulos I, Kossidas K, Panagopoulos G, Garratt K: Cardiac tamponade complicating coronary perforation during angioplasty: short-term outcomes and long-term survival. *J Invasive Cardiol* 25:486–491, 2013.
138. Suh WW, Grill DE, Rihal CS, et al: Unrestricted availability of intracoronary stents is associated with decreased abrupt vascular closure rates and improved early clinical outcomes. *Catheter Cardiovasc Interv* 55:294–302, 2002.
139. Cutlip DE, Windecker S, Mehran R, et al: Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 115:2344–2351, 2007.
140. Cutlip D, Baim D, Ho K, et al: Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation* 103:1967–1971, 2001.
141. Urban P, Gershlick AH, Guagliumi G, et al: Safety of coronary sirolimus-eluting stents in daily clinical practice: one-year follow-up of the e-Cypher registry. *Circulation* 113:1434–1441, 2006.
142. Moreno R, Fernandez C, Hernandez R, et al: Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. *J Am Coll Cardiol* 45:954–959, 2005.
143. Park DW, Park SW, Park KH, et al: Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. *Am J Cardiol* 98:352–356, 2006.
144. Kuchulakanti PK, Chu WW, Torguson R, et al: Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. *Circulation* 113:1108–1113, 2006.
145. Ong AT, McFadden EP, Regar E, et al: Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol* 45:2088–2092, 2005.
146. Virmani R, Guagliumi G, Farb A, et al: Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 109:701–705, 2004.
147. Joner M, Finn AV, Farb A, et al: Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 48:193–202, 2006.
148. Tada T, Byrne RA, Simunovic I, et al: Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. *JACC Cardiovasc Interv* 6:1267–1274, 2013.
149. Dores H, Raposo L, Campante Teles R, et al: Stent thrombosis with second- versus first-generation drug-eluting stents in real-world percutaneous coronary intervention: analysis of 3806 consecutive procedures from a large-volume single-center prospective registry. *J Invasive Cardiol* 25:330–336, 2013.
150. Navarese EP, Tandjung K, Claessen B, et al: Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: comprehensive network meta-analysis. *BMJ* 347:f6530, 2013.
151. Mehran R, Dangas G, Abizaid A, et al: Angiographic patterns of in-stent restenosis. Classification and implications for long-term outcome. *Circulation* 100:1872–1878, 1999.
152. Alfonso F, Cequier A, Angel J, et al: Value of the American College of Cardiology/American Heart Association angiographic classification of coronary lesion morphology in patients with in-stent restenosis. Insights from the Restenosis Intra-stent Balloon angioplasty versus elective Stenting (RIBS) randomized trial. *Am Heart J* 151:681–689, 2006.
153. Colombo A, Orlic D, Stankovic G, et al: Preliminary observations regarding angiographic pattern of restenosis after rapamycin-eluting stent implantation. *Circulation* 107:2178–2180, 2003.
154. Lemos PA, Saia F, Ligthart JM, et al: Coronary restenosis after sirolimus-eluting stent implantation: morphological description and mechanistic analysis from a consecutive series of cases. *Circulation* 108:257–260, 2003.
155. Stabile E, Escolar E, Weigold G, et al: Marked malapposition and aneurysm formation after sirolimus-eluting coronary stent implantation. *Circulation* 110:e47–e48, 2004.
156. Gupta RK, Sapra R, Kaul U: Early aneurysm formation after drug-eluting stent implantation: an unusual life-threatening complication. *J Invasive Cardiol* 18:E140–E142, 2006.
157. Alfonso F, Moreno R: Vergas J: Mycotic aneurysms after sirolimus-eluting coronary stenting. *Catheter Cardiovasc Interv* 67:327–328, 2006.
158. Singh H, Singh C, Aggarwal N, et al: Mycotic aneurysm of left anterior descending artery after sirolimus-eluting stent implantation: a case report. *Catheter Cardiovasc Interv* 65:282–285, 2005.
159. Group TS: The Thrombolysis in Myocardial Infarction (TIMI) trial:phase I findings. *N Engl J Med* 312:932–936, 1985.
160. Gibson CM, Cannon CP, Daley WL, et al: TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation* 93:879–888, 1996.
161. Gibson C, Cannon C, Murphy S, et al: Relationship of TIMI myocardial perfusion grade to mortality following thrombolytic administration. *Circulation* 101:125–130, 2000.
162. The GUSTO Angiographic Investigators: The effects of tissue plasminogen activator, streptokinase, or both on coronary artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 329:1615–1622, 1993.
163. Gibson C, Ryan K, Murphy S, et al: Impaired coronary blood flow in non-culprit arteries in the setting of acute myocardial infarction. *J Am Coll Cardiol* 34:974–982, 1999.
164. Stone GW, Brodie BR, Griffin JJ, et al: Prospective, multicenter study of the safety and feasibility of primary stenting in acute myocardial infarction: in-hospital and 30-day results of the

PAMI stent pilot trial. Primary Angioplasty in Myocardial Infarction Stent Pilot Trial Investigators. *J Am Coll Cardiol* 31:23–30, 1998.
165. Gibson CM, Cannon CP, Murphy SA, et al: Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. *Circulation* 105:1909–1913, 2002.
166. Gibson CM, Dodge JT, Goel M, et al: Angioplasty guidewire velocity: a new simple method to calculate absolute coronary blood velocity and flow. *Am J Cardiol* 80:1536–1539, 1997.
167. Fischer JJ, Samady H, McPherson JA, et al: Comparison between visual assessment and quantitative angiography versus fractional flow reserve for native coronary narrowings of moderate severity. *Am J Cardiol* 90:210–215, 2002.
168. Fleming RM, Kirkeeide RL, Smalling RW, Gould KL: Patterns in visual interpretation of coronary arteriograms as detected by quantitative coronary arteriography. *J Am Coll Cardiol* 18:945–951, 1991.
168a. Brown BG, Bolson E, Frimer M, et al: Quantitative coronary arteriography: estimation of dimensions, hemodynamic resistance, and atheroma mass of coronary artery lesions using the arteriogram and digital computation. *Circulation* 55(2):329, 1977.
169. Garrone P, Biondi-Zoccai G, Salvetti I, et al: Quantitative coronary angiography in the current era: principles and applications. *J Interv Cardiol* 22:527–536, 2009.
170. Garcia JA, Movassaghi B, Casserly IP, et al: Determination of optimal viewing regions for X-ray coronary angiography based on a quantitative analysis of 3D reconstructed models. *Int J Cardiovasc Imaging* 25:455–462, 2009.
171. Tuinenburg JC, Koning G, Hekking E, et al: American College of Cardiology/European Society of Cardiolgoy International Study of Angiographic Data Compression phase II: the effects of varying JPEG data compression levels on the quantitative assessment of the degree of stenosis in digital coronary angiography. Joint Photographic Experts Group. *J Am Coll Cardiol* 35:1380–1387, 2000.
172. Tuinenburg JC, Koning G, Seppenwoolde Y, Reiber JH: Is there an effect of flat-panel-based imaging systems on quantitative coronary and vascular angiography? *Catheter Cardiovasc Interv* 68:561–566, 2006.
173. Herrington DM, Siebes M, Sokol DK, et al: Variability in measures of coronary lumen dimensions using quantitative coronary angiography. *J Am Coll Cardiol* 22:1068–1074, 1993.
174. Steigen TK, Claudio C, Abbott D, et al: Angiographic core laboratory reproducibility analyses: implications for planning clinical trials using coronary angiography and left ventriculography end-points. *Int J Cardiovasc Imaging* 24:453–462, 2008.
175. Peterson ED, Lansky AJ, Anstrom KJ, et al: Evolving trends in interventional device use and outcomes: results from the National Cardiovascular Network Database. *Am Heart J* 139:198–207, 2000.
176. Tsuchida K, Garcia-Garcia HM, Ong AT, et al: Revisiting late loss and neointimal volumetric measurements in a drug-eluting stent trial: analysis from the SPIRIT FIRST trial. *Catheter Cardiovasc Interv* 67:188–197, 2006.
177. Semeraro O, Agostoni P, Verheye S, et al: Re-examining minimal luminal diameter relocation and quantitative coronary angiography—intravascular ultrasound correlations in stented saphenous vein grafts: methodological insights from the randomised RRISC trial. *EuroIntervention* 4:633–640, 2009.
178. Mauri L, Orav EJ, O'Malley AJ, et al: Relationship of late loss in lumen diameter to coronary restenosis in sirolimus-eluting stents. *Circulation* 111:321–327, 2005.
179. Ellis SG, Popma JJ, Lasala JM, et al: Relationship between angiographic late loss and target lesion revascularization after coronary stent implantation: analysis from the TAXUS-IV trial. *J Am Coll Cardiol* 45:1193–1200, 2005.
180. Agostoni P, Valgimigli M, Abbate A, et al: Is late luminal loss an accurate predictor of the clinical effectiveness of drug-eluting stents in the coronary arteries? *Am J Cardiol* 97:603–605, 2006.
181. Pocock SJ, Lansky AJ, Mehran R, et al: Angiographic surrogate end points in drug-eluting stent trials: a systematic evaluation based on individual patient data from 11 randomized, controlled trials. *J Am Coll Cardiol* 51:23–32, 2008.
182. Mauri L, Orav EJ, Candia SC, et al: Robustness of late lumen loss in discriminating drug-eluting stents across variable observational and randomized trials. *Circulation* 112:2833–2839, 2005.
183. Green NE, Chen SY, Hansgen AR, et al: Angiographic views used for percutaneous coronary interventions: a three-dimensional analysis of physician-determined vs. computer-generated views. *Catheter Cardiovasc Interv* 64:451–459, 2005.
184. Ramcharitar S, Daeman J, Patterson M, et al: First direct in vivo comparison of two commercially available three-dimensional quantitative coronary angiography systems. *Catheter Cardiovasc Interv* 71:44–50, 2008.
185. Tu S, Koning G, Jukema W, Reiber JH: Assessment of obstruction length and optimal viewing angle from biplane X-ray angiograms. *Int J Cardiovasc Imaging* 26:5–17, 2010.
186. Yong AS, Ng AC, Brieger D, et al: Three-dimensional and two-dimensional quantitative coronary angiography, and their prediction of reduced fractional flow reserve. *Eur Heart J* 32:345–353, 2011.
187. Schuurbiers JC, Lopez NG, Ligthart J, et al: In vivo validation of CAAS QCA-3D coronary reconstruction using fusion of angiography and intravascular ultrasound (ANGUS). *Catheter Cardiovasc Interv* 73:620–626, 2009.
188. Lee JB, Chang SG, Kim SY, et al: Assessment of three dimensional quantitative coronary analysis by using rotational angiography for measurement of vessel length and diameter. *Int J Cardiovasc Imaging* 28:1627–1634, 2012.
189. Porto I, Dato I, Todaro D, et al: Comparison of two- and three-dimensional quantitative coronary angiography to intravascular ultrasound in the assessment of intermediate left main stenosis. *Am J Cardiol* 109:1600–1607, 2012.

60 Intravascular Ultrasound

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KEY POINTS

- Intravascular ultrasound (IVUS) is the first clinical imaging method to directly visualize atherosclerosis and other pathologic conditions within the walls of blood vessels.
- Improvements in core IVUS technology have allowed for higher-resolution images and greater operator convenience.
- IVUS has provided significant insights into biologically mediated processes of the vasculature, such as the extent of plaque burden, vascular remodeling, and restenosis.
- IVUS is a practically useful tool in clarifying situations in which angiography results are equivocal or difficult to interpret, selecting the appropriate catheter-based intervention, and optimizing the results of coronary procedures.
- Advanced technical developments currently being explored may further enhance the usefulness of IVUS in both research and clinical arenas of interventional cardiology, particularly with sophisticated therapeutic technologies to modify local vascular biology.

Intravascular ultrasound (IVUS) is the first clinical imaging method to directly visualize atherosclerosis and other pathologic conditions within the walls of blood vessels. Because the ultrasound signal is able to penetrate below the luminal surface, the entire cross section of an artery—including the complete thickness of a plaque—can be imaged in real time. This offers the opportunity to gather diagnostic information about the process of atherosclerosis and to directly observe the effects of various interventions on the plaque and arterial wall.

The first ultrasound imaging catheter system was developed by Bom and colleagues in Rotterdam in 1971 for intracardiac imaging of chambers and valves.[1] In the early to mid-1980s, several groups began work on catheter systems designed to image plaque and facilitate balloon angioplasty and other catheter-based interventions. The first images of human vessels were recorded by Yock and colleagues in 1988, with coronary images produced the next year by the same group and by Hodgson and colleagues.[2] The intervening period has seen rapid technical improvements of the systems, with significant enhancement in image quality and miniaturization of the imaging catheters.

IMAGING SYSTEMS AND PROCEDURES

Basic Principles

IVUS imaging systems use reflected sound waves to visualize the vessel wall in a two-dimensional, tomographic format, analogous to a histologic cross section. These systems use significantly higher frequencies than noninvasive echocardiography, achieving greater radial resolutions at the expense of limited beam penetration. The resolution, depth of penetration, and attenuation of the acoustic pulse by tissue are dependent on the geometric and frequency properties of the transducer. Current IVUS catheters used in the coronary arteries have center frequencies ranging from 20 to 45 megahertz (MHz), providing theoretical lower limits of resolution (calculated as half the wavelength) of 31 and 19 μm, respectively. In practice, the radial resolution is at least two to five times poorer (i.e., 80 to 150 μm) and is determined by factors such as the length of the emitted pulse and the position of the imaged structures relative to the transducer. There are two basic catheter designs, based on solid-state or mechanical approaches (Fig. 60-1). Both types of catheters generate a 360-degree, cross-sectional image plane that is perpendicular to the catheter tip.

Solid-State Dynamic Aperture System

In the solid-state approach, the individual elements of a circumferential array of transducer elements, mounted near the tip of the catheter, are activated with different time delays to create an ultrasound beam that sweeps the circumference of the vessel. As the number of elements has increased, there have been progressive improvements in lateral resolution. Complex miniaturized integrated circuits in the catheter tip control the timing and integration of the transducer activation and route the resulting echocardiographic information to a computer, where cross-sectional images are reconstructed and displayed in real time. One of the technical advantages of the multielement approach is the ability to manipulate the beam electronically—achieving, for example, the ability to focus at different depths.

The current solid-state coronary catheter system (Volcano Corporation, San Diego, CA) has 64 transducer elements arranged around the catheter tip and uses a center frequency of 20 MHz. The latest coronary catheters in a rapid-exchange configuration are 3.5 Fr in scanner diameter and thus compatible with a 5-Fr guide catheter. Larger intracardiac echocardiography (ICE) or peripheral imaging catheters are produced in both over-the-wire and rapid-exchange configurations. As an exception, a phased-array catheter (8- or 10 Fr) for ICE imaging (Siemens Healthcare, Erlangen, Germany) uses a different technology, adapted from transesophageal echocardiography, which provides a sector ultrasound image with capabilities of color/spectral Doppler and real-time three-dimensional imaging. The catheter is compatible with multiple-frequency imaging (5 to 10 MHz) so that the operator can determine the desired trade-off between resolution and penetration (up to 15 cm).

Mechanically Rotating Single-Transducer System

In the mechanical approach, a single transducer element is rotated at 1800 rpm, inside a protective sheath at the distal tip of a catheter, via a flexible torque cable that is spun by an external motor drive unit attached to the proximal end of the catheter. Images from each angular position of the transducer are collected by a computerized image array processor, which synthesizes a cross-sectional ultrasound image of the vessel. Mechanical IVUS systems are commercially available from several manufacturers in slightly different configurations. Currently available coronary imaging catheters use a 40- or 45-MHz transducer with a distal crossing profile of 3.2 Fr, compatible with 6-Fr (Infraredx, Burlington, MA; Volcano) or 5-Fr guide catheters (Boston Scientific Corporation, Natick, MA; Terumo Corporation, Tokyo, Japan). Larger catheters with lower center frequencies are also available for intracardiac and peripheral imaging.

The catheters are advanced over a standard guidewire using a short rail section located distal to the protective sheath at the catheter tip. To improve the trackability and pushability, one manufacturer (Terumo) provides an imaging catheter with a second, long-rail section located proximally in addition to the standard short-rail section at the catheter tip. Unlike the solid-state catheter that incorporates the transducer

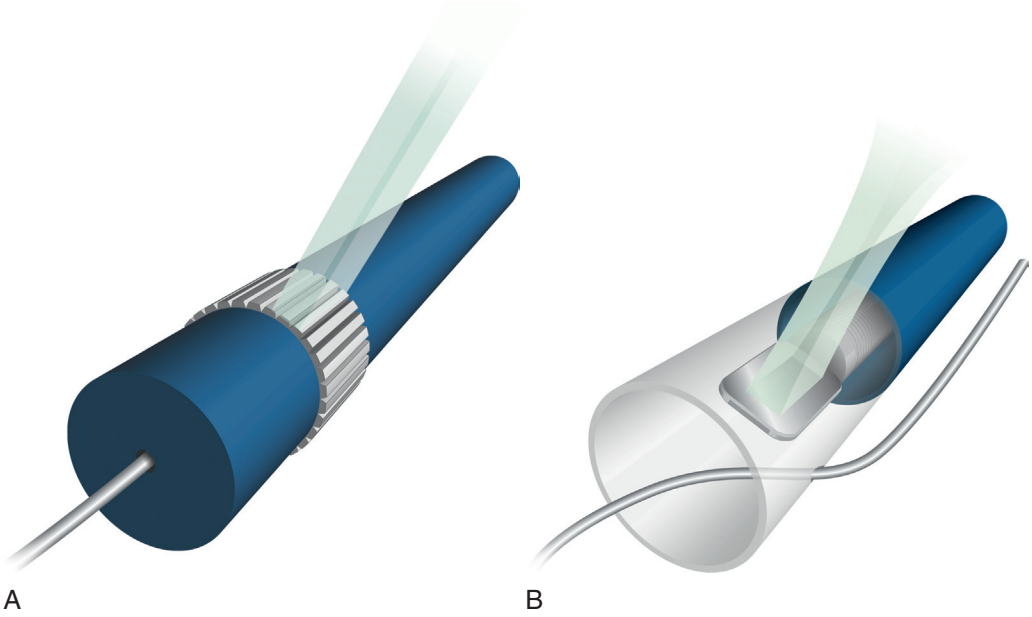

FIGURE 60-1 Diagrams of the two basic imaging catheter designs: solid-state (**A**) and mechanical (**B**) approaches.

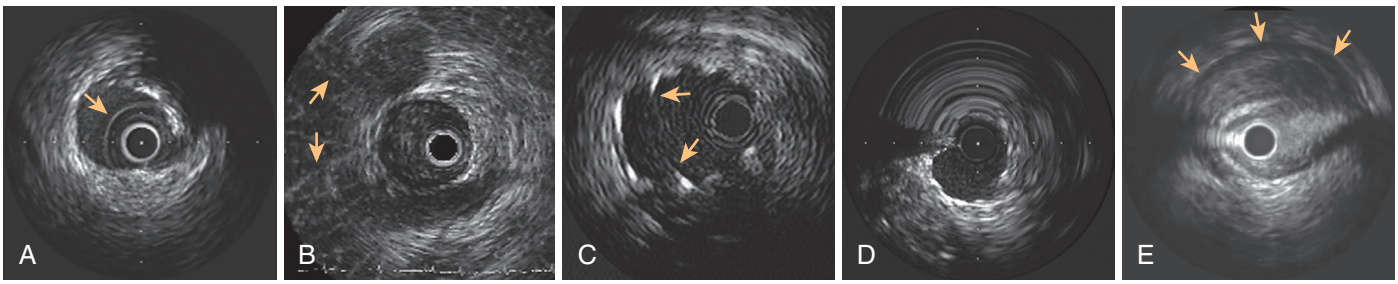

FIGURE 60-2 Common image artifacts. **A,** A "halo" or a series of bright rings immediately surrounding the mechanical intravascular ultrasound catheter (*arrow*) is usually caused by air bubbles that need to be flushed out. **B,** Radiofrequency noise (*arrows*) appears as alternating radial spokes or random white dots in the far-field. The interference is usually caused by other electrical equipment in the cardiac catheterization laboratory. **C,** "White cap" artifacts caused by side lobe echoes (*arrows*) originate from a strong reflecting surface, such as metal stent struts or calcification. Smearing of the strut image can lead to the mistaken impression that the struts are protruding into the lumen, potentially interfering with area measurements and the assessment of apposition, dissection, and so on. **D,** Nonuniform rotational distortion (NURD) results in a wedge-shaped, smeared appearance in one or more segments of the image (between 9 and 4 o'clock in this example). **E,** A "wrinkling" (or "accordion") artifact is caused by an artificial vessel kink associated with intravascular instrumentation (a guidewire or imaging catheter); this results in an abrupt change of arterial dimensions with external compression by a heterogeneous or low-echoic structure (*arrows*) partially surrounding the artery.

assembly surrounding the guidewire lumen, the fact that the guidewire runs outside the catheter, parallel to the imaging segment, results in a shadow artifact in the mechanical IVUS image (the *guidewire artifact*).

Head-to-Head Comparisons

Mechanical systems have traditionally offered advantages in image quality compared with the solid-state systems because of their higher center frequencies and the larger effective aperture of a transducer element. In particular, near-field resolution is excellent with mechanical catheters, and digital subtraction of the ring-down artifact is not required. In addition, a stationary outer sheath of mechanical catheters allows the transducer to be moved through a segment of interest in a precise and controlled manner.

Conversely, the longer, rapid-exchange design of the solid-state catheter may track better than the short-rail design of the mechanical systems in complex coronary anatomy. The distance of the transducer from the catheter tip is shorter than that of mechanical systems, which may also be beneficial in IVUS-guided intervention with chronic total occlusion (CTO) lesions. The solid-state catheter includes no moving parts and therefore is free from nonuniform rotational image distortion (NURD) (Fig. 60-2). This artifact can occur with mechanical systems when bending of the drive cable interferes with uniform transducer rotation, causing a wedge-shaped, smeared image to appear in one or more segments of the image. This may be corrected by straightening the catheter and motor drive assembly, lessening tension on the guide catheter, or loosening the hemostatic valve of the Y-adapter.

Overall, technical improvements are continuously being made in both systems, and good-quality images can be achieved with either of them in most cases. With both systems, serial cross-sectional images can be reconstructed into a longitudinal display mode, and both still frames and video images can be digitally archived on local storage memory or on a remote server using Digital Imaging and Communications in Medicine (DICOM) Standard 3.0. Either system can be

installed directly into the cineangiogram system, enabling operators to quickly and easily incorporate IVUS interrogations into their interventional procedures.

Imaging Procedures

Before IVUS imaging, an intravenous injection of 5000 to 10,000 units of heparin or equivalent anticoagulation should be administered (an activated clotting time of >250 seconds is recommended). Intracoronary nitroglycerin (100 to 200 µg) should also be routinely administered before delivery of the IVUS catheter to induce maximal vasodilation and prevent vasospasm. The image integrity of the IVUS system should be checked before the catheter is inserted. Mechanical catheters require a saline flush before insertion to eliminate any air in the protective sheath. Incomplete flushing can leave microbubbles adjacent to the transducer, resulting in poor image quality once the catheter is inserted (see Fig. 60-2, *A*). With a solid-state catheter, the catheter tip is first positioned in the aorta or a large proximal coronary vessel (not adjacent to any vessel wall) so that the ring-down artifact (a "halo" surrounding the catheter) can be electronically subtracted from the image before the catheter enters the coronary artery. If a significant ring-down artifact is observed with a mechanical catheter, microbubbles within the protective sheath may be suspected, requiring repeated saline flush procedures until the artifact is removed (see Fig. 60-2, *A*).

The technique for delivering IVUS catheters is similar to that used for standard angioplasty or stent catheters. The imaging element is advanced at least 10 mm distal to the area of interest over a standard 0.014-inch angioplasty guidewire, and the length of the target vessel is systematically scanned by retracting the transducer within the protective sheath (mechanical system) or by withdrawal of the entire catheter (solid-state system). Automated pullback devices withdraw the imaging element at a steady rate of 0.5 or 1.0 mm per second, which allows accurate axial registration of each cross section for serial studies or precise longitudinal distance measurements. Recent technological advances also allow coregistration of the ultrasound image with contrast angiography, providing precise localization of the ultrasound findings on the angiogram. Unless the patient complains of chest discomfort or myocardial ischemia is suspected, image acquisition is recommended to include the distal vessel, the lesion site, and the entire proximal vessel back to the aorta. Accurate evaluation of the aortoostial segment requires that the guide catheter be disengaged slightly from the ostium.

Safety

As with other interventional procedures, the risks of spasm, dissection, and thrombosis exist when intravascular imaging catheters are used. Early multicenter studies documented complication rates of 1% to 3%, including transient spasm as the most frequently reported event. Major complications, such as dissection, thrombosis, and abrupt closure with "certain relation" to IVUS, were identified in fewer than 0.5% of the cases. These studies were performed with first-generation catheters in the early 1990s, and it is likely that the incidence of spasm and other complications is substantially lower with the current generation of catheters. No acceleration in the progression of atheroma or allograft vasculopathy of arteries previously imaged by IVUS (compared with noninstrumented arteries) has been reported.[3,4]

IMAGE INTERPRETATION

Three-Layered Appearance of Arterial Wall

The interpretation of IVUS images relies on the fact that the layers of a diseased arterial wall can be identified separately. In muscular or transitional arteries, such as the coronary, iliofemoral, renal, and popliteal systems, relative echolucency of the media compared with the intima and the adventitia gives rise to a three-layered appearance (bright–dark–bright) (Fig. 60-3). The lower ultrasound reflectance of the media is caused by the presence of less collagen and elastin than in the neighboring layers. Because the intimal layer reflects ultrasound more strongly compared with the media, a spillover effect, known as "blooming," may be seen at the intima–media border. This results in a slight overestimation of the thickness of the intima and a corresponding underestimation of the medial thickness. Conversely, the media can appear artifactually thick when ultrasound signal attenuation occurs within the intimal layer. Compared with the intima–media border that may not be correctly delineated, the media–adventitia border, corresponding to the external elastic membrane (EEM), is accurately rendered because a step-up in echo reflectivity occurs at this boundary and no blooming appears. The adventitia and periadventitial tissues are similar enough in echoreflectivity that a clear outer adventitial border cannot be defined.

Several deviations from the classic three-layered appearance are encountered in practice. In truly normal coronary arteries from young patients, echoreflectivity of the intima and the internal lamina may not be sufficient to resolve a clear inner layer. This is particularly true when

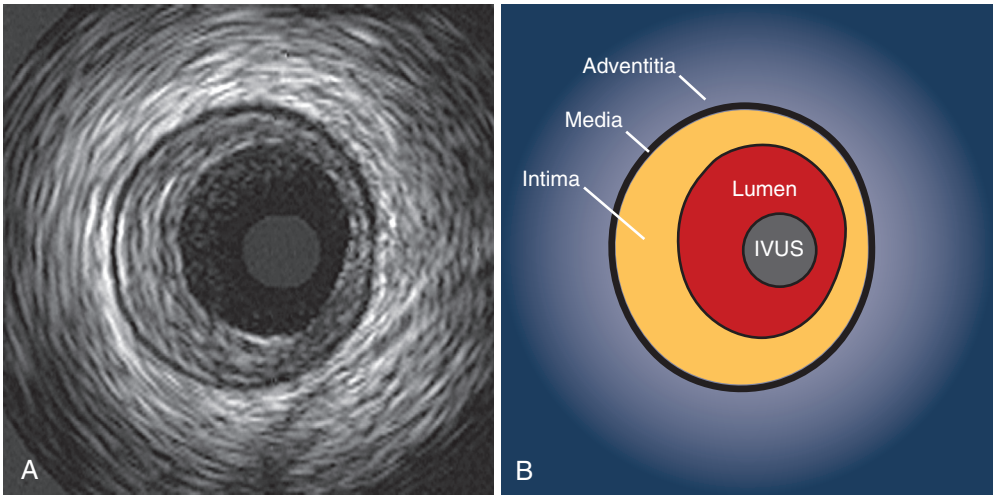

FIGURE 60-3 Intravascular ultrasound image (**A**) and schematic diagram (**B**) demonstrate the classic three-layered appearance of the intima (plaque), the media, and the adventitia. In many cases, the media is difficult to resolve clearly in some portion of the image, but in this image, it stands out in all sectors. Notice the speckled appearance of the blood within the lumen, particularly near the luminal border.

the media has a relatively high content of elastin. At the other end of the spectrum, patients with a significant plaque burden may have thinning of the media underlying the plaque, often to the degree that the media is indistinct or undetectable in at least some part of the IVUS cross section. This problem can be exacerbated by the blooming phenomenon. Even in these cases, however, the inner adventitial boundary (at the level of the EEM) is usually identifiable. For this reason, the plaque-plus-media cross-sectional area (CSA) is adopted as a surrogate measure for plaque CSA alone. Adding in the media represents only a tiny percentage increase in the total CSA of the plaque.

Image Orientation

The determination of image orientation within the artery is another important aspect of image interpretation. The IVUS beam penetrates beyond the artery, providing images of perivascular structures including the pericardium, the myocardium, and the cardiac veins. Because these structures have a characteristic appearance when viewed from various positions within the arterial tree, they provide useful landmarks with regard to longitudinal and cross-sectional image orientation (Fig. 60-4).[5] The pericardium appears as a bright and relatively thick layer with varying degrees of "spoke-like" reverberations created by the interwoven fibrous strands. The myocardium is often viewed on the side opposite to the pericardium as a variable pattern of homogenous, low-echoic gray-scale signals.

By default, current IVUS systems display the cross-sectional image as viewed from the ostium of the coronary artery tree. Therefore in the left anterior descending (LAD) artery, the left circumflex (LCx) artery and the diagonal branches should emerge approximately 90 degrees counterclockwise from the pericardium, whereas septal branches typically emerge on the side opposite the pericardium (i.e., on the myocardium side). The distal LAD is accompanied by one or two anterior interventricular vein (AIV) branches, which run parallel to the LAD for a variable distance.

In the LCx artery, the great cardiac vein (GCV) runs superior to the LCx in most cases and immediately inferior to the left auricle.

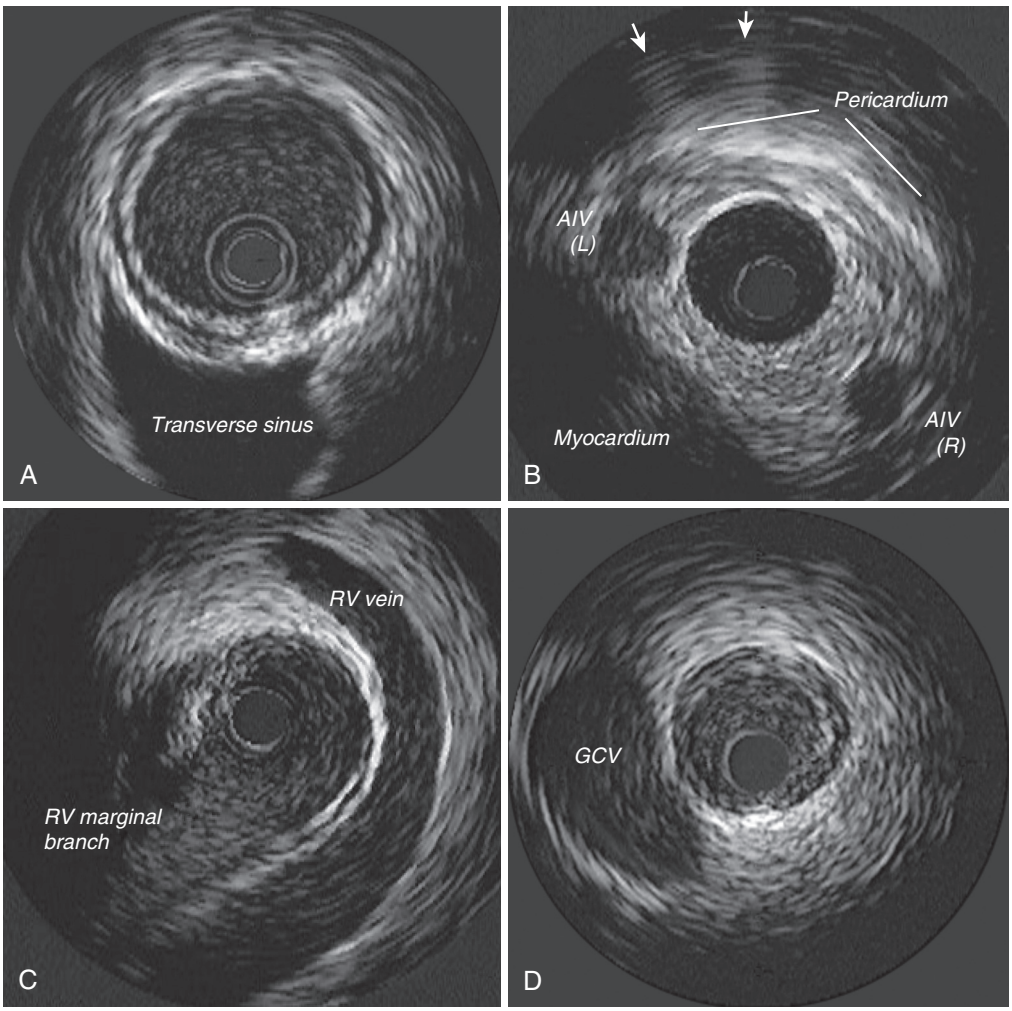

FIGURE 60-4 Perivascular landmarks. **A,** In the proximal portion of the left main coronary artery, a clear echo-free space filled with pericardial fluid, called the transverse sinus, is found adjacent to the artery, immediately outside the left lateral aspect of the aortic root. **B,** In this distal cross section from the left anterior descending (LAD) coronary artery, the right (R) and left (L) branches of the anterior interventricular vein (AIV) are seen to straddle the coronary artery. The pericardium appears as a typical bright stripe with rays emitting from it *(arrows)*. **C,** At the level of the middle right coronary artery, the veins arc over the artery, typically at a position just adjacent to the right ventricular (RV) marginal branches. **D,** The great cardiac vein (GCV), running superiorly to the left circumflex (LCx) coronary artery, appears as a large, low-echoic structure with fine blood speckle. Recurrent atrial branches emerge from the LCx artery in an orientation directed toward the GCV, whereas the obtuse marginal branches emerge opposite the GCV and course inferiorly to cover the lateral myocardial wall.

Therefore, viewed from the LCx, the recurrent arterial branches emerge in an orientation directed toward the GCV. In contrast, the obtuse marginal branches emerge opposite the GCV and course inferiorly to cover the lateral myocardial wall.

Unlike other epicardial coronary arteries typically accompanied by parallel venous structures, the proximal and middle right coronary artery (RCA) segments show a unique vein appearance: the vein arc crosses around the RCA in a "horseshoe" pattern, often at a position adjacent to the right ventricular (RV) marginal branches. The RV branches commonly have a geographic relationship with the pericardium similar to the diagonal branches of the LAD (roughly 90 degrees counterclockwise from the pericardium). The recurrent atrial branches typically emerge opposite the RV marginal branches.

Longitudinal image orientation facilitates accurate stent implantation in terms of optimal stent edge positioning, whereas cross-sectional image orientation is important particularly in terms of guidewire direction in the treatment of CTO lesions. In off-line IVUS analysis, accurate longitudinal and cross-sectional orientation is essential for linking images of different phases of the same lesion in detail. The cross-sectional image orientation as presented on the screen can vary between serial imaging runs. The combination of perivascular landmarks and branching patterns allows the experienced operator to identify the vessel and the segment from the IVUS image alone; this can then provide a reference to the actual orientation of the image in space.

Quantitative Measurements

Unlike coronary angiograms, IVUS has an intrinsic distance calibration, which is usually displayed as a grid on the image. Electronic caliper (diameter) and tracing (area) measurements can be performed at the tightest cross section and at reference segments located proximal and distal to the lesion. The reference segment is typically selected as the most normal-looking cross section (i.e., largest lumen with smallest plaque burden) occurring within 10 mm of the lesion with no intervening major side branches.

In principle, all ultrasound measurements should be performed at the leading edge of boundaries because of the higher accuracy and reproducibility compared with those at the trailing edge.[5a] For vessel measurement, the interface between the media and the leading edge of adventitia that corresponds to the EEM is used. In cross sections with large plaque burden or significant calcification, the circumference of EEM may not be fully identifiable because of ultrasound signal attenuation or acoustic shadowing. Extrapolation from the closest identifiable EEM border is acceptable only if the attenuation or acoustic shadowing involves a relatively small arc (<90 degrees). For lumen measurement, the interface between the lumen and the leading edge of the intima is used. Stagnant blood flow or the use of higher-frequency IVUS can increase the intensity of blood speckle, which may obscure the blood–tissue interface on a still image. A review of moving images can help identify the true lumen border. During the procedure, saline can be injected through the guide catheter to reduce blood speckle. Metal struts of stents are seen as bright focal points in a circular-arrayed pattern on the IVUS scan, and stent measurement is performed at the leading edge of stent strut in the same way as in the nonstented segment.

Vessel and lumen diameter measurements are important in everyday clinical practice, where accurate sizing of devices is needed. All diameter measurements are performed relative to the center of mass rather than the center of the IVUS catheter. The maximum and minimum diameters (i.e., the major and minor axes of an elliptical cross section) are the most commonly used dimensions. The ratio of maximum to minimum diameter defines a measure of symmetry.

Area measurements of vessel, lumen, and stent are performed with computer planimetry, using the interfaces of the leading edges. Plaque CSA (i.e., plaque-plus-media CSA) is calculated as the difference between the EEM and lumen CSAs. The ratio of plaque to EEM CSA is termed *percent plaque area*, *plaque burden*, or *percent cross-sectional narrowing*. Neointimal hyperplasia within the stent has low echoreflectivity at follow-up IVUS imaging, and its area is calculated as the difference between the stent and lumen CSAs. With motorized pullback, area measurements can be added to calculate volumes using the Simpson's rule. For standardized data expression, the volume is presented as a volume index or average area, calculated as the absolute volume divided by the length of the analyzed segment.

Arterial remodeling is a bidirectional vessel response represented as the increase or decrease in vessel size that occurs during the development of atherosclerosis. In clinical settings, direct evidence of remodeling can be derived from serial changes in the EEM CSA in two or more IVUS measurements obtained at different times. In single-time-point studies, measurements of reference sites are used as a surrogate for the original vessel size before the artery became diseased. The reference segment or segments should be measured without any major intervening side branches. Classification of arterial remodeling includes positive (or adaptive) remodeling, no or intermediate remodeling, and negative (or constrictive) remodeling. A remodeling index (the ratio of the EEM CSA at the lesion site to that at the reference site) as a continuous variable may also be used, in combination with the categorical classifications (positive remodeling = remodeling index >1.0 or 1.05; negative remodeling = remodeling index <1.0 or 0.95).[6]

Plaque Composition on Gray-Scale Intravascular Ultrasound

Early changes of atherosclerotic disease ("fatty streaks") are too thin to be visualized with IVUS. As plaque continues to develop, it can be detected with IVUS because it has different acoustic properties, depending on the composition of the plaque (Fig. 60-5). Regions of calcification are recognized as an intensely bright, echoreflective interface that creates a dense shadow more peripherally from the catheter, a phenomenon known as *acoustic shadowing*. This acoustic shadowing, often accompanied by "reverberations" (regularly spaced arcs deep to the initial bright interface), precludes determination of the true thickness of a calcium deposit as well as visualization of any deeper tissue. Calcium deposits are described qualitatively as superficial or deep, according to the leading-edge location of the acoustic shadowing within the inner versus outer half of the plaque-plus-media thickness. The arc of calcium can be measured in degrees with the use of an electronic protractor centered on the lumen.

Densely fibrous tissue also appears as bright (echoreflective) on the ultrasound scan and can cause signal attenuation or partial acoustic shadowing. The extent of shadowing depends on the thickness and density of the fibrotic component as well as the transducer power. Fatty plaque has less echoreflectivity than fibrous plaque due to extensive lipid infiltration. The brightness of the adventitia can be used as a gauge to discriminate predominantly fatty from fibrous plaque: an area of plaque that appears darker than the adventitia is considered fatty. In some cases with an image of extremely good quality, IVUS may identify the presence of a lipid pool from the appearance of a dark region within the plaque. However, the sensitivity and specificity of gray-scale IVUS for the detection of lipid accumulations are both relatively low. False channels within the plaque can give a similar appearance, and occasionally, shadowing from an adjacent calcified or fibrous region can mimic the appearance of a lipid pool.

Advanced Tissue Characterization

Radiofrequency Ultrasound Signal Analysis

Because visual interpretation of conventional gray-scale IVUS images is limited in the precise detection and quantification of specific plaque components, several advanced signal analysis techniques have been developed and introduced into the research and clinical arenas. One commercialized approach is to identify tissue components using computer-assisted analysis of raw radiofrequency (RF) signals in the reflected ultrasound beam.[7] This RF-IVUS analysis is based on the fact that greater information contained in the backscattered ultrasound signal than is revealed by the conventional amplitude-based image presentation alone.

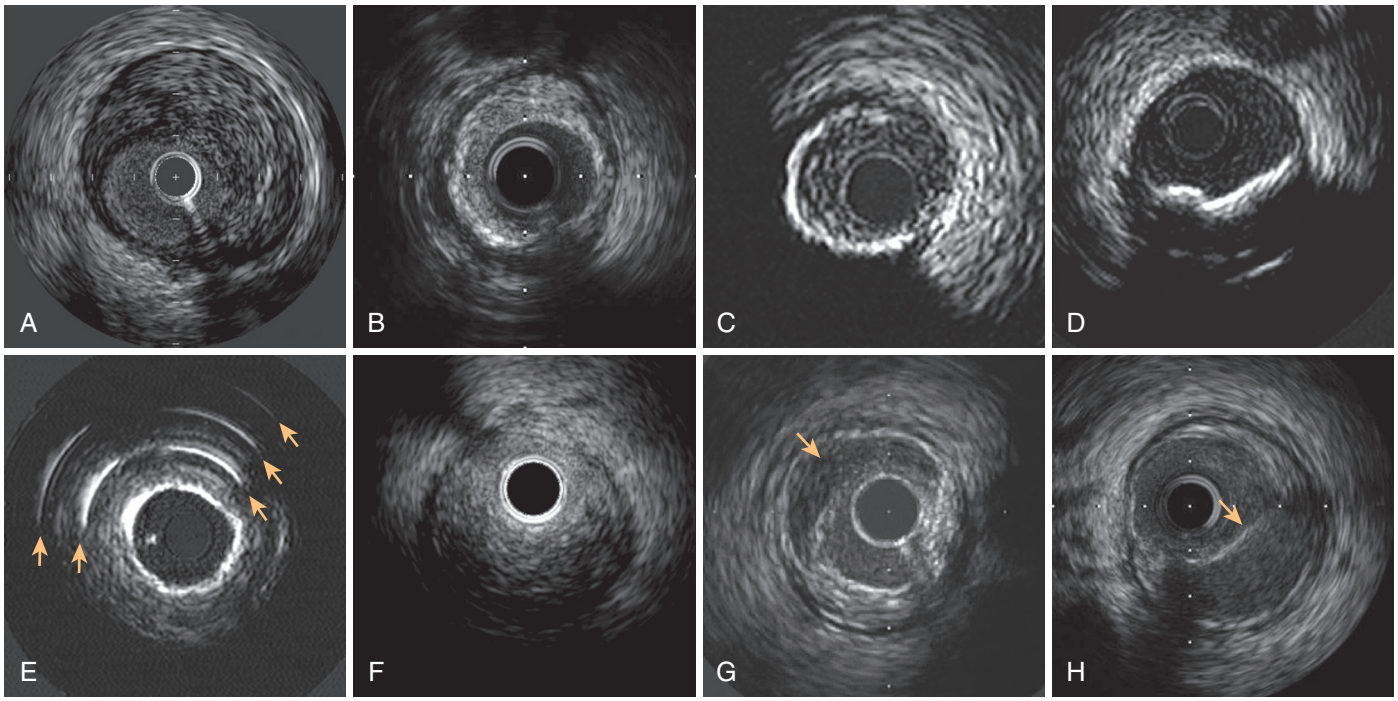

FIGURE 60-5 Plaque characterization by gray-scale interventional ultrasound. **A,** Soft (fatty) plaque. **B,** Fibrous plaque. **C,** Deep calcification. **D,** Superficial calcification. **E,** Circumferential, "napkin-ring" calcification with multiple arcs of reverberation *(arrows)*. **F,** Large plaque burden with deep ultrasound signal attenuation (despite absence of bright calcium) suggesting fibroatheroma with a necrotic core or pathologic intimal thickening with a lipid pool. **G,** Plaque with a large low-echoic region suggesting a lipid pool *(arrow)*. **H,** Ruptured (ulcerated) plaque with a remnant of a fibrous flap *(arrow)*.

One system (IB-IVUS, Terumo) simply uses integrated backscatter (IB) values, calculated as the average power of the backscattered ultrasound signal from a sample tissue volume, to differentiate tissue types. Two other systems employ spectral RF analyses with a classification tree algorithm developed from ex vivo coronary datasets (Virtual Histology, Volcano) or a pattern recognition technique based on the degree of spectral similarity between the backscattered signal and a reference library of spectra from known tissue types (iMap, Boston Scientific). All systems generate color-mapped images of the vessel wall, with a distinct color for each plaque component category (Fig. 60-6).

When combined with automated pullback and border detection techniques, these systems can provide a quantitative assessment of each tissue category over a three-dimensional coronary artery volume. All systems have demonstrated a correlation of IVUS-determined plaque compositions with corresponding histopathology of coronary specimens.[7] Current technical limitations include limited spatial resolution (100 to 250 μm); no classifications for thrombus, blood, or intimal hyperplasia; and potential errors caused by poor ultrasound penetration through extensive calcification.

Intravascular Ultrasound Combined With Near-Infrared Spectroscopy

Spectroscopy determines chemical compositions based on the analysis of spectra induced by interaction of light with tissue materials. Among the various spectroscopic techniques, the diffuse reflectance near-infrared spectroscopy (NIRS) is the frontrunner, showing the ability to identify the lipid component of atherosclerotic plaques in clinical settings. The commercially available coronary spectroscopy system (TVC Imaging System, Infraredx) incorporates a dual-modality imaging catheter that provides simultaneous IVUS and NIRS imaging for coregistered acquisition of structural and compositional information. The 3.2-Fr imaging catheter is compatible with a 6-Fr guide and is configured similarly to conventional mechanical IVUS catheters in a rapid-exchange design with a protective outer sheath, except for an NIRS probe mounted adjacent to an extended bandwidth IVUS transducer. Unlike other light-based imaging techniques, this system does not require removal of blood from the imaging field. The light reflected from tissue is analyzed by a spectrometer.

With the use of a diagnostic algorithm, the processed data are color coded and displayed in a two-dimensional map of the vessel called a "chemogram" with the spatial (circumferential and longitudinal) information (see Fig. 60-6, *E*). The current system is specifically designed for the detection of lipid-rich plaque, which is exhibited yellow on the chemogram, and a color scale from red to yellow indicates increasing algorithm probability of a lipid component of the vessel wall. The chemogram data are also laid in a halo surrounding the cross-sectional IVUS image in real time (see Fig. 60-6, *D*). A summary of the results for each 2-mm section of artery is displayed as a block chemogram and is also portrayed in the central catheter artifact of the cross-sectional IVUS image. A lipid core burden index is computed as the fraction of valid pixels within the scanned region that exceed a lipid probability of 0.6, multiplied by 1000. The accuracy of NIRS has been validated in coronary autopsy specimens and subsequently in vivo.[8,9]

DIAGNOSTIC APPLICATIONS

Abnormal Lesion Morphology

Dissection appears as a fissure or separation within intima or plaque (Figs. 60-7). The severity of a dissection can be quantified according to depth (intimal, medial, or adventitial) and extent (circumferential and longitudinal). Intrastent dissection is characterized as separation of neointimal hyperplasia from stent struts.

Intramural (intravascular) hematoma is recognized as an accumulation of blood within the medial space that displaces the internal elastic membrane inward and the EEM outward (Fig. 60-8). On the IVUS image, it is observed typically as a homogenous, hyperechoic,

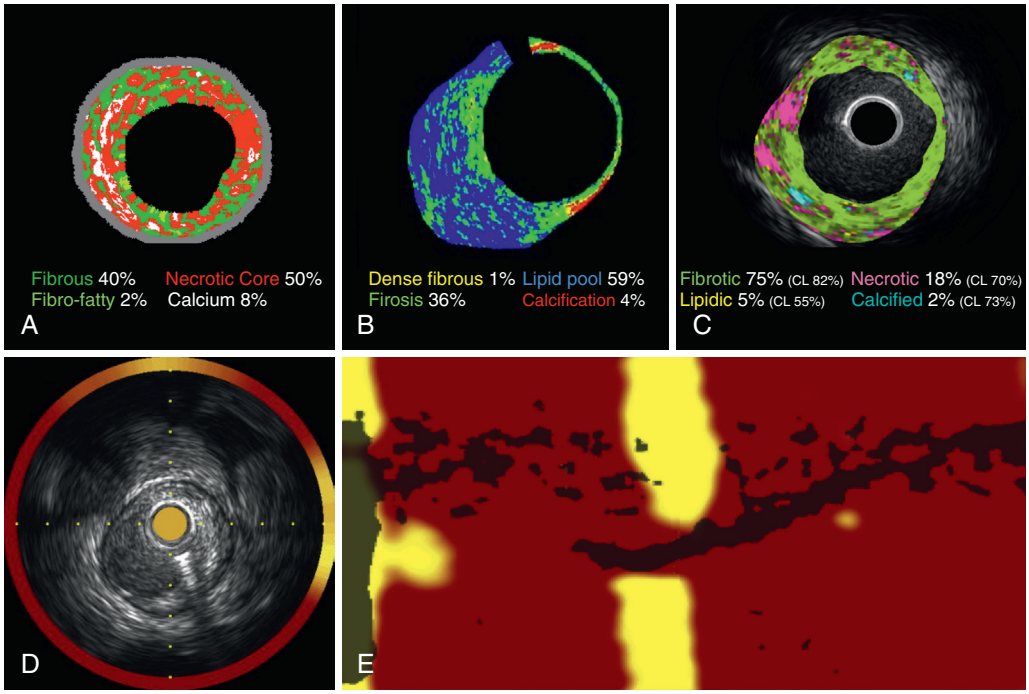

FIGURE 60-6 Examples of plaque characterization by radiofrequency–intravascular ultrasound (RV-IVUS) analyses and near-infrared spectroscopy (NIRS). **A,** Virtual Histology system (Volcano). Plaque components are determined by analyses of spectral RF signals with a classification algorithm. **B,** Integrated backscatter (IB)-IVUS (Terumo). **C,** iMap (Boston Scientific). Classification of tissue is made based on the degree of similarity between the sample and a reference frequency spectrum. This method enables confidence level (CL) assessment of each plaque component. **D,** NIRS-IVUS. Spectroscopy data are laid in a halo surrounding the cross-sectional IVUS image in real time. A color scale from red to yellow indicates increasing algorithm probability of lipid content. **E,** A chemogram (a two-dimensional map of spectroscopy data). The x-axis represents millimeters of pullback in the artery, and the y-axis represents degrees of rotation.

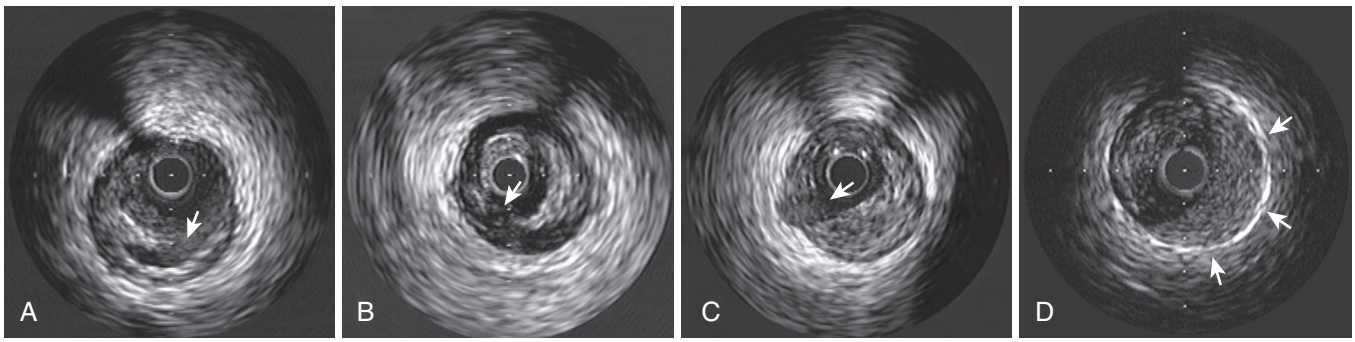

FIGURE 60-7 Four examples of dissection. **A,** A superficial (intimal) dissection starting at 6 o'clock and extending clockwise. The dissection flap does not extend far into the lumen. **B,** A deeper (medial) dissection with a flap that extends into the lumen may compromise flow or precede abrupt closure. Injection of contrast in this setting can demonstrate free fluid flow behind the flap to better define the extent of tear. **C,** Eccentric plaque with a deep (adventitial) dissection at 8 o'clock that penetrates the external elastic lamina and extends into the adventitia. **D,** Intramural hematoma appears as an accumulation of blood within the medial space, displacing the internal elastic membrane inward and the external elastic membrane outward.

crescent-shaped area, but it may have a heterogeneous or layered appearance when contrast dye or saline is trapped in the false lumen. Entry and exit points may or may not be observed.

Extramural (extravascular) hematoma is visualized outside the arterial wall. It manifests with an irregular shape and an echodim pattern due to the dilution of red blood cell concentration and dissemination through an echogenic adventitia or perivascular tissue (see Fig 60-8, *H*). Extramural hematoma is most often realized after an interventional procedure, such as atherectomy or recanalization of CTO lesions, and requires careful attention to antithrombolytic and antiplatelet treatment.

True aneurysm is defined as having an intact vessel wall and a maximum lumen area 50% larger than the proximal reference. In contrast, pseudoaneurysm shows a loss of vessel wall integrity and damage to adventitia or perivascular tissue.

Thrombus is typically recognized as an intraluminal mass, often with a layered, lobulated, or pedunculated appearance (see Fig. 60-8, *F*). Acute thrombus may appear as a relatively echodense mass with

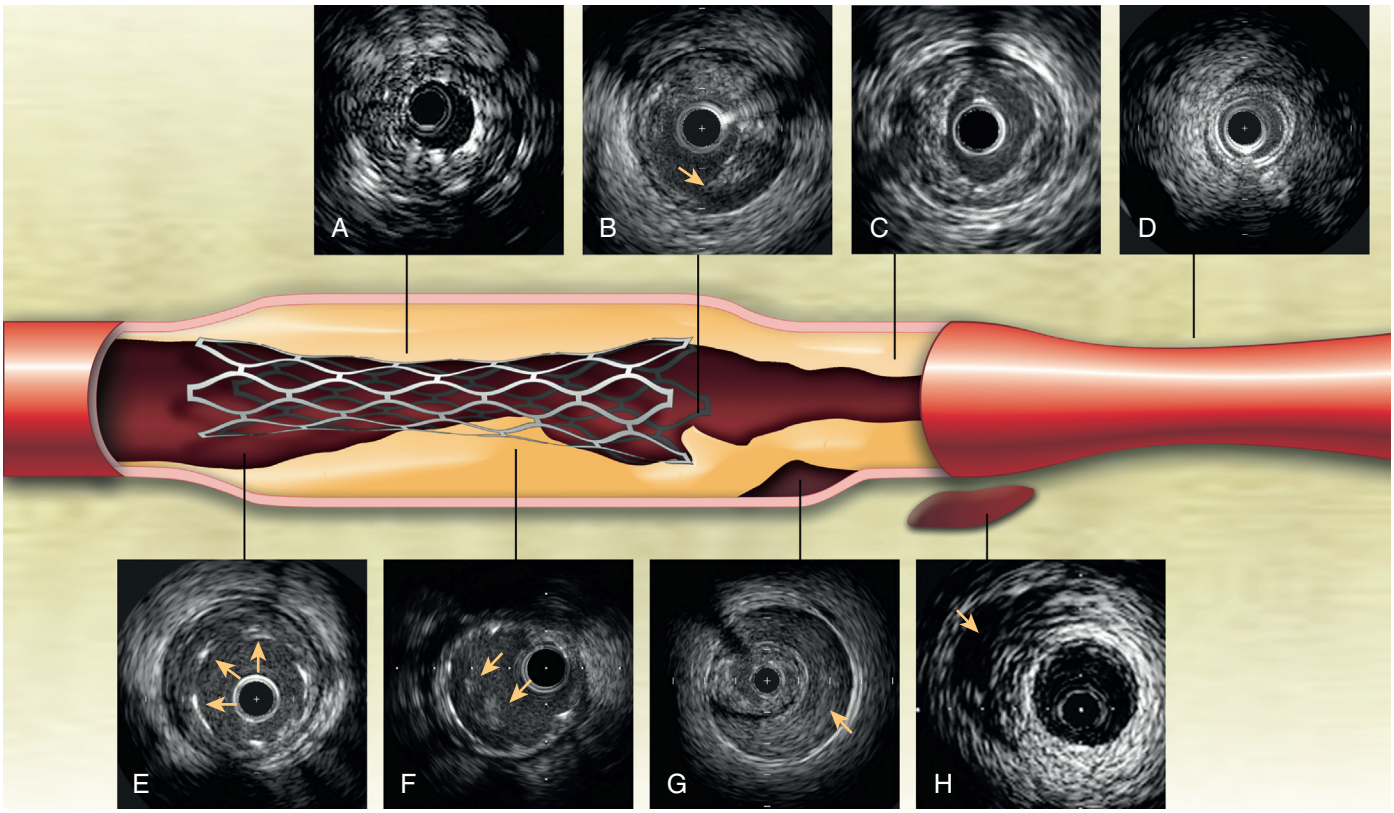

FIGURE 60-8 Problems with stent deployment detected by intravascular ultrasound (IVUS). The diagram indicates the locations of the cross sections shown in the IVUS images. **A,** Incomplete expansion relative to the ends of the stent and the reference segments. **B,** An edge dissection with a disruption of plaque (*arrow*) at the stent margin. **C,** Significant residual plaque burden at the segment uncovered by the stent. **D,** Spasm at the adjacent nonstented segment. **E,** Incomplete apposition, in which there is a gap between a portion of the stent (*arrows*) and the vessel wall. **F,** Tissue protrusion (plaque prolapse, thrombus, or both) (*arrows*) within the stent. **G,** Intramural (intravascular) hematoma detected as an accumulation of blood within the medial space (*arrows*) starting from the edge of the stent. **H,** Extramural (extravascular) hematoma *(arrow)* visualized as an irregularly shaped, echodim pattern in the perivascular tissue.

speckling or scintillation, whereas old organized thrombus often has a darker ultrasound appearance. Thrombus is also more likely than soft plaque to have the appearance of blood flow in microchannels. However, none of these IVUS features is pathognomonic for thrombus, and slow blood flow, air bubbles, stagnant contrast, and echolucent plaque should be considered as differential diagnoses. Injection of contrast or saline may disperse the stagnant flow from the lumen, often allowing differentiation of stasis from thrombus.

Unstable Plaque

Gray-Scale Intravascular Ultrasound

By gray-scale IVUS, morphologic features associated with clinical instability or high risk for cardiovascular events after percutaneous coronary intervention (PCI) include noncalcified plaque with ultrasound attenuation, an echolucent zone within plaque, and scattered spotty calcification. In particular, echoattenuated plaque (or attenuated signal plaque, defined as the absence of the ultrasound signal behind plaque that is either hypoechoic or isoechoic to the reference adventitia but contains no bright calcium) likely represents either fibroatheroma with a necrotic core or pathologic intimal thickening with a lipid pool (see Fig. 60-5, *F*).[10]

Plaque rupture is diagnosed when a hypoechoic cavity within the plaque is connected with the lumen and a remnant of the ruptured fibrous cap is observed at the connecting site (see Fig. 60-5, *H*). Ruptured plaques are often eccentric, less calcified, large in plaque burden, positively remodeled, and associated with thrombus. In patients with acute coronary syndrome (ACS), multiple plaque ruptures are frequently detected by three-vessel IVUS examination, suggesting that ACS is associated with pancoronary destabilization. However, lumen compromise and clinical symptoms likely depend on the severity of the original or coexisting stenosis or on thrombus formation, not solely on plaque rupture.

Extensive positive remodeling has also been shown to correlate with unstable plaque. Culprit lesions responsible for ACS typically represent extensive positive remodeling. Multiple clinical studies have also shown that preinterventional positive remodeling or large plaque burden assessed by IVUS predicts unfavorable acute- and long-term outcomes after PCI. Pathology studies support this clinical IVUS finding by demonstrating that lesions with positive remodeling frequently exhibit large, soft, lipid-rich plaques with increased inflammatory cell infiltrate. A clinical study with synergy of IVUS and optical coherence tomography has also linked positive remodeling with thinning of the fibrous cap in serial coronary examinations.[11]

Advanced Tissue Characterization

A number of clinical studies have indicated that plaque vulnerability, as determined by RF-IVUS (large lipid or necrotic core, or thin-cap fibroatheroma [TCFA]) is related to unstable lesion characteristics, clinical presentations, and future adverse events. Among them, the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) trial, one of the largest natural history trials, prospectively employed three-vessel imaging with Virtual Histology IVUS (VH-IVUS) in 697 patients with ACS.[12] In this trial, a

fibroatheroma (defined by VH-IVUS as the presence of >10% confluent necrotic core) was classified as a TCFA if more than 30 degrees of the necrotic core abutted the lumen in three or more consecutive frames. Multivariate analysis identified three baseline IVUS characteristics that independently predicted events at 3 years: (1) plaque burden greater than 70% (hazard ratio [HR], 5.03); (2) VH-determined TCFA (HR, 3.35); and (3) minimal luminal area (MLA) less than 4.0 mm^2 (HR, 3.21). Major adverse cardiac events (MACE) occurred in 18% of those lesions with all three of these characteristics and in fewer than 1% of lesions with none of them. These results were replicated in several other prospective trials in which VH-determined TCFA was again associated with an increased occurrence of cardiac events.[13,14]

Identification of lipid-core plaque by NIRS-IVUS may also help identify vulnerable atherosclerosis. A higher prevalence of lipid-core plaque in patients with ACS has been reported compared with those with stable angina.[15] Another study revealed that most culprit lesions of ST-segment elevation myocardial infarction (STEMI) are characterized by a large, often circumferential lipid-core plaque concentrated at the culprit site.[16] In this study, a maximum lipid core burden index over a 4-mm length greater than 400 was found to be a signature of plaques causing STEMI. In a study of early coronary artery disease, NIRS-IVUS also demonstrated a higher lipid content in the vascular wall in patients with endothelial dysfunction than in those with normal endothelial function.[17] Finally, several large, prospective, multicenter studies are ongoing to evaluate the ability of NIRS-IVUS to predict long-term coronary events, including the PROSPECT-II trial (900 ACS patients) and the Lipid-Rich Plaque (LPR) study (9000 patients with ACS or stable angina). The ongoing PROSPECT-II trial also includes a substudy cohort that is being randomized to everolimus-eluting bioresorbable vascular scaffold versus guideline-determined medical therapy for plaque stabilization.

Serial Monitoring of Disease Progression or Regression

The ability of IVUS to quantify arterial wall disease in a precise and reproducible manner allows serial evaluation of atherosclerotic plaque or transplant vasculopathy for the assessment of disease progression or regression. In serial studies for this purpose, the same IVUS system (in terms of catheter type, imaging console, and pullback device) should be used for serial imaging procedures at baseline and follow-up in a given patient. The use of automated pullback is mandatory for accurate axial registration of analysis segments. Some investigators recommend electrocardiogram (ECG)-gated image acquisition with a dedicated pullback device or software-based ECG-gated frame analysis of IVUS images obtained with a conventional pullback device, although the exact impact of these approaches on the outcomes of clinical studies has not been documented. A certain length of untreated coronary segment (typically 30 to 50 mm) is preselected for serial analyses using anatomic landmarks such as major side branches. Volume data are often normalized by pullback length (expressed as mean area) or by vessel size (expressed as percent volume) for comparative analysis.

The change of the intima or the plaque volume measured by IVUS has been increasingly used as a surrogate end point in clinical trials of the natural history of atherosclerosis and transplant vasculopathy and in monitoring the results of pharmacologic interventions such as lipid lowering. Relying on angiographic assessment alone for accurate evaluation of disease progression or regression is extremely challenging, particularly with a diffuse extent of disease and a variable degree of arterial remodeling. One pending question is whether disease progression or regression measured by gray-scale IVUS effectively reflects an increased or decreased risk of future cardiovascular events. Although several clinical trials suggest a significant association, a discrepancy between the imaging end point and clinical outcome has also been implied in some studies.[18-21] Clinical trials using IB-IVUS or Virtual Histology have demonstrated stabilization of plaque composition by antiatherosclerotic agents despite lack of change in total plaque volume observed by conventional IVUS measurement.[22,23] More recently, the Reduction in Yellow Plaque by Intensive Lipid-Lowering Therapy (YELLOW) trial, a prospective, randomized, single-center trial to determine the impact of statin therapy on intracoronary plaque lipid content assessed by NIRS, also demonstrated significant reduction of lipid content in obstructive lesions after short-term (7 weeks) intensive statin therapy.[24] Advanced tissue characterization techniques may supplement the simple plaque quantification by gray-scale IVUS, thereby enhancing the usefulness of IVUS-defined end points in the evaluation of new pharmacologic therapies.

Myocardial Bridging

Myocardial bridging (MB) is a common congenital coronary anomaly that is located most frequently in the LAD. Although most patients are presumed to be asymptomatic, MB can cause typical or atypical angina, arrhythmia, or myocardial infarction, most likely because of direct compression effects on the MB segment or accelerated atherosclerosis in the segment proximal to the MB. In vivo diagnosis of MB has traditionally been made with coronary angiography, based on the characteristic "milking" effect. For this reason, MB can be underdiagnosed in patients who have weak systolic arterial compression. IVUS can detect MB with much greater sensitivity, both by functional assessment (systolic arterial compression) and by a characteristic echolucent band (halo) appearance partially surrounding the artery. In a consecutive series, MB was identified by IVUS in 23% of 331 patients, whereas angiography alone detected MB in only 3%.[25] A histopathologic study demonstrated that the characteristic halo on the IVUS image of MB corresponds to muscle tissue overlying the coronary artery.[26] The direct assessment of muscle tissue by IVUS regarding length, thickness, and location, in combination with a functional measurement of systolic arterial compression, may provide prognostic information in specific patients and determine the indication and strategy of treatment, especially when unroofing surgery is considered (7% to 9% of symptomatic MB patients may require surgery due to refractory angina despite medical treatment).

INTERVENTIONAL APPLICATIONS

Angiographic Lesion Ambiguity

Preinterventional IVUS has been used to clarify situations in which angiography results are equivocal or difficult to interpret, especially in ostial lesions or tortuous segments in which the angiogram may not lay out the vessel well for interpretation. Particularly, in the assessment of left main coronary artery (LMCA) disease, angulations, calcification, or spasm in this location can lead to poor catheter engagement and confounded angiographic interpretation (Fig. 60-9). Several investigators have demonstrated that a high percentage of patients with angiographically normal LMCA are seen to have disease by IVUS. Conversely, another IVUS study demonstrated that fewer than half of the angiographically ambiguous LMCA lesions had significant stenosis.[27] This was especially true for ostial LMCA disease, in which only 36% of the lesions had a significant stenosis, and 41% had plaque burden less than 50% as assessed by IVUS. Therefore patients with LMCA disease merit IVUS or physiologic assessment before a blind decision about treatment strategy is made, because the result of detailed evaluation can dramatically alter management and prognosis.

At bifurcation lesions including distal LMCA disease, the extent of side-branch involvement can be difficult to assess by angiography alone, and the decision to pursue revascularization or protection of the side branch is often dependent on ambiguous demonstration of these complex lesions. The combination of plaque and carina shift after balloon dilation or stenting may cause severe narrowing or occlusion of a side branch, particularly in the presence of preexisting ostial disease. Conversely, the ostium of a jailed side branch can falsely appear stenosed on coronary angiography. This "pseudo" side-branch encroachment is caused by spasm, flow disturbance, or dye streaming due to jailing of the branch orifice by the stent. Although true or pseudo encroachment may be identified by looking across from the

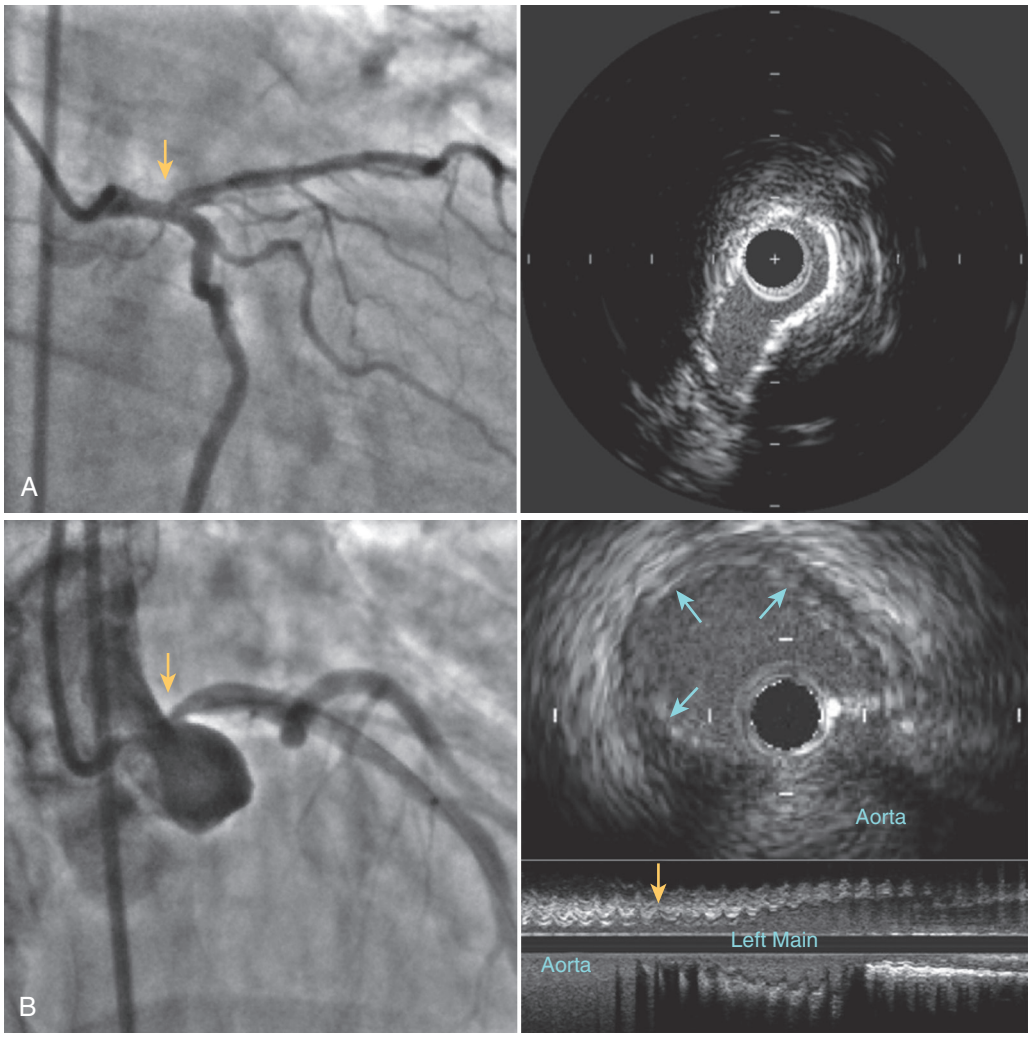

FIGURE 60-9 Two examples of left main coronary artery (LMCA) assessment by intravascular ultrasound (IVUS). **A,** A moderate stenosis *(orange arrow)* is observed at the distal LMCA segment by angiography *(left)*. IVUS reveals a significant lumen narrowing with napkin-ring superficial calcification at the corresponding segment *(right)*. **B,** A significant stenosis *(orange arrow)* at the orifice of the LMCA is suspected by angiography *(left)*. IVUS demonstrates reverse vessel tapering of the corresponding segment *(orange arrow)* with only mild plaque accumulation *(blue arrows) (right)*.

parent artery into the ostium of the branch, accurate assessment requires direct IVUS imaging of the side branch.

Intermediate Lesions

Intermediate coronary lesions identified by angiography (40% to 70% angiographic stenosis) represent a challenge for revascularization decision making. A number of physiologic studies have demonstrated that a considerable number of intermediate lesions referred for elective interventions are in fact hemodynamically insignificant and can be successfully managed with medical treatment alone. In early studies of proximal coronary lesions, MLA measured by IVUS demonstrated reasonable correlations with results from physiologic assessments. The ischemic MLA threshold was identified as 3.0 to 4.0 mm^2 for major (non-LMCA) epicardial coronary arteries based on physiologic assessment with coronary flow reserve, fractional flow reserve (FFR), or stress scintigraphy. Among patients with intermediate coronary lesions in whom intervention was deferred based on IVUS findings (MLA >4.0 mm^2), only 2.8% had target-lesion revascularization, and the composite event rate was 4.4% at up to 2 years.[28]

Later studies expanded the study population to encompass a wide variety of lesions and indicated that the diagnostic accuracies and optimal MLA cutoff values can vary depending on lesion location, vessel size, and amount of myocardium supplied by the target vessel.[29-31] Overall, a metaanalysis of 11 clinical studies comparing IVUS and FFR identified the best MLA cutoff value to define the functional significance as 2.61 mm^2 in non-LMCA trials.[32] However, the pooled sensitivity and specificity of MLA were only 0.79 (95% confidence interval [CI], 0.76 to 0.83) and 0.65 (95% CI, 0.62 to 0.67), respectively. Recent prospective multicenter trials also reported limited correlations between IVUS and FFR,[31] indicating IVUS-measured MLA is only one of many factors affecting coronary flow hemodynamics.

Compared with non-LMCA lesions, the IVUS-determined MLA appears to have better accuracy to predict significant FFR in LMCA lesions (MLA cutoff = 5.35 mm^2; pooled sensitivity, 0.90, and specificity, 0.90, in the metaanalysis previously cited),[32-35] presumably due to relatively fewer variations in this location with respect to vessel anatomy and the amount of downstream myocardial burden. The clinical safety of deferred revascularization based on the IVUS-MLA was evaluated in a prospective multicenter study in which the predefined IVUS criterion of an MLA equal to or greater than 6 mm^2 was used for patients with intermediate LMCA disease. In this study, cardiac death and event-free survival were both comparable in the deferred

versus the revascularized group over a 2-year follow-up period.[36] Another study group also confirmed the safety of IVUS-guided deferral of revascularization for intermediate LMCA disease but used a larger MLA cutoff value (7.5 mm^2), which was predetermined based on the lower range of normal LMCA MLA in their clinical database.[37] In practice, however, the judgment should be made in conjunction with other information, such as the presence of diabetes,[38] plaque burden at the MLA site, and FFR.[39]

Preinterventional Plaque Assessment

Preinterventional IVUS imaging is useful in determining the appropriate catheter-based intervention strategy. With current IVUS catheters, most significant stenoses can be safely imaged before intervention, providing detailed information about the circumferential and longitudinal extent of the plaque and the character of the tissue involved. When observed by IVUS, angiographically hazy lesions represent a spectrum of morphologies, including calcium, dissection, thrombus, and excessive plaque burden with extreme remodeling. In particular, the presence, location, and extent of calcium can significantly affect the results of intervention (see Fig. 60-5). After balloon angioplasty, dissections are often observed at the junction of calcified and noncalcified plaque, where shear forces from dilation are high. For lesions with extensive superficial calcium, plaque modification through the use of rotational atherectomy may be required before balloon dilation or stent implantation. Conversely, even for lesions with significant calcification on fluoroscopy, IVUS may find the calcification to be distributed in a deep portion of the vessel wall or to have a calcium arc of less than 180 degrees. In these cases, stand-alone stenting is usually adequate to achieve lumen expansion large enough for a drug-eluting stent (DES).

Evaluation of plaque composition by preinterventional IVUS may also predict the occurrence of distal emboli during balloon dilation or stenting that may result in the "slow-flow" or "no-reflow" phenomenon leading to periprocedural myocardial infarction (MI). In gray-scale IVUS, predictive findings include large plaque burden with ultrasound signal attenuation (non–calcium-related), a large low-echoic region suggesting a lipid pool, and thrombus-containing plaque (see Fig. 60-5).[40] Recent studies with IB-IVUS, VH-IVUS, or NIRS-IVUS also demonstrated that the amount of lipid or necrotic core at preintervention was related to findings suggesting distal emboli.[41-46] Identification of high-risk plaques may help in selecting lesions suitable for distal protection devices.[47]

Selection of Device Size and Length

When assessed by IVUS, angiographically "normal" reference segments for PCI have a plaque burden of 35% to 51%. Precise measurements of vessel size and lesion length by IVUS can guide the optimal sizing of devices to be employed. IVUS-guided balloon sizing was first systematically pursued by the Clinical Outcomes with Ultrasound Trial (CLOUT), followed by a randomized multicenter study (the Balloon Equivalent to Stent Study [BEST]) in which the nominal balloon size chosen was the closest size to the media-to-media diameter measured at the lesion site and inflation pressure was determined based on the compliance curve to attain the target diameter. In a contemporary DES trial of complex lesions (Angiography Versus IVUS Optimization [AVIO]), the size of the postdilation balloon was selected based on the average of the media-to-media diameters at multiple sites within the stented segment. The precise vessel size measurement is also critically important for size selection of self-expanding stents or full-bioresorbable coronary scaffolds, because undersizing of these devices is not amendable once they are deployed in the lesion.

Assessment of true lesion length by IVUS dictates the exact length of stent necessary to appropriately scaffold a lesion. Numerous IVUS studies of DES have identified greater reference plaque burden as an independent predictor of subsequent stent edge restenosis or thrombosis (Fig. 60-10).[48-51] The STLLR (The Impact of Stent Deployment Techniques on Clinical Outcomes of Patient Treated With the CYPHER Stent) trial also demonstrated that geographic miss had a significant negative impact on both clinical efficacy and safety at 1 year after DES implantation.[52] Complete coverage of reference disease is currently recommended; however, longer stent length has also been reported to be independently associated with DES restenosis and thrombosis. On-line IVUS guidance can facilitate the determination of appropriate stent length for anchoring the stent ends in relatively plaque-free vessel segments while minimizing stent length for complete lesion coverage. One practical approach was proposed in a single-center registry in which stepwise IVUS criteria (plaque burden <50% as the primary target zone) were used to determine the optimal landing zone for DES.[53]

Common Stent Problems at Deployment

Postinterventional IVUS can identify several stent deployment issues (see Fig. 60-8). Incomplete stent expansion (or stent underexpansion)

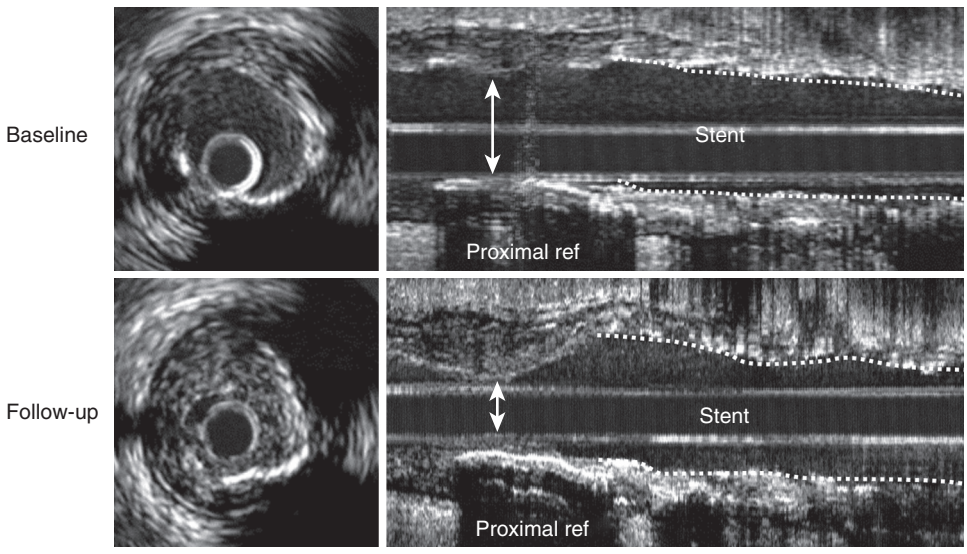

FIGURE 60-10 Proximal disease development 8 months after implantation of a drug-eluting stent. The new stenosis at the proximal stent margin was primarily caused by plaque proliferation despite minimal neointimal hyperplasia observed inside the stent *(lower images)*. Baseline intravascular ultrasound shows a significant residual plaque at the corresponding uncovered segment *(upper images)*.

is defined as inadequate expansion of a portion of the stent compared with the distal and proximal reference dimensions; this may occur, for example, where dense fibrous or calcified plaque is present. Incomplete stent apposition (ISA) or stent malapposition occurs when part of the stent structure is not fully in contact with the vessel wall; this is defined by IVUS as one or more struts clearly separated from the vessel wall with evidence of blood speckle behind the strut in a segment not associated with any side branches. Isolated ISA observed after deployment usually is not directly linked to adverse clinical events, provided that the lumen is large enough to preserve blood flow. On the other hand, significant ISA possibly increases local flow disturbances, delays healing or increases the potential risk for stent deformation at subsequent procedures. An early clinical study demonstrated an unexpectedly high percentage of these IVUS-detected stent deployment issues, even after angiographically successful results. These observations led to the concept of the high-pressure stent deployment technique used today.

After stent implantation, IVUS may reveal tears at the edge of the stent (or edge dissections) in 10% to 15% of the cases. These tears have been attributed both to shear forces created at the junction between the metal edge of the stent and the adjacent, more compliant tissue and to the effect of balloon expansion beyond the edge of the stent (the "dog-bone" phenomenon). Minor, non–flow-limiting edge dissections do not appear to have an impact on late angiographic in-stent restenosis (ISR).[54,55] In fact, when imaged at follow-up, 75% were healed—a frequency similar to that seen after balloon angioplasty.[56] In contrast, significant residual dissections can lead to an increased risk of early MACE. The practical strategy is to make a determination from the IVUS image as to whether the tear is flow-limiting. If this is the case, an additional stent is placed to cover this region. By angiography, the tears are typically recognized as haziness at the stent edge. However, when investigated by IVUS, angiographic hazy lesions can represent a spectrum of abnormal anatomic morphologies and periprocedural complications, such as calcium, dissection, thrombus, hematoma, spasm, and excessive residual plaque burden at the reference segment (see Fig. 60-8). The etiology of persistent haziness can be precisely defined by IVUS because it has higher sensitivity than contrast angiography for detecting abnormal entities in the vessel wall. In addition, IVUS can demonstrate the precise location and severity of these findings.

Optimization of Stent Expansion

There is compelling evidence that procedure-related factors are important contributors to the development of both restenosis and thrombosis after stent implantation, regardless of stent type. In particular, stent underexpansion represents the most consistent risk factor across clinical IVUS studies. In the bare-metal stent (BMS) era, the predicted risk for restenosis was reported to decrease 19% for every 1-mm^2 increase in minimum stent area (MSA).[57] IVUS studies of BMS thrombosis also reported extremely high incidences of stent underexpansion (52% to 78%) in patients with early (acute or subacute) stent thrombosis,[58,59] a result that was subsequently replicated in DES studies (42% to 85% in patients with early thrombosis).[48,51,60,61]

Several investigators have evaluated the predictive value of IVUS-determined MSA for ISR in various types of stents. With receiver-operating characteristic (ROC) analysis, the optimal diagnostic thresholds of MSA that best predict long-term stent patency were reported to be 5.0 to 5.7 mm^2 for DES and 6.4 to 6.5 mm^2 for BMS.[62-65] IVUS-determined MSA remains an independent predictor of restenosis (odds ratio (OR), 0.48 to 0.77), irrespective of DES type, including sirolimus-, paclitaxel-, zotarolimus-, and everolimus-eluting stents.[64,66]

In bifurcation lesions, inadequate postprocedural MSA and increased neointimal hyperplasia are the major mechanisms of restenosis in the side branch ostium. In a series of cases of unprotected LMCA disease treated with single- or two-stent strategies, the MSA cutoffs that best predicted subsequent restenosis were 5.0 mm^2 (ostial LCx), 6.3 mm^2 (ostial LAD), 7.2 mm^2 (within the polygon of confluence zone), and 8.2 mm^2 (LMCA).[67] Stent underexpansion was again identified as an independent predictor for MACE at 2 years (adjusted HR, 5.56; 95% CI, 1.99 to 15.49; $P = .001$), and the MACE-free survival rate was significantly lower in patients with underexpansion (observed at one or more segments) compared with no underexpansion ($90 \pm 3\%$ vs. $98 \pm 1\%$; log-rank $P = .001$).

Unlike BMS, the relative benefit of obtaining a larger MSA to ensure a greater "safety margin" for an unexpected amount of neointima (the "bigger is better" theory) can significantly vary among DES types, depending on the variability of subsequent neointimal proliferation. Also, given the wide variety of clinical backgrounds, patient risk factors, lesion morphologies, and disease complexities in clinical practice, it is unlikely that a single prespecified MSA end point could be effectively applied to all target lesions. Nevertheless, the ability of IVUS to assess the results of stent implantation more precisely than angiography significantly contributes to enhanced clinical judgment for individual patients. The utility of IVUS to ensure adequate stent expansion cannot be overemphasized, particularly if there are clinical risk factors for DES failure (e.g., diabetes, renal failure).

Guidance for Complex Interventions

IVUS is useful in several aspects during complex interventions such as PCI on distal LMCA lesions, as discussed previously, and CTO lesions. In lesions with abrupt-type occlusion, the entry point at the CTO ostium is often difficult to identify by angiography. If there is a side branch located near the entrance of the CTO, the IVUS catheter can be inserted into the side branch to examine the target for wire penetration.[68] Also, the IVUS catheter may possibly be inserted into the subintimal space to determine the direction of the true lumen. A true lumen is surrounded by all three layers of the vessel (i.e., intima, media, and adventitia). Side branches may provide another clue: They should communicate with the true but not with the false lumen. However, insertion of the IVUS catheter into the subintimal space carries the potential risk of enlarging the subintimal space.

In PCI on CTO lesions, the solid-state catheter is often preferred, because the distance of its transducer from the catheter tip is shorter than that of mechanical systems (10 versus 20 to 33 mm, respectively). For this type of application, a shorter-tip solid-state catheter (2.5 mm tip-to-imaging distance) is also available (Eagle Eye Platinum ST, Volcano). The longer monorail design of solid-state catheters may also offer better trackability and less frequent catheter trapping, which can occasionally be caused by separation of the IVUS catheter and guidewire within the complex lesion anatomy. Finally, as with other interventional procedures, proper balloon and stent sizes as well as acute complications can accurately be evaluated by IVUS. Particularly, intramural or extramural hematoma (or perforation) can occur during the CTO procedure. Early detection and precise assessment of these conditions are crucial for safe and effective treatment of CTO lesions.

Stent Problems at Follow-Up

Restenotic Lesions

The primary mechanism of restenosis can be accurately identified by IVUS, and it significantly affects the treatment strategy in patients with restenotic lesions. In nonstent interventions, the majority of late lumen loss was caused by negative arterial remodeling (a decrease in EEM-CSA); only about a quarter of the late loss is caused by tissue proliferation. In contrast, late loss in stented lesions is primarily caused by neointimal proliferation rather than by chronic stent recoil. However, initial stent underexpansion can result in clinically significant lumen compromise, even with minimal neointimal hyperplasia (Fig. 60-11). An IVUS study of ISR lesions after BMS demonstrated that 20% of lesions had an MSA of less than 5.0 mm^2, and an additional 4.5% had other mechanical problems that contributed to restenosis.[69] In most of these cases, stent underexpansion or other mechanical problems were not suspected angiographically at the time of reintervention. An IVUS

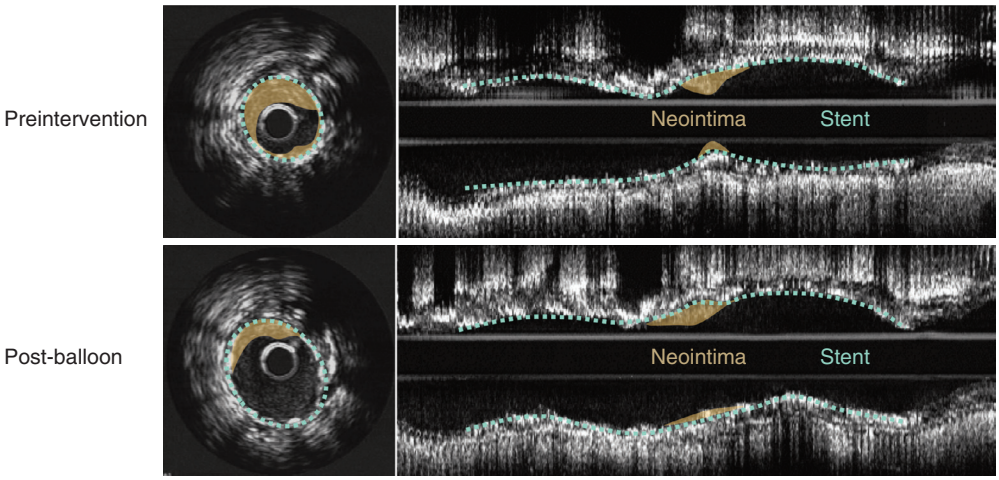

FIGURE 60-11 Drug-eluting stent (DES) restenosis results primarily from stent underexpansion. Preinterventional intravascular ultrasound (*upper images*) reveals significant stent underexpansion at the midsegment with only a small amount of focal neointimal hyperplasia. This type of in-stent restenosis can be successfully treated with mechanical optimization by balloon dilation *(lower images)* and may not require additional DES implantation within the original restenotic stent.

study of DES restenosis also reported that 21% of ISR lesions had an MSA of less than 5.0 mm^2 at the MLA site, 38% of which were not associated with significant neointimal hyperplasia.[70] For this type of ISR, mechanical optimization is the first priority, and IVUS can be helpful to differentiate mechanical issues from exaggerated neointimal proliferation that may truly require DES implantation within the original restenotic stent.

For DES treatment of ISR, early clinical studies suggested a hypothesis that full DES coverage of the original stent might be important for the prevention of recurrent restenosis. However, this aggressive optimization strategy has been associated with several clinical issues and may not be feasible in every case. In a retrospective IVUS study of BMS restenosis treated with sirolimus-eluting stents, 77% of the uncovered BMS segments maintained adequate lumen patency at follow-up.[71] Therefore as long as the original BMS is well expanded and has a segment with sufficient lumen area, conservative coverage with DES can be a clinical option (the "spot stenting" strategy). Another study from the TAXUS (Boston Scientific) stent trials evaluated follow-up IVUS results in patients who did not require revascularization at 9 months.[72] At 3 years, revascularization was required in 4.9% of paclitaxel-eluting stents and 6.7% of BMS. Multivariate analysis identified MLA at 9 months as a significant predictor of later revascularization for both stent types. Several investigators have used advanced tissue characterization techniques of IVUS to assess atherosclerotic changes of in-stent neointima (so-called neoatherosclerosis), although the validity of this application and its clinical implications are yet to be established.

Late-Acquired Incomplete Stent Apposition

With serial IVUS performed immediately after the procedure and at follow-up, ISA can be classified as baseline or late-acquired (Fig. 60-12). At follow-up, baseline ISA may have resolved or may persist; therefore ISA observed at follow-up could be either persistent baseline ISA (persistent ISA) or newly developed ISA in a segment in which struts were completely apposed to the vessel wall at baseline (late-acquired ISA, or LISA).

Despite optimal angiographic results with high-pressure balloon dilation baseline ISA can be observed with IVUS in 8% to 30% of DES recipients. This morphologic abnormality primarily results from selection of an undersized stent, stent underexpansion, or insufficient stent conformability in calcified or complex-shaped lesions (the so-called mechanical ISA).

LISA was first brought into the spotlight in intracoronary brachytherapy trials (9.3% average incidence by IVUS). However, subsequent IVUS studies revealed that it also occurs in up to 5% to 6% of balloon-expandable BMS recipients. In DES, the incidence of LISA varies significantly among different DES types and patient populations. In elective stenting, clinical trials of second-generation DES showed lower incidences of LISA, particularly in phosphorylcholine-coated zotarolimus-eluting stents (0.4% in the ENDEAVOR I to IV trials), compared with reports of 8% to 13% in patients treated with first-generation sirolimus- or paclitaxel-eluting stents.[73] Higher incidences were observed in more complex studies enrolling patients with acute MI or CTO and in those treated with atherectomy before stenting. A metaanalysis of seven randomized trials reported that the risk of LISA in patients with a DES was four times higher than in those with a BMS (OR, 4.36; 95% CI, 1.74 to 10.94; $P = .002$).[74]

LISA primarily results from structural vessel wall changes that occur during the follow-up period ("biologic ISA"), in contrast to "mechanical ISA" seen with initial stent deployment. The most commonly reported mechanisms for LISA are "dissolution of thrombus" present at the baseline, and "regional positive vessel remodeling" disproportional to peristent plaque area change.[75] Whereas thrombus dissolution can be seen in patients with any type of stent deployed for treatment of thrombus-containing lesions, abnormal positive vessel remodeling is observed more frequently in patients who received a DES or brachytherapy. With regard to vessel remodeling, incompletely apposed struts are seen primarily in eccentric plaques, and the gaps develop mainly on the disease-free side of the vessel wall.[76] The combination of mechanical injury at stent implantation and biologic injury by DES components may predispose the vessel wall to chronic, pathologic dilatation in the setting of little underlying plaque.[77]

Theoretically, long persistence of incompletely apposed DES struts might be associated with delayed reendothelialization, allowing fibrin and platelet deposition. A significant gap or aneurysm formation can also reduce local blood flow, promoting platelet adhesion and the coagulation cascade. However, it is still debatable whether LISA independently contributes to the occurrence of stent thrombosis. Most clinical trials have failed to show a prospective association between LISA and later thrombotic events, whereas multiple IVUS studies have demonstrated that LISA is frequently observed in lesions of late DES thrombosis. This discrepancy may represent a multifactorial process of late DES thrombosis involving several other factors or pathways. Most prospective studies were underpowered to detect a possible

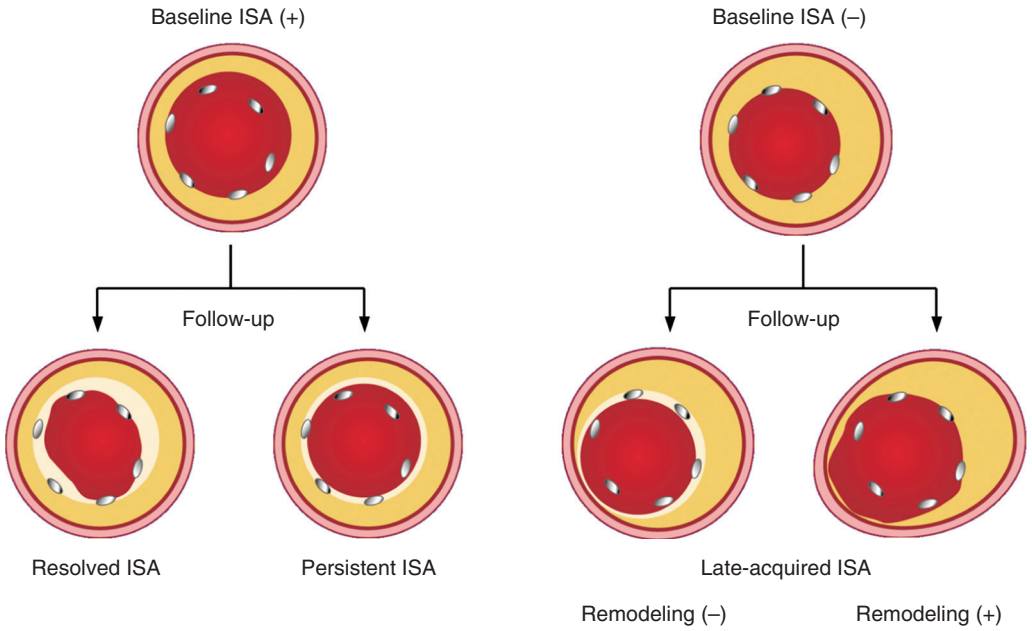

FIGURE 60-12 Classification of incomplete stent apposition (ISA). Baseline ISA can either resolve (resolved ISA) or remain (persistent ISA) at follow-up. Late-acquired ISA without vessel expansion is typically seen in thrombus-containing lesions, whereas late-acquired ISA with focal, positive vessel remodeling is more characteristic with brachytherapy and drug-eluting stents.

relationship of LISA with rare thrombotic events. A literature-based metaanalysis suggested a significantly higher risk of late or very late DES thrombosis in patients with late (persistent or late-acquired) ISA compared with those without LISA (OR, 6.51; $P = .02$).[74] However, careful interpretation is still required because of the inherent limitations of literature-based analyses of heterogeneous studies.

Another methodologic issue with respect to the clinical relevance of LISA is lack of appropriate grading or classification. Reported LISA is a spectrum ranging from tiny incomplete apposition to extensive aneurysm formation, and LISA associated with late thrombosis is often at the extreme end of this spectrum (Fig. 60-13). Finally, the late development of ISA may simply represent a pathologic process within the arterial wall, such as chronic inflammation with endothelial dysfunction weakening the vessel structure rather than serving as a direct cause of thrombosis.[77] To accurately identify LISA posing a risk for future events across the spectrum, a better understanding of this phenomenon is essential.

Strut Fracture

Stent strut fracture is not a rare phenomenon in peripheral artery stenting (it occurs in up to 65% of cases of femoropopliteal stenting and can also occur after DES implantation in coronary lesions. By angiography, strut fracture is diagnosed as complete or partial separation of the stent at follow-up where there had been contiguity of the stent at baseline. IVUS can directly visualize stent struts, offering more detailed morphologic assessment and classifications. By IVUS, strut fracture is defined as longitudinal strut discontinuity and can be categorized on the basis of its morphologic characteristics as strut separation, strut subluxation, or strut intussusception (Figs. 60-14 and 60-15).[73] Another recently proposed classification focuses on potential mechanisms of the strut fracture, categorizing them on the basis of the presence (type I) or absence (type II) of aneurysm at the fracture site.[78] Studies using angiography or IVUS have reported the incidence of DES fracture to be between 0.8% and 7.7%; ISR or stent thrombosis occurred in 22% to 88% of these cases.[73]

Theoretically, strut fracture of the DES can reduce the local drug dose delivered to the arterial wall, as well as affecting the mechanical scaffolding of the affected lesion segment. In addition, the irregular edge of the fractured strut may chronically stimulate the vessel wall during cardiac movement. Conversely, deployment of long and rigid stents in angulated lesions with hinge motion can lead to significant alteration of local physiology, so that the strut fracture may help restore the original dynamic state, at least in some cases. The exact incidence and clinical implications of strut fractures remain to be further investigated in large clinical studies.

Impact of Intravascular Ultrasound Guidance on Long-Term Outcomes

A number of studies have provided evidence for the long-term benefits of IVUS in both BMS and DES implantation (Tables 60-1 and 60-2). In the DES era, the clinical impact of IVUS guidance was assessed for complex lesions (e.g., unprotected LMCA, bifurcation, long lesions) and in unselected patient populations. The largest prospective multicenter registry (8582 patients) including unselected patients treated with second-generation DES was the Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents (ADAPT-DES),[79] in which IVUS guidance was significantly associated with lower incidences of definite or probable stent thrombosis (0.7% vs. 1.5%, $P = .002$), MI (3.5% vs. 5.6%, $P < .0001$), and ischemia-driven target-lesion revascularization (4.8% vs. 6.0%, $P = .02$) at 2 years.

On the other hand, controversial results were also reported in some IVUS-guided stent trials. This discrepancy may have resulted, in part, from underpowered study design, differing procedural end points for IVUS-guided stenting, or various adjunctive treatment strategies that were used in these trials in response to suboptimal IVUS findings. Overall, two metaanalyses of clinical BMS studies have demonstrated that IVUS-guided stenting significantly lowers long-term angiographic restenosis and target lesion or vessel revascularization, with a neutral effect on death and nonfatal MI compared with an angiographic optimization (Table 60-3).[80,81] More recently, four large metaanalyses of IVUS-guided DES studies also indicated that IVUS guidance can offer significantly lower rates of restenosis, mortality, MI, stent thrombosis, and MACE compared with angiographic guidance alone (see Table 60-3).[82-85]

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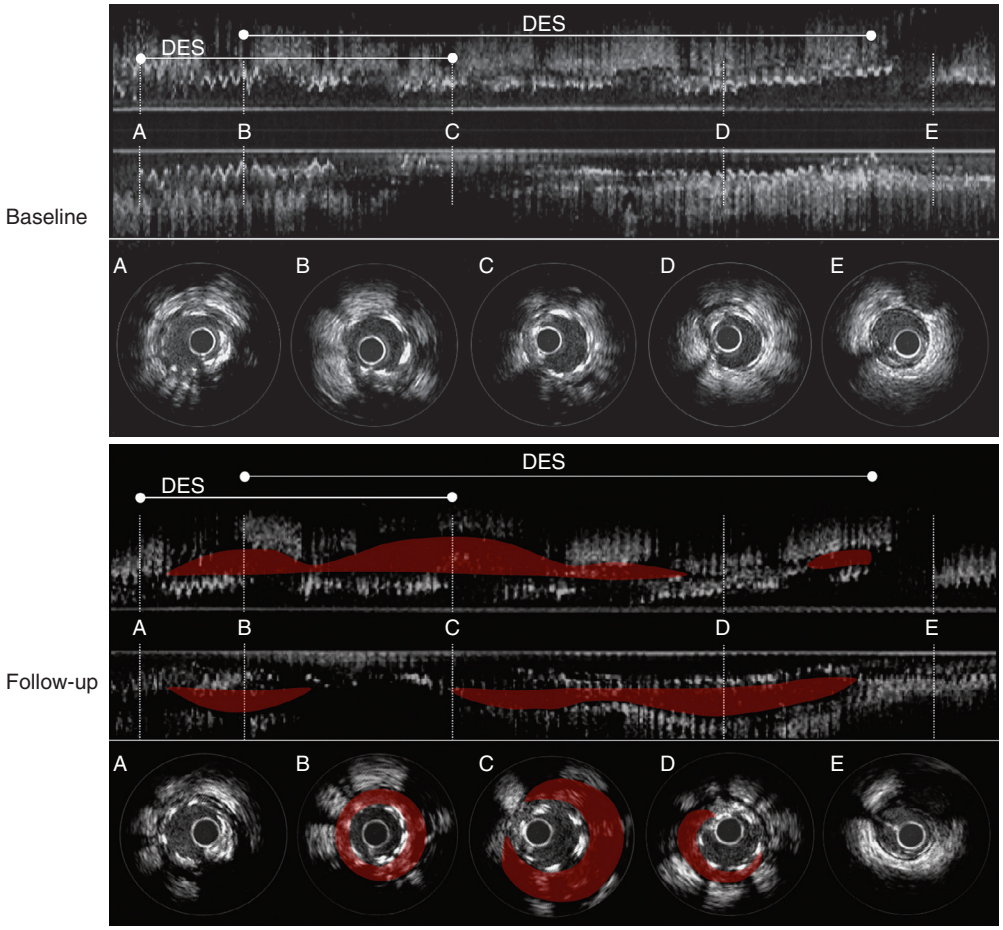

FIGURE 60-13 Extensive late-acquired incomplete stent apposition observed at follow-up *(lower images)* after implantation of two overlapping drug-eluting stents (DES). At follow-up, large gaps between the stent and the vessel wall (*red areas)* are detected throughout the stented segment, whereas the stent struts are well apposed to the vessel wall at baseline *(upper images)*.

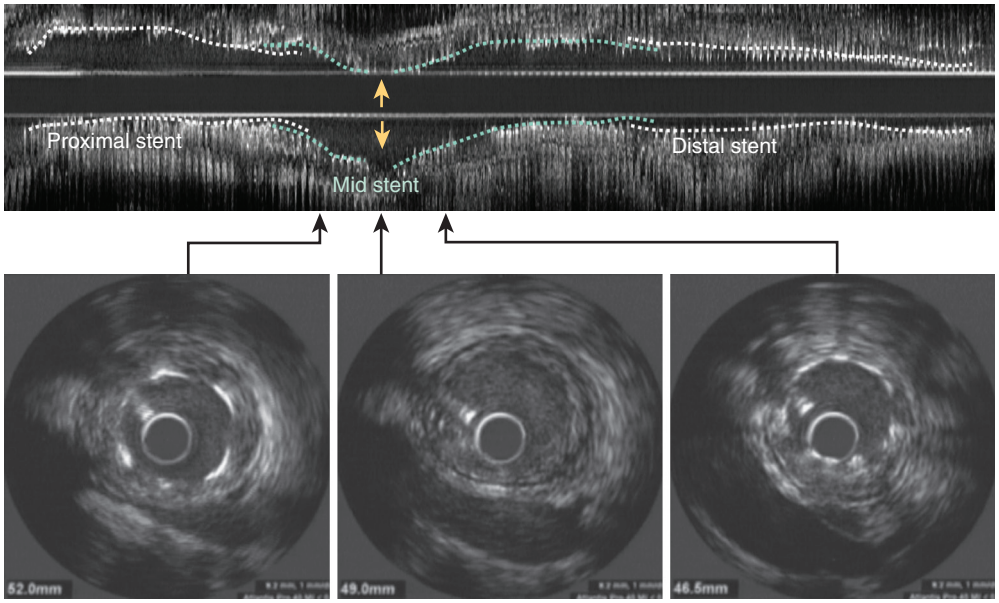

FIGURE 60-14 Stent strut discontinuity (fracture) observed 8 months after deployment of three overlapping drug-eluting stents. On the cross-sectional intravascular ultrasound (IVUS) image (*bottom row, middle image),* an abnormal paucity of stent struts, not seen at baseline, was detected at a portion of the mid-stent. The longitudinal IVUS image *(top)* shows an acute-angled bend at the corresponding segment (*arrows*). In this particular case, however, the stent fracture (complete separation type) was not associated with increased intimal hyperplasia.

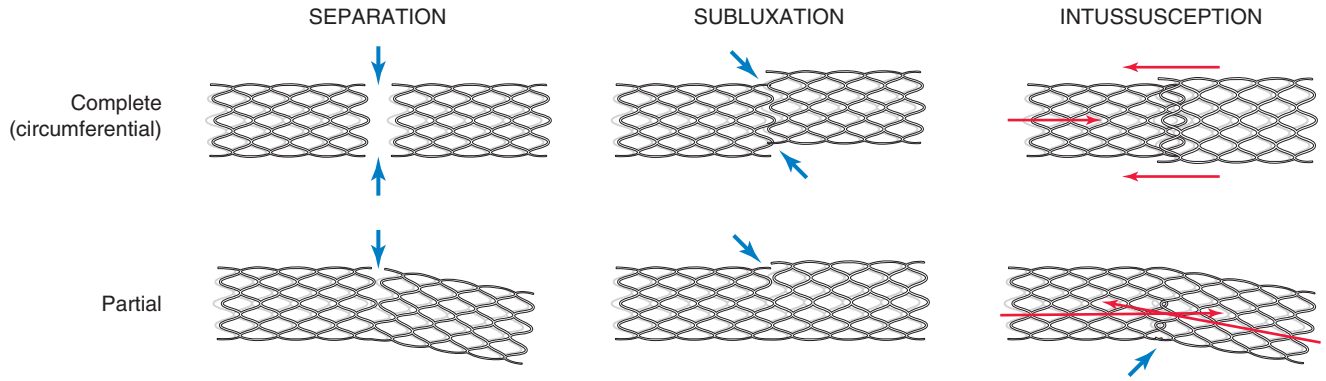

FIGURE 60-15 Stanford classification of stent strut fracture.[73] By intravascular ultrasound, strut fracture is defined as longitudinal strut discontinuity and can be categorized on the basis of its morphologic characteristics. *Blue* and *red arrows* represent stent fracture and resulting movement of the stent segments, respectively.

TABLE 60-1 Intravascular Ultrasound Versus Angiographic Guidance of Bare-Metal Stent Implantation

Study	*N*	Population	Study Design	IVUS Criteria for Optimal Deployment	Criteria Fulfilled (%)	End Points	Results
Albiero et al	312	De novo Native	Multicenter Registry	Complete apposition, no ref disease, MSA ≥60% of average ref VA (early phase) or MSA ≥ distal ref LA (late phase)	NA	6-mo angiography	IVUS better (early phase)
Blasini et al	212	De novo and restenotic Native and SVG	Single center Registry	Complete apposition, no residual dissection, MSA >8 mm^2 and/or 90% of average ref LA	50	6-mo angiography	IVUS better
Choi et al	278	De novo Native	Single center Registry	Complete apposition, no residual dissection, MSA ≥80% of distal ref LA	NA	Acute closure 6-mo MACE	IVUS better
Gaster et al	108	De novo and restenotic Native	Single center Randomized	MUSIC criteria	64	6-mo angiography, CFR, FFR, TVR, 2.5-yr MACE	IVUS better
AVID	759	De novo Native and SVG	Multicenter Randomized	MUSIC criteria	NA	12-mo TLR	IVUS better (subset analysis)
CENIC	54,526	De novo and restenotic Native and SVG	Multicenter Registry	Operator discretion	—	In-hospital MACE	IVUS better
CRUISE	499	De novo and restenotic Native	Multicenter Nonrandomized	Operator discretion	—	9-mo TVR	IVUS better
DIPOL	259	De novo Native	Multicenter Randomized	Complete apposition, MSA >7.5 mm^2 or 80% of average ref LA	>90	6-mo MACE	IVUS better
OPTICUS	550	De novo and restenotic Native	Multicenter Randomized	MUSIC criteria	56	6-mo angiography 12-mo MACE	No difference
PRESTO	9,070	De novo and restenotic Native	Multicenter Nonrandomized	Operator discretion	—	9-mo MACE	No difference
RESIST	155	De novo Native	Multicenter Randomized	MSA >80% of average ref LA	80	6-mo angiography 18-mo MACE	IVUS better (nonsignificant reduction)
SIPS	269	De novo and restenotic Native	Single center Randomized	MLA >65% of average ref LA	69	6-mo angiography 2-yr TLR	IVUS better
TULIP	144	Long lesions >20 mm	Single center Randomized	Complete apposition, MLD ≥80% of average ref diameter MSA ≥ distal ref LA	89	6-mo angiography 12-mo MACE	IVUS better

AVID, Angiography Versus IVUS-Directed Stent Placement trial; *CENIC,* Central Nacional de Intervenções Cardiovasculares; *CFR,* coronary flow reserve; *CRUISE,* Can Routine Ultrasound Influence Stent Expansion study; *DIPOL,* Direct Stenting Versus Optimal Angioplasty; *FFR,* fractional flow reserve; IVUS, intravascular ultrasound; *LA,* lumen area; *MACE,* major adverse cardiac events; *MLD,* minimal lumen diameter; *MSA,* minimum stent area; *MUSIC,* Multicenter Ultrasound-Guided Stent Implantation in Coronaries; *OPTICUS,* Optimization With ICUS to Reduce Stent Restenosis; *PRESTO,* Prevention of Restenosis With Tranilast and Its Outcomes trial; *ref,* reference vessel; *RESIST,* Restenosis After Intravascular Ultrasound Stenting; *SIPS,* Strategy for IVUS-Guided PTCA and Stenting; *SVG,* saphenous vein graft; *TLR,* target lesion revascularization; *TVR,* target vessel revascularization; *TULIP,* Thrombocyte Activity Evaluation and Effects of Ultrasound Guidance in Long Intracoronary Stent Placement; *VA,* vessel area.

TABLE 60-2 Intravascular Ultrasound Versus Angiographic Guidance of Drug-Eluting Stent Implantation

Study	*N*	Population	Study Design	IVUS Criteria for Optimal Deployment	Criteria Fulfilled (%)	End Points	Results
Agostoni et al	58	De novo Left main	Single center Registry	Operator discretion	—	14-mo MACE	No difference
Chen et al	628	De novo Left main	Multicenter Registry	Operator discretion	—	1-yr MACE, stent thrombosis, MI	No difference (MACE) IVUS better (stent thrombosis, MI)
Costantini et al	1350	De novo and restenotic Native	Single center Registry	Operator discretion	—	3-yr MACE stent thrombosis	IVUS better
Fujimoto et al	480	De novo Native and SVG	Single center Registry	Operator discretion	—	8-mo angiography, MACE, TLR	No difference
Hur et al	8371	De novo and restenotic Native and SVG	Multicenter Registry	Operator discretion	—	3-yr death	IVUS better
Jakabčin et al	210	De novo Native Complex lesions	Single center Randomized	Good apposition, optimal stent expansion with MSA of 5 mm^2 or >90% of distal ref LA for small vessel, and no edge dissection	NA	18-mo MACE	No difference
Kim et al	758	De novo Native Bifurcation (BMS + DES)	Single center Registry	Operator discretion	—	4-yr MACE, stent thrombosis	IVUS better
Roy et al	1768	De novo and restenotic Native and SVG	Single center Registry	Operator discretion	—	30-day and 12-mo MACE, stent thrombosis	IVUS better
Youn et al	341	De novo Native, STEMI	Single center Registry	Operator discretion	—	3-yr death, MI, TVR, TLR	No difference
ADAPT-DES	8582	De novo and restenotic Native and SVG	Multicenter Registry	Operator discretion	—	2-yr stent thrombosis, MI	IVUS better
AVIO	284	De novo Native	Multicenter Randomized	SA > "AOR" determined by the size of an optimal postdilation balloon based on media-to-media diameter measurements	48	Postprocedure MLD 9-mo MACE	IVUS better (postprocedure MLD)
COBIS	487	De novo Native Bifurcation	Multicenter Registry	Operator discretion	—	1-yr death or MI	IVUS better
EXCELLENT	1421	De novo Native	Multicenter Nonrandomized	Operator discretion	—	1-yr MACE, stent thrombosis, MI	Angiography better
IRIS-DES	3244	De novo Native	Multicenter Registry	Operator discretion	—	2-yr MACE	IVUS better (in patients with a stent length >22 mm)
MAIN-COMPARE	975	De novo Native Left main (BMS + DES)	Multicenter Registry	Operator discretion	—	3-yr mortality	IVUS better
MATRIX	1504	De novo and restenotic Native and SVG	Multicenter Registry	Operator discretion	—	2-yr TVF, MACE, stent thrombosis	IVUS better
RESET	543	De novo Native Long lesions requiring a stent ≥28 mm	Multicenter Randomized	Operator discretion	—	1-yr MACE	IVUS better (per protocol)

ADAPT-DES, Assessment of Dual AntiPlatelet Therapy With Drug-Eluting Stents; *AOR,* achievable optimal result; *AVIO,* Angiography Versus IVUS Optimization; *COBIS,* Korean Bifurcation Registry; *CSA,* cross-sectional area; *EXCELLENT,* Efficacy of Xience/Promus Versus Cypher in Reducing Late Loss After Stenting; *IRIS-DES,* Interventional Cardiology Research In-cooperation Society–Drug-Eluting Stents; *IVUS,* intravascular ultrasound; *LA,* lumen area; *MACE,* major adverse cardiac events; *MAIN-COMPARE,* Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization; *MATRIX,* Comprehensive Assessment of Sirolimus-Eluting Stents in Complex Lesions; *MI,* myocardial infarction; *MLD,* minimum lumen diameter; *MSA,* minimum stent area; *NA,* not applicable; *ref,* reference vessel; *RESET,* Real Safety and Efficacy of a 3-Month Dual Antiplatelet Therapy Following Zotarolimus-Eluting Stents Implantation; *SA,* stent area; *STEMI,* ST-segment elevation myocardial infarction; *SVG,* saphenous vein graft; *TLR,* target lesion revascularization; *TVF,* target vessel failure; *TVR,* target vessel revascularization.

TABLE 60-3 Intravascular Ultrasound Versus Angiographic Guidance of Stent Implantation: Metaanalyses

	Stent Type	No. of Patients	Studies (RCT)	OUTCOMES IMPROVED BY IVUS GUIDANCE		
				Outcome	OR	*P*
Casella et al	BMS	2,972	9 (5)	MACE	0.79	.03
				Binary restenosis	0.75	.01
				Revascularization	0.62	.00003
Parise et al	BMS	2193	7 (7)	MACE	0.69	.03
				Binary restenosis	0.64	.02
				Revascularization	0.66	.004
Ahn et al	DES	26,503	17 (3)	MACE	0.74	<.001
				Mortality	0.61	<.001
				Myocardial infarction	0.57	<.001
				Stent thrombosis	0.59	<.001
				TVR	0.82	.022
Jang et al	DES	24,849	15 (3)	MACE	0.79	.001
				Mortality	0.64	<.001
				Myocardial infarction	0.57	<.001
				Stent thrombosis	0.59	.002
				TVR	0.81	.01
Jang et al Propensity score matched subanalysis	DES	13,545	9	MACE	0.79	.01
				Mortality	0.58	.01
				Myocardial infarction	0.56	.04
				Stent thrombosis	0.52	.004
Klersy et al	DES	18,707	12 (3)	MACE	0.80	<.001
				Mortality	0.60	<.001
				Myocardial infarction	0.59	.001
				Stent thrombosis	0.58	.007
Zhang et al	DES	19,619	11 (1)	MACE	0.87	.008
				Mortality	0.59	<.001
				Stent thrombosis	0.58	<.0001
Zhang et al Propensity score matched subanalysis	DES	5,300	6	Mortality	0.73	.04
				Myocardial infarction	0.63	.01
				Stent thrombosis	0.57	.004

BMS, Bare-metal stents; *DES,* drug-eluting stents; *RCT,* randomized controlled trial; IVUS, intravascular ultrasound; *MACE,* major adverse cardiac events; *OR,* odds ratio; *TVR,* target vessel revascularization.

In comparison with the BMS studies, most of the reported DES studies were registries (rather than randomized control trials), in which IVUS-guided stent optimization was performed based on the individual operator's discretion. In contrast, the majority of the BMS trials used prespecified IVUS criteria for optimal stent expansion. It is also noteworthy that IVUS guidance appears to contribute to reduced hard end points (death, MI, or thrombotic events) in DES implantation, whereas improved restenosis and revascularization rates represent predominant benefits of IVUS-guided BMS implantation.

SUMMARY AND FUTURE PERSPECTIVES

IVUS has evolved into an indispensable tool for research and clinical purposes with mounting evidence supported by large-scale clinical trials. Although advances in intravascular optical coherence tomography now allow rapid assessment of microscopic details of coronary surface structures, the demand for IVUS remains high because of its ability to provide a more complete picture of the vessel wall due to the greater tissue penetration of the ultrasound signal and its practical usefulness (i.e., no need for blood clearance) for real-time procedural guidance and assessment of treatment effects.

Current technical efforts in invasive imaging are aimed not only at further improvement in anatomic information acquisition but also at biologic or physiologic assessment of the target segment. These enhancements may allow a more comprehensive evaluation of the novel treatment device with both mechanical and biologic effects and could help realize the ultimate goal of delivering the most effective treatment to individual patients with truly low rates of complications.

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REFERENCES

1. Bom N, Lancee CT, Van Egmond FC: An ultrasonic intracardiac scanner. *Ultrasonics* 10:72–76, 1972.
2. Yock P, Linker D, Saether O, et al: Intravascular two-dimensional catheter ultrasound: initial clinical studies (abstract). *Circulation* 78(Suppl II):II–21, 1988.
3. Guedes A, Keller PF, L'Allier PL, et al: Long-term safety of intravascular ultrasound in nontransplant, nonintervened, atherosclerotic coronary arteries. *J Am Coll Cardiol* 45(4):559–564, 2005.
4. Ramasubbu K, Schoenhagen P, Balghith MA, et al: Repeated intravascular ultrasound imaging in cardiac transplant recipients does not accelerate transplant coronary artery diseasec. *J Am Coll Cardiol* 41(10):1739–1743, 2003.
5. Fitzgerald PJ, Yock C, Yock PG: Orientation of intracoronary ultrasonography: looking beyond the artery. *J Am Soc Echocardiogr* 11(1):13–19, 1998.

5a. Mintz GS, Nissen SE, Anderson WD, et al: American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS): a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 37(5):1478–1492, 2001.

6. Hibi K, Ward MR, Honda Y, et al: Impact of different definitions on the interpretation of coronary remodeling determined by intravascular ultrasound. *Catheter Cardiovasc Interv* 65(2):233–239, 2005.
7. Honda Y, Fitzgerald PJ: Frontiers in intravascular imaging technologies. *Circulation* 117(15):2024–2037, 2008.
8. Gardner CM, Tan H, Hull EL, et al: Detection of lipid core coronary plaques in autopsy specimens with a novel catheter-based near-infrared spectroscopy system. *JACC Cardiovasc Imaging* 1(5):638–648, 2008.
9. Waxman S, Dixon SR, L'Allier P, et al: In vivo validation of a catheter-based near-infrared spectroscopy system for detection of lipid core coronary plaques: initial results of the SPECTACL study. *JACC Cardiovasc Imaging* 2(7):858–868, 2009.
10. Tian J, Ren X, Vergallo R, et al: Distinct morphological features of ruptured culprit plaque for acute coronary events compared to those with silent rupture and thin-cap fibroatheroma: a combined optical coherence tomography and intravascular ultrasound study. *J Am Coll Cardiol* 63(21):2209–2216, 2014.
11. Yamada R, Okura H, Kume T, et al: Relationship between arterial and fibrous cap remodeling: a serial three-vessel intravascular ultrasound and optical coherence tomography study. *Circ Cardiovasc Interv* 3(5):484–490, 2010.
12. Stone GW, Maehara A, Lansky AJ, et al: A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 364(3):226–235, 2011.
13. Calvert PA, Obaid DR, O'Sullivan M, et al: Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) Study. *JACC Cardiovasc Imaging* 4(8):894–901, 2011.
14. Cheng JM, Garcia-Garcia HM, de Boer SP, et al: In vivo detection of high-risk coronary plaques by radiofrequency intravascular ultrasound and cardiovascular outcome: results of the ATHEROREMO-IVUS study. *Eur Heart J* 35(10):639–647, 2014.
15. Madder RD, Smith JL, Dixon SR, Goldstein JA: Composition of target lesions by near-infrared spectroscopy in patients with acute coronary syndrome versus stable angina. *Circ Cardiovasc Interv* 5(1):55–61, 2012.
16. Madder RD, Goldstein JA, Madden SP, et al: Detection by near-infrared spectroscopy of large lipid core plaques at culprit sites in patients with acute ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv* 6(8):838–846, 2013.
17. Choi BJ, Prasad A, Gulati R, et al: Coronary endothelial dysfunction in patients with early coronary artery disease is associated with the increase in intravascular lipid core plaque. *Eur Heart J* 34(27):2047–2054, 2013.
18. Barter PJ, Caulfield M, Eriksson M, et al: Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 357(21):2109–2122, 2007.
19. Cannon CP, Braunwald E, McCabe CH, et al: Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 350(15):1495–1504, 2004.
20. Nissen SE, Tardif JC, Nicholls SJ, et al: Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med* 356(13):1304–1316, 2007.
21. von Birgelen C, Hartmann M, Mintz GS, et al: Relationship between cardiovascular risk as predicted by established risk scores versus plaque progression as measured by serial intravascular ultrasound in left main coronary arteries. *Circulation* 110(12):1579–1585, 2004.
22. Kawasaki M, Sano K, Okubo M, et al: Volumetric quantitative analysis of tissue characteristics of coronary plaques after statin therapy using three-dimensional integrated backscatter intravascular ultrasound. *J Am Coll Cardiol* 45(12):1946–1953, 2005.
23. Serruys PW, Garcia-Garcia HM, Buszman P, et al: Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque. *Circulation* 118(11):1172–1182, 2008.
24. Kini AS, Baber U, Kovacic JC, et al: Changes in plaque lipid content after short-term intensive versus standard statin therapy: the YELLOW trial (reduction in yellow plaque by aggressive lipid-lowering therapy). *J Am Coll Cardiol* 62(1):21–29, 2013.
25. Tsujita K, Maehara A, Mintz GS, et al: Comparison of angiographic and intravascular ultrasonic detection of myocardial bridging of the left anterior descending coronary artery. *Am J Cardiol* 102(12):1608–1613, 2008.
26. Yamada R, Turcott RG, Connolly AJ, et al: Histological characteristics of myocardial bridge with an ultrasonic echolucent band: comparison between intravascular ultrasound and histology. *Circ J* 78(2):502–504, 2014.
27. Sano K, Mintz GS, Carlier SG, et al: Assessing intermediate left main coronary lesions using intravascular ultrasound. *Am Heart J* 154(5):983–988, 2007.
28. Abizaid AS, Mintz GS, Mehran R, et al: Long-term follow-up after percutaneous transluminal coronary angioplasty was not performed based on intravascular ultrasound findings: importance of lumen dimensions. *Circulation* 100(3):256–261, 1999.
29. Kang SJ, Lee JY, Ahn JM, et al: Validation of intravascular ultrasound-derived parameters with fractional flow reserve for assessment of coronary stenosis severity. *Circ Cardiovasc Interv* 4(1):65–71, 2011.
30. Koo BK, Yang HM, Doh JH, et al: Optimal intravascular ultrasound criteria and their accuracy for defining the functional significance of intermediate coronary stenoses of different locations. *JACC Cardiovasc Interv* 4(7):803–811, 2011.
31. Waksman R, Legutko J, Singh J, et al: FIRST: Fractional Flow Reserve and Intravascular Ultrasound Relationship Study. *J Am Coll Cardiol* 61(9):917–923, 2013.
32. Nascimento BR, de Sousa MR, Koo BK, et al: Diagnostic accuracy of intravascular ultrasound-derived minimal lumen area compared with fractional flow reserve—meta-analysis: pooled accuracy of IVUS luminal area versus FFR. *Catheter Cardiovasc Interv* 84(3):377–385, 2014.
33. Kang SJ, Lee JY, Ahn JM, et al: Intravascular ultrasound-derived predictors for fractional flow reserve in intermediate left main disease. *JACC Cardiovasc Interv* 4(11):1168–1174, 2011.
34. Jasti V, Ivan E, Yalamanchili V, et al: Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. *Circulation* 110(18):2831–2836, 2004.
35. Park SJ, Ahn JM, Kang SJ, et al: Intravascular ultrasound-derived minimal lumen area criteria for functionally significant left main coronary artery stenosis. *JACC Cardiovasc Interv* 7(8):868–874, 2014.
36. de la Torre Hernandez JM, Hernandez Hernandez F, Alfonso F, et al: Prospective application of pre-defined intravascular ultrasound criteria for assessment of intermediate left main coronary artery lesions results from the multicenter LITRO study. *J Am Coll Cardiol* 58(4):351–358, 2011.
37. Fassa AA, Wagatsuma K, Higano ST, et al: Intravascular ultrasound-guided treatment for angiographically indeterminate left main coronary artery disease: a long-term follow-up study. *J Am Coll Cardiol* 45(2):204–211, 2005.
38. Abizaid AS, Mintz GS, Abizaid A, et al: One-year follow-up after intravascular ultrasound assessment of moderate left main coronary artery disease in patients with ambiguous angiograms. *J Am Coll Cardiol* 34(3):707–715, 1999.
39. Okabe T, Mintz GS, Lee SY, et al: Five-year outcomes of moderate or ambiguous left main coronary artery disease and the intravascular ultrasound predictors of events. *J Invasive Cardiol* 20(12):635–639, 2008.
40. Okura H, Taguchi H, Kubo T, et al: Atherosclerotic plaque with ultrasonic attenuation affects coronary reflow and infarct size in patients with acute coronary syndrome: an intravascular ultrasound study. *Circ J* 71(5):648–653, 2007.
41. Goldstein JA, Maini B, Dixon SR, et al: Detection of lipid-core plaques by intracoronary near-infrared spectroscopy identifies high risk of periprocedural myocardial infarction. *Circ Cardiovasc Interv* 4(5):429–437, 2011.
42. Hong YJ, Jeong MH, Choi YH, et al: Impact of plaque components on no-reflow phenomenon after stent deployment in patients with acute coronary syndrome: a virtual histology-intravascular ultrasound analysis. *Eur Heart J* 32(16):2059–2066, 2009.
43. Kawamoto T, Okura H, Koyama Y, et al: The relationship between coronary plaque characteristics and small embolic particles during coronary stent implantation. *J Am Coll Cardiol* 50(17):1635–1640, 2007.
44. Schultz CJ, Serruys PW, van der Ent M, et al: First-in-man clinical use of combined near-infrared spectroscopy and intravascular ultrasound: a potential key to predict distal embolization and no-reflow? *J Am Coll Cardiol* 56(4):314, 2010.
45. Uetani T, Amano T, Ando H, et al: The correlation between lipid volume in the target lesion, measured by integrated backscatter intravascular ultrasound, and post-procedural myocardial infarction in patients with elective stent implantation. *Eur Heart J* 29(14):1714–1720, 2008.
46. Wu X, Maehara A, Mintz GS, et al: Virtual histology intravascular ultrasound analysis of non-culprit attenuated plaques detected by grayscale intravascular ultrasound in patients with acute coronary syndromes. *Am J Cardiol* 105(1):48–53, 2010.
47. Brilakis ES, Abdel-Karim AR, Papayannis AC, et al: Embolic protection device utilization during stenting of native coronary artery lesions with large lipid core plaques as detected by near-infrared spectroscopy. *Catheter Cardiovasc Interv* 80(7):1157–1162, 2012.
48. Fujii K, Carlier SG, Mintz GS, et al: Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol* 45(7):995–998, 2005.
49. Sakurai R, Ako J, Morino Y, et al: Predictors of edge stenosis following sirolimus-eluting stent deployment (a quantitative intravascular ultrasound analysis from the SIRIUS trial). *Am J Cardiol* 96(9):1251–1253, 2005.
50. Kang SJ, Cho YR, Park GM, et al: Intravascular ultrasound predictors for edge restenosis after newer generation drug-eluting stent implantation. *Am J Cardiol* 111(10):1408–1414, 2013.
51. Liu X, Doi H, Maehara A, et al: A volumetric intravascular ultrasound comparison of early drug-eluting stent thrombosis versus restenosis. *JACC Cardiovasc Interv* 2(5):428–434, 2009.
52. Costa MA, Angiolillo DJ, Tannenbaum M, et al: Impact of stent deployment procedural factors on long-term effectiveness and safety of sirolimus-eluting stents (final results of the multicenter prospective STLLR trial). *Am J Cardiol* 101(12):1704–1711, 2008.
53. Morino Y, Tamiya S, Masuda N, et al: Intravascular ultrasound criteria for determination of optimal longitudinal positioning of sirolimus-eluting stents. *Circ J* 74(8):1609–1616, 2010.
54. Hong MK, Park SW, Lee NH, et al: Long-term outcomes of minor dissection at the edge of stents detected with intravascular ultrasound (abstract 799). *Am J Cardiol* 86(7):791–795, 2000.
55. Nishida T, Colombo A, Briguori C, et al: Outcome of nonobstructive residual dissections detected by intravascular ultrasound following percutaneous coronary intervention. *Am J Cardiol* 89(11):1257–1262, 2002.
56. Sheris SJ, Canos MR, Weissman NJ: Natural history of intravascular ultrasound-detected edge dissections from coronary stent deployment. *Am Heart J* 139(1 Pt 1):59–63, 2000.
57. Kasaoka S, Tobis JM, Akiyama T, et al: Angiographic and intravascular ultrasound predictors of in-stent restenosis. *J Am Coll Cardiol* 32(6):1630–1635, 1998.
58. Cheneau E, Leborgne L, Mintz GS, et al: Predictors of subacute stent thrombosis: results of a systematic intravascular ultrasound study. *Circulation* 108(1):43–47, 2003.
59. Uren NG, Schwarzacher SP, Metz JA, et al: Predictors and outcomes on stent thrombosis: an intravascular ultrasound registry. *Eur Heart J* 23(2):124–132, 2001.
60. Choi SY, Witzenbichler B, Maehara A, et al: Intravascular ultrasound findings of early stent thrombosis after primary percutaneous intervention in acute myocardial infarction: a Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) substudy. *Circ Cardiovasc Interv* 4(3):239–247, 2011.
61. Okabe T, Mintz GS, Buch AN, et al: Intravascular ultrasound parameters associated with stent thrombosis after drug-eluting stent deployment. *Am J Cardiol* 100(4):615–620, 2007.
62. Sonoda S, Morino Y, Ako J, et al: Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the sirius trial. *J Am Coll Cardiol* 43(11):1959–1963, 2004.
63. Morino Y, Honda Y, Okura H, et al: An optimal diagnostic threshold for minimal stent area to predict target lesion revascularization following stent implantation in native coronary lesions. *Am J Cardiol* 88(3):301–303, 2001.
64. Doi H, Maehara A, Mintz GS, et al: Impact of post-intervention minimal stent area on 9-month follow-up patency of paclitaxel-eluting stents: an integrated intravascular ultrasound analysis from the TAXUS IV, V, and VI and TAXUS ATLAS Workhorse, Long Lesion, and Direct Stent Trials. *JACC Cardiovasc Interv* 2(12):1269–1275, 2009.
65. Hong MK, Mintz GS, Lee CW, et al: Intravascular ultrasound predictors of angiographic restenosis after sirolimus-eluting stent implantation. *Eur Heart J* 27(11):1305–1310, 2006.
66. Song HG, Kang SJ, Ahn JM, et al: Intravascular ultrasound assessment of optimal stent area to prevent in-stent restenosis after zotarolimus-, everolimus-, and sirolimus-eluting stent implantation. *Catheter Cardiovasc Interv* 83(6):873–878, 2014.
67. Kang SJ, Ahn JM, Song H, et al: Comprehensive intravascular ultrasound assessment of stent area and its impact on restenosis and adverse cardiac events in 403 patients with unprotected left main disease. *Circ Cardiovasc Interv* 4(6):562–569, 2011.
68. Sumitsuji S, Inoue K, Ochiai M, et al: Fundamental wire technique and current standard strategy of percutaneous intervention for chronic total occlusion with histopathological insights. *JACC Cardiovasc Interv* 4(9):941–951, 2011.
69. Castagna MT, Mintz GS, Leiboff BO, et al: The contribution of "mechanical" problems to in-stent restenosis: an intravascular ultrasonographic analysis of 1090 consecutive in-stent restenosis lesions. *Am Heart J* 142(6):970–974, 2001.
70. Kang SJ, Mintz GS, Park DW, et al: Mechanisms of in-stent restenosis after drug-eluting stent implantation: intravascular ultrasound analysis. *Circ Cardiovasc Interv* 4(1):9–14, 2011.
71. Sakurai R, Ako J, Hassan AH, et al: Neointimal progression and luminal narrowing in sirolimus-eluting stent treatment for bare metal in-stent restenosis: a quantitative intravascular ultrasound analysis. *Am Heart J* 154(2):361–365, 2007.
72. Doi H, Maehara A, Mintz GS, et al: Impact of in-stent minimal lumen area at 9 months poststent implantation on 3-year target lesion revascularization-free survival: a serial intravascular

ultrasound analysis from the TAXUS IV, V, and VI trials. *Circ Cardiovasc Interv* 1(2):111–118, 2008.
73. Honda Y: Drug-eluting stents. Insights from invasive imaging technologies. *Circ J* 73(8):1371–1380, 2009.
74. Hassan AK, Bergheanu SC, Stijnen T, et al: Late stent malapposition risk is higher after drug-eluting stent compared with bare-metal stent implantation and associates with late stent thrombosis. *Eur Heart J* 31(10):1172–1180, 2009.
75. Hur SH, Ako J, Honda Y, et al: Late-acquired incomplete stent apposition: morphologic characterization. *Cardiovasc Revasc Med* 10(4):236–246, 2009.
76. Ako J, Morino Y, Honda Y, et al: Late incomplete stent apposition after sirolimus-eluting stent implantation: a serial intravascular ultrasound analysis. *J Am Coll Cardiol* 46(6):1002–1005, 2005.
77. Cook S, Ladich E, Nakazawa G, et al: Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation* 120(5):391–399, 2009.
78. Doi H, Maehara A, Mintz GS, et al: Classification and potential mechanisms of intravascular ultrasound patterns of stent fracture. *Am J Cardiol* 103(6):818–823, 2009.
79. Witzenbichler B, Maehara A, Weisz G, et al: Relationship between intravascular ultrasound guidance and clinical outcomes after drug-eluting stents: the assessment of dual antiplatelet therapy with drug-eluting stents (ADAPT-DES) study. *Circulation* 129(4):463–470, 2014.
80. Casella G, Klauss V, Ottani F, et al: Impact of intravascular ultrasound-guided stenting on long-term clinical outcome: a meta-analysis of available studies comparing intravascular ultrasound-guided and angiographically guided stenting. *Catheter Cardiovasc Interv* 59(3):314–321, 2003.
81. Parise H, Maehara A, Stone GW, et al: Meta-analysis of randomized studies comparing intravascular ultrasound versus angiographic guidance of percutaneous coronary intervention in pre-drug-eluting stent era. *Am J Cardiol* 107(3):374–382, 2011.
82. Ahn JM, Kang SJ, Yoon SH, et al: Meta-analysis of outcomes after intravascular ultrasound-guided versus angiography-guided drug-eluting stent implantation in 26,503 patients enrolled in three randomized trials and 14 observational studies. *Am J Cardiol* 113(8):1338–1347, 2014.
83. Jang JS, Jin HY, Seo JS, et al: Meta-analysis of plaque composition by intravascular ultrasound and its relation to distal embolization after percutaneous coronary intervention. *Am J Cardiol* 111(7): 968–972, 2013.
84. Klersy C, Ferlini M, Raisaro A, et al: Use of IVUS guided coronary stenting with drug eluting stent: a systematic review and meta-analysis of randomized controlled clinical trials and high quality observational studies. *Int J Cardiol* 170(1):54–63, 2013.
85. Zhang Y, Farooq V, Garcia-Garcia HM, et al: Comparison of intravascular ultrasound versus angiography-guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients. *EuroIntervention* 8(7):855–865, 2012.

61 High-Risk Vulnerable Plaques: Definition, Diagnosis, and Treatment

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KEY POINTS

- High-risk atherosclerotic plaques, also called *vulnerable plaques* (VPs), display specific features that predispose patients to intracoronary thrombosis from plaque rupture, plaque erosion, or calcified nodules.
- The interplay among pathophysiologic processes in the atheroma, including plaque progression, inflammation, lipid metabolism, plaque rupture, and healing, determines a variety of outcomes, ranging from asymptomatic disease to acute coronary syndromes and sudden cardiac death.
- Inflammatory plaque regulation, plaque neovascularization, intraplaque hemorrhage, and defective efferocytosis play pivotal roles in plaque vulnerability and offer potential targets for the diagnosis and treatment of VPs.
- Plaque instability can be detected by several invasive and noninvasive technologies according to the properties of VPs.
- The rate of progression to plaque rupture remains low, which makes prediction of adverse clinical events challenging.
- Advances in clinical and translational research have provided insight into the natural history of plaques, but further study is required.
- Systemic, regional, and local therapies are used for VPs. Systemic treatment with pharmacologic agents has demonstrated the most compelling evidence for plaque regression and reduction of adverse clinical outcomes.

Despite a steady decrease in the incidence of acute coronary events, cardiovascular disease continues to be the major cause of death worldwide, with 17.6 million deaths per year, representing about one third of total global deaths, and with an expected increase to 23.4 million deaths by the year 2030.[1-5]

Coronary atherosclerosis is a condition that can remain asymptomatic over decades. Prevention of the transition from asymptomatic, nonobstructive disease to symptomatic, occlusive disease could reduce the death rate dramatically. The transition correlates with *acute coronary thrombosis*, also known as *atherothrombosis*. It occurs mostly because of plaque rupture or erosion and less frequently because of calcific nodules.[6] In the United States, atherothrombosis is responsible for more than 1 million acute coronary events per year.[3,7,8]

The suspected precursor lesion for plaque rupture is the thin-cap fibroatheroma (TCFA).[6] It can be detected by invasive imaging techniques,[9] but morphologic features alone may not be enough to identify a TCFA that is likely to rupture. Many stabilize, and the plaque never ruptures. Others remain as TCFAs, and a minority rupture. Because few ruptured plaques produce obstructive thrombosis, the incidence of adverse clinical events related to TCFAs is low, and it has been difficult to apply the concept of vulnerable plaques (VPs) preceding coronary thrombosis and acute coronary syndrome (ACS) in clinical cardiology.

This chapter describes a systematic approach to VPs. First, we review the definition, incidence, risk factors, and anatomic locations of VPs and consider the composition and pathophysiologic aspects of these lesions as a means to understand plaque vulnerability. Then we summarize the field of invasive plaque imaging, comment on noninvasive imaging modalities, and describe therapeutic approaches, including pharmacologic prevention and aggressive percutaneous coronary intervention (PCI).

CLINICAL CHARACTERISTICS OF VULNERABLE PLAQUES

Definition

A high-risk VP is a nonobstructive, silent coronary lesion that suddenly becomes obstructive and symptomatic (Fig. 61-1). Pioneering studies by Ambrose and Fuster in 1988 described the baseline angiographic characteristics of lesions that produced acute myocardial infarctions (AMIs).[10] The investigators found that lesions evolving to complete occlusion had a mean percent diameter stenosis of 48%. Many studies have reproduced these findings, supporting the concept that most lesions responsible for AMI evolve from nonobstructive disease.[11]

Incidence

The number of nonobstructive, asymptomatic plaques that progress to obstructive, symptomatic lesions manifesting as acute events constitutes the estimated incidence of this condition. Several studies have retrospectively addressed this issue. One study included 1228 patients who underwent PCI for symptomatic coronary artery disease (CAD). The incidence of nonobstructive, nonculprit lesions that required additional PCI was 12.4% in the first year and 5% to 7% per year for years 2 to 5 after the initial procedure (Fig. 61-2).[12] A second study included 3747 post-PCI patients from the National Heart, Lung, and Blood Institute (NHLBI) registry.[13] The incidence of nonobstructive, nonculprit lesions that required additional PCI was 6% in the first year, ranging from 4.4% to 12.8% according to the number of vessels involved (Fig. 61-3). Although relevant historically, these studies overestimate the number of events per year.

Another study included a total of 1059 patients evaluated by computed tomography angiography (CTA). VPs were classified according to the presence or absence of positive remodeling and low-attenuation ("soft") morphology seen on imaging.[14] The prevalence of VPs was only 4.5%, but the incidence of acute coronary events was 11% for plaques with one high-risk variable and up to 22% for plaques with both variables. Absence of these high-risk variables was a strong protective predictor, with an incidence of coronary events as low as 0.5%.

A study using optical coherence tomography (OCT) reported a 12% incidence of TCFAs in sites other than the culprit lesion responsible for the ACS.[15] The investigators found that most TCFAs occurred in the proximal segments of the coronary vasculature. Despite an incidence of 11% to 22%, the actual area occupied by the plaques in the coronary circulation may not be large.

Groups led by Cheruvu and Virmani performed detailed histopathologic analyses of the entire vasculature of 50 human hearts and demonstrated that only 1.1% to 1.6% of the coronary vessel area was occupied by TCFAs.[6,16] Of all lesions studied, 10.8% corresponded to TCFAs.[16] This finding is in agreement with another study that identified an 11% incidence of TCFAs and a slightly higher incidence among patients with ACS, suggesting a more unstable profile of the coronary lesions in these subjects.[17]

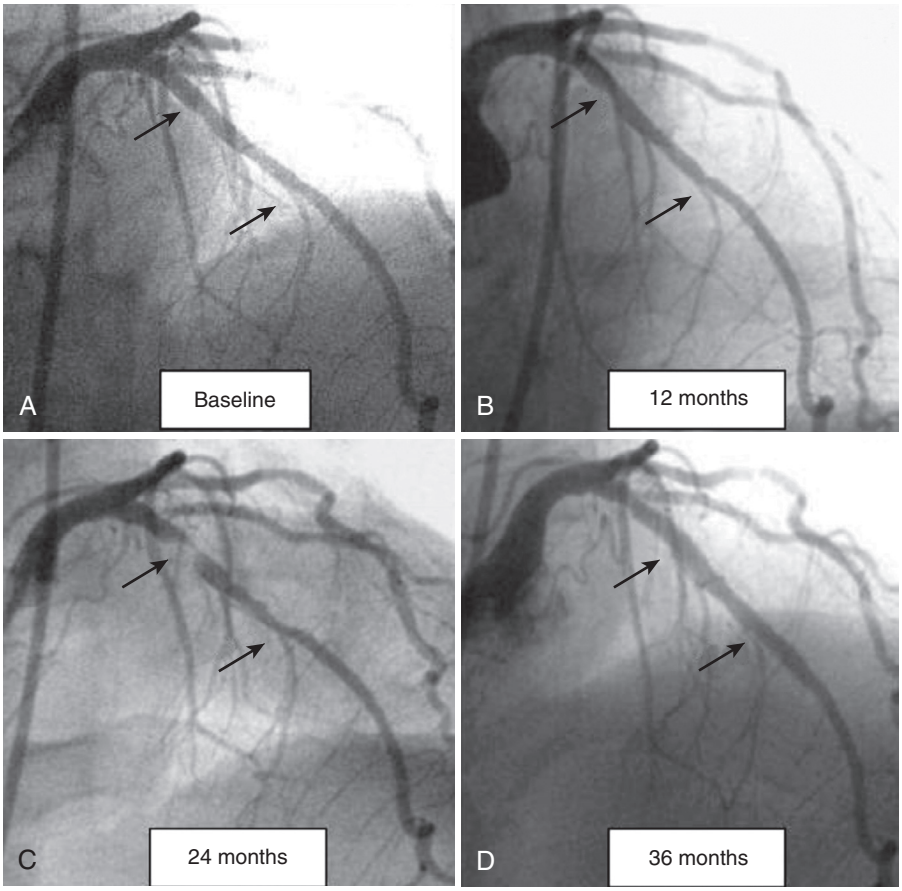


FIGURE 61-1 Sequential coronary angiograms of the left anterior descending coronary artery were performed at 12-month intervals. Rapid progression from nonobstructive and asymptomatic to severely obstructive and symptomatic fulfills the clinical definition of vulnerable plaques. **A,** Normal vessel seen by angiography. **B,** Nonobstructive, asymptomatic coronary disease in the proximal segment *(arrows)*. **C,** Obstructive, symptomatic coronary disease with acute coronary syndrome *(arrows)*. **D,** The degree of stenosis is 10% to 20% 12 months after local therapy with a stent (36 months after the baseline angiogram). (Courtesy Mount Sinai Medical Center Cardiac Catheter Laboratory, New York, NY.)

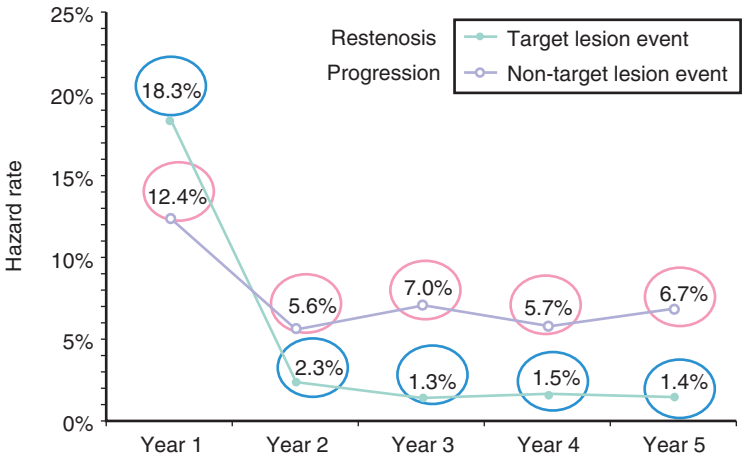


FIGURE 61-2 Hazard rates per year for target-lesion *(blue)* and non–target lesion *(red)* events after percutaneous coronary intervention were derived from a life table survival analysis. Target-lesion events include any repeat revascularization or other event (i.e., death, myocardial infarction [MI], acute coronary syndrome [ACS], congestive heart failure [CHF]) attributed to the target lesion. Non–target-lesion events include all repeat revascularizations involving the target vessel outside the target lesion, any non–target vessel revascularization, and any death, MI, ACS, or CHF that was not attributable to the target lesion. (Modified from Cutlip DE, Chhabra AG, Baim DS, et al: Beyond restenosis: five-year clinical outcomes from second-generation coronary stent trials. *Circulation* 110:1226-1230, 2004.)

These retrospective and pathologic studies provided the foundation for the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) trial, the first prospective study of the natural history of VPs.[18] A total of 697 patients with ACS underwent three-vessel coronary angiography and gray-scale and radiofrequency assessment, also known as intravascular ultrasound with intravascular ultrasound and virtual histology (IVUS-VH) analysis. The incidence of nonculprit lesions responsible for major adverse cardiovascular events (MACEs) was 11.6% at 3.4 years. However, most of these events were rehospitalizations for progressive angina. Cardiac death or AMI affected only 4.9% of the population. Three independent variables predicted these events: a plaque burden of 70% or greater (hazard ratio [HR] = 5.03, $P < .001$), a minimal luminal area of 4 mm^2 or less (HR = 3.21, $P = .001$), and IVUS-VH–derived TCFA morphology (HR = 3.35, $P < .001$). Plaques exhibiting all three features had an HR up to 11.05 ($P < .001$). Nevertheless, the prevalence of these high-risk plaques was only 4.2%.

The PROSPECT trial results supported the idea that VPs are uncommon, are composed of a combination of anatomic features, and are associated with mild or "soft" events rather than death and AMI. VPs are predominately asymptomatic and harmless in most cases. They can manifest simultaneously in multiple segments, highlighting a

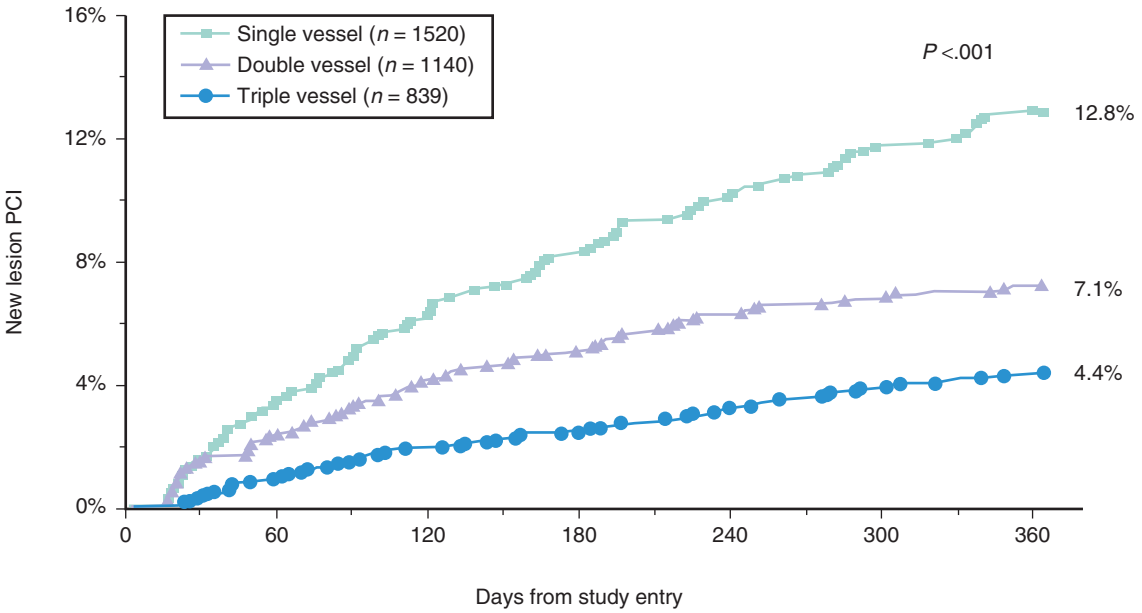


FIGURE 61-3 Kaplan-Meier analysis of non–target-lesion percutaneous coronary intervention (PCI) required in the first year after PCI, according to the initial degree of coronary artery disease. (Modified from Glaser R, Selzer F, Faxon DP, et al: Clinical progression of incidental, asymptomatic lesions discovered during culprit vessel coronary intervention. *Circulation* 111:143-149, 2005.)

proinflammatory milieu that may respond to systemic rather than focal therapies. Moreover, plaque rupture does not always lead to ACS, and prior studies have found evidence of old healed areas within the atheroma (i.e., fibroinflammatory lipid plaque) that occurred without causing a clinical event.[19] About 30% to 40% of ACS cases result from processes other than plaque rupture.[6,19] These and other limitations seriously challenge the VP hypothesis, and the current clinical approach therefore employs systemic therapy as a preventive tool for all and imaging for a few patients.

Risk Factors

Multiple regression analysis in retrospective studies has identified multivessel CAD at baseline (i.e., three- and two-vessel CAD), previous PCI, and age younger than 65 years as independent predictors of VPs. Treatment with statins failed to protect patients in the first year.[13] IVUS studies also identified age, hypertension, diabetes mellitus (DM), heart failure, and dyslipidemia as predictors of IVUS-derived TCFAs.[20] DM is strongly associated with higher rates of IVUS-derived TCFAs (21.6% vs. 13.1%, $P = .01$) and with rates up to 54.4% among patients with a diagnosis of DM for more than 10 years.[21] The incidence of TCFAs was seven times higher for men than women.[16]

Serum myeloperoxidase is a potential biomarker of plaque vulnerability.[22,23] Similarly, inhibition of lipoprotein-associated phospholipase A_2 ameliorates inflammation and decreases atherosclerotic plaque formation. Levels of biomarkers play a key role in necrotic core expansion or contraction, as demonstrated by the Integrated Biomarkers and Imaging Study 2 (IBIS-2).[24]

In isolated studies, levels of high-sensitivity C-reactive protein (hs-CRP), white blood cells, interleukin-18, and tumor necrosis factor-α (TNF-α) inversely correlated with fibrous cap thickness. However, hs-CRP appeared to be the only independent predictor by regression analysis.[25] Although hs-CRP has been postulated as a modulator of neovascularization,[26] the clinical evidence for primary prevention by hs-CRP is limited and subject to debate. Further research is needed to elucidate the role of biomarkers for predicting plaque rupture and coronary events.[27-29] Serum levels of micro-RNAs have been proposed as markers of early ACS and for identifying high-risk plaques.[30]

Anatomic Distribution

The proximal segment is responsible for 80% of AMIs in all three major coronary vessels,[31] a finding that has been reproduced by in vivo OCT studies (Fig. 61-4).[32,33] At bifurcations of segments, the TCFA is predominately located in the proximal rim as evaluated by OCT and IVUS.[34]

The characteristics of high-risk VPs determine the pathophysiology and offer targets for diagnostic evaluation by various imaging techniques. High-risk lesions are positively remodeled, have large plaque burden, and are usually located in the proximal segments of the coronary arteries.

Plaque Rupture and Erosion

Plaque rupture is the most common cause of atherothrombosis, including 70% to 75% of all adverse cardiac events and up to 85% of events among hypercholesterolemic white men. In plaque rupture, disease progresses through lipid core expansion and macrophage accumulation at the edges of the plaque, leading to fibrous cap disruption (Fig. 61-5).

The second most common cause of atherothrombosis is plaque erosion. Included initially in "other causes of coronary thrombosis," plaque erosion gained attention in the past decade as a significant substrate for coronary thrombosis and sudden cardiac death among premenopausal women.[16] Plaque erosion is associated with cigarette smoking, suggesting that thrombosis in these patients may be related to a systemic prothrombogenic pathway rather than a local atherothrombotic mechanism.

Unlike plaque rupture, erosion occurs in plaques with no specific features suitable for detection. Most of these plaques exhibit histologic patterns similar to plaques responsible for stable angina. They are characterized by a thick, smooth muscle cell–rich fibrous cap, reduced necrotic core areas, and a low degree of inflammation (Fig. 61-6). They also display neutral or negative remodeling, preserved integrity of the internal elastic lamina without disruption of the tunica media, and intact histology of the contractile elastic lamellae (Fig. 61-7).[35,36] Patients with plaque erosion also demonstrate chronic or late-stage

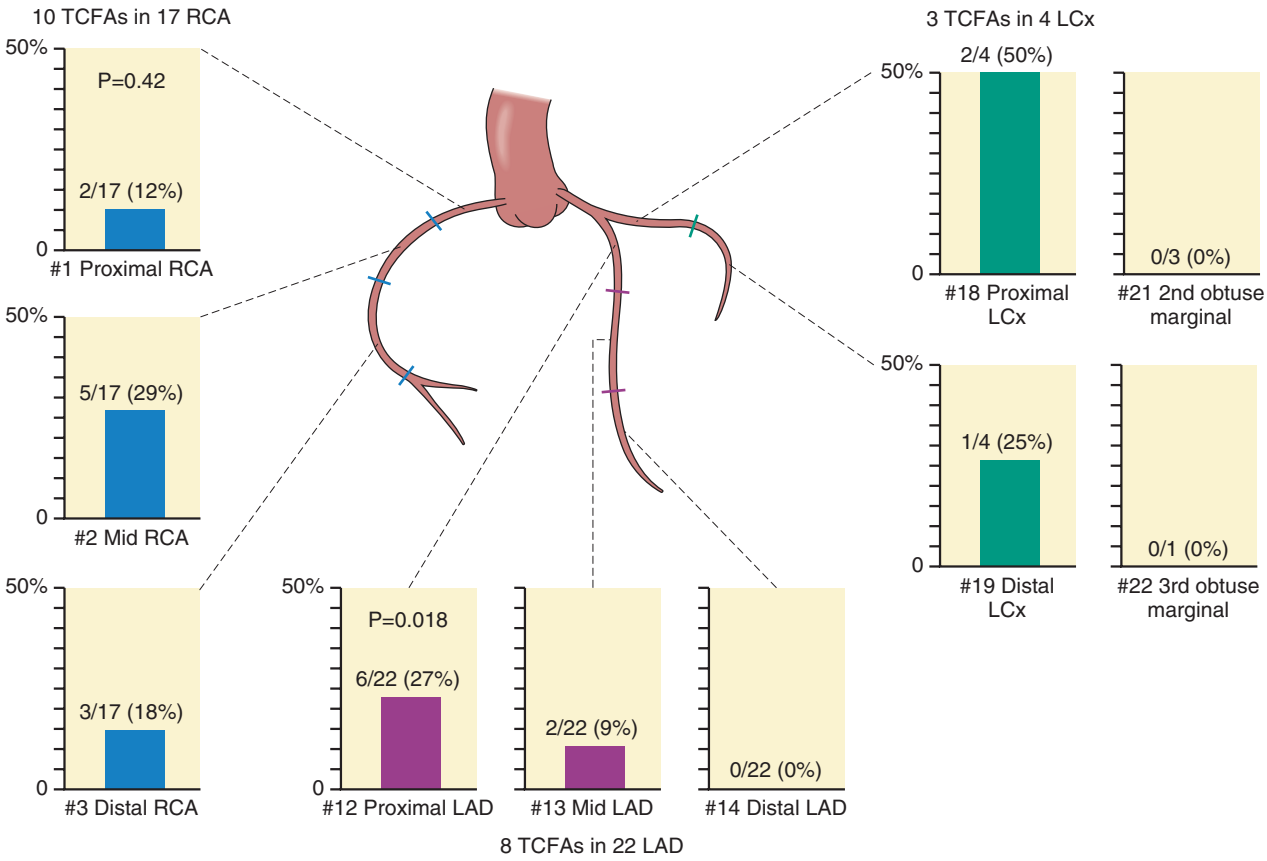


FIGURE 61-4 Distribution of thin cap fibroatheromas (TCFAs) in the proximal, middle, and distal segments of the three coronary arteries. *LAD,* Left anterior descending coronary artery; *LCx,* left circumflex coronary artery; *RCA,* right coronary artery. (From Tanaka A, Imanishi T, Kitabata H, et al: Distribution and frequency of thin-capped fibroatheromas and ruptured plaques in the entire culprit coronary artery in patients with acute coronary syndrome as determined by optical coherence tomography. *Am J Cardiol* 102:975-979, 2008.)

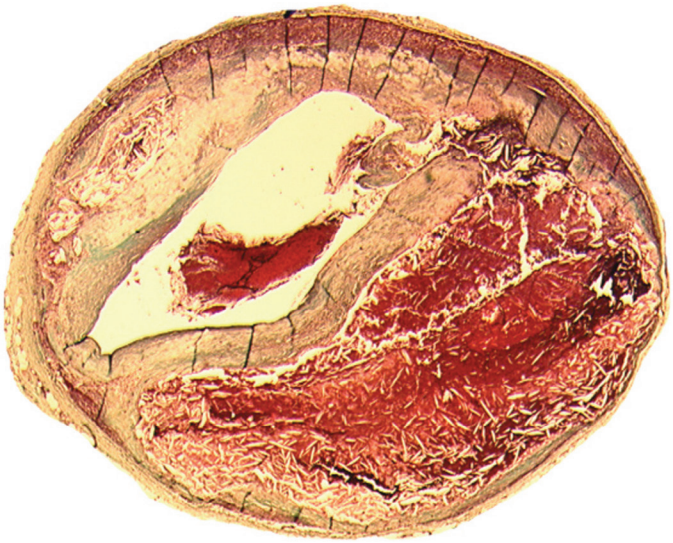


FIGURE 61-5 Cross section of a coronary artery containing a ruptured plaque at the shoulder of the fibrous cap with a nonocclusive thrombus superimposed. The large, necrotic core can be identified by cholesterol crystals and extensive intraplaque hemorrhage due to plaque rupture. Trichrome stain renders the thrombus red, the collagen blue, and the lipid colorless. (Courtesy Dr. K. Raman Purushothaman, Mount Sinai Hospital, New York, NY.)

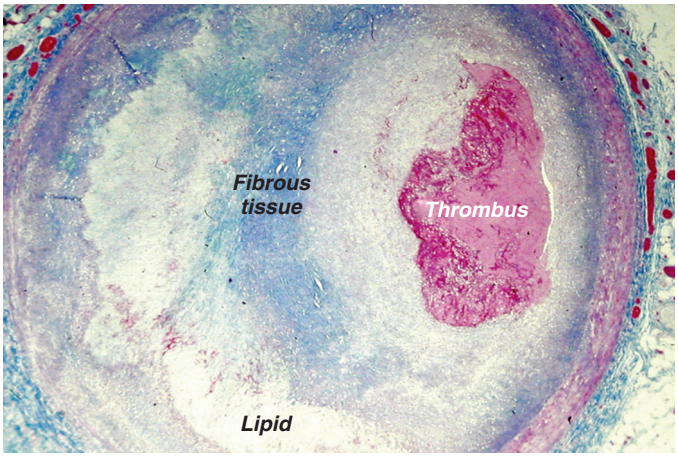


FIGURE 61-6 Plaque erosion. In the cross section of a coronary artery containing a stenotic atherosclerotic plaque with an occlusive thrombosis superimposed, the endothelium is missing at the plaque-thrombus interface, but the plaque surface is otherwise intact. Trichrome stain renders the thrombus red, the collagen blue, and the lipid colorless. (Courtesy Dr. Erling Falk, Aarhus, Denmark.)

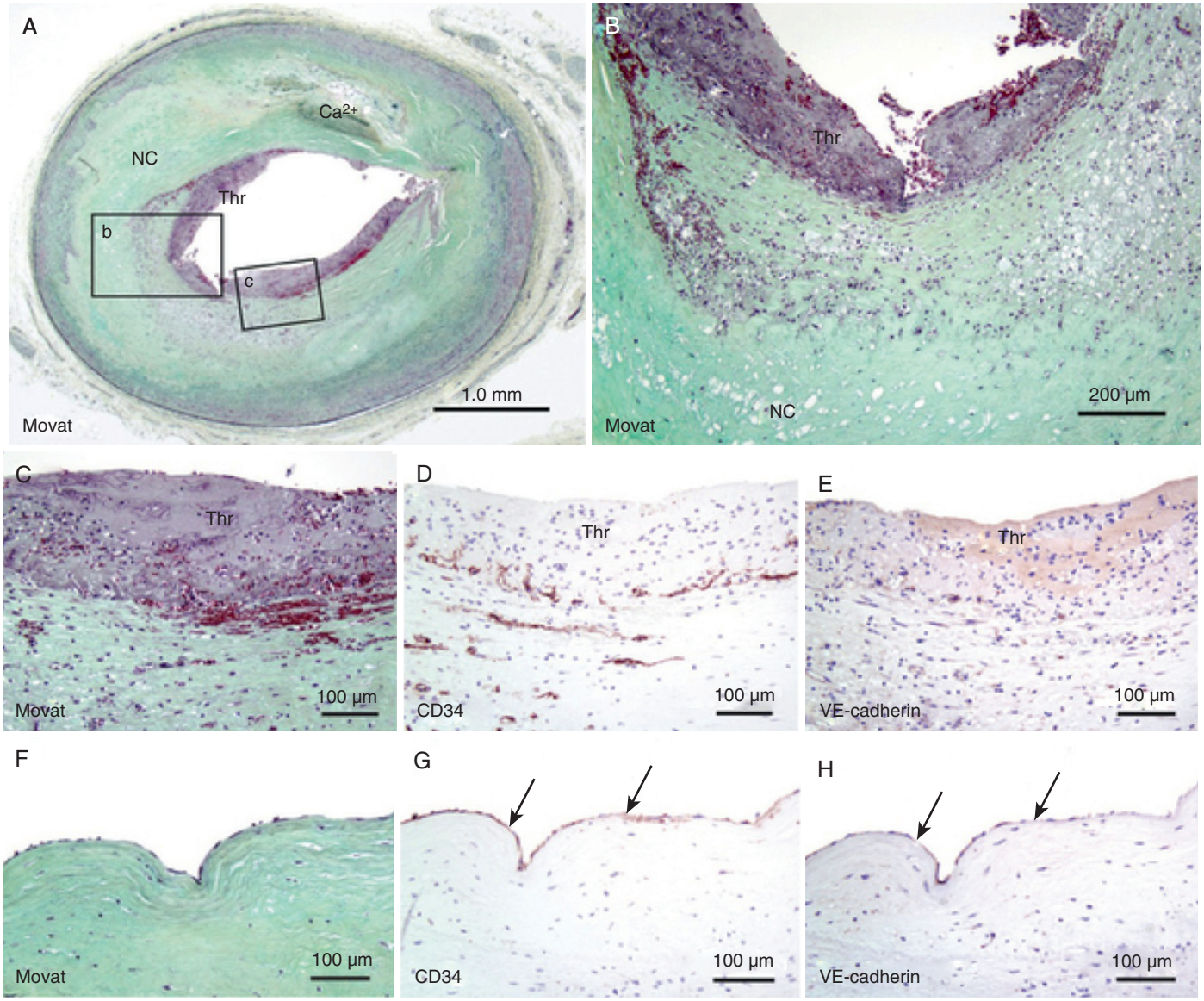


FIGURE 61-7 Plaque rupture. **A** through **E,** Histologic sections show plaque erosion with acute thrombus. **F,** Histologic sections show an adjacent lesion without thrombus. A 46-year-old man with a history of non–ST-segment elevation acute myocardial infarction and sirolimus-eluting stent placement in the proximal left anterior descending coronary artery (LAD) 5 years antemortem died suddenly and was sent to autopsy for suspected stent thrombosis. Histology showed a patent stented segment with no thrombosis in the LAD; acute plaque erosion with a nonocclusive thrombus was identified in the proximal left circumflex coronary artery (LCx). A low-power image of the proximal LCx (**A**) shows plaque erosion with nonocclusive platelet-rich thrombi (Thr) and underlying fibroatheroma with an early necrotic core (NC) and focal, mild calcification (Ca^{2+}) (Movat pentachrome stain); *boxes b* and *c* indicate the sections magnified in parts **B** and **C**, respectively. A high-power image (**B**) shows luminal thrombus and an underlying early NC with foamy macrophages. A high-power image (**C**) shows a luminal surface lacking endothelium, which is in contact with an acute thrombus. Lack of endothelium at the luminal surface is confirmed by immunostaining for two endothelial markers: CD34 (**D**) and VE-cadherin (**E**). A high-power image of an adjacent section (**F**) shows a normal endothelialized surface, which is confirmed by immunostaining for CD34 (**G**) and VE-cadherin (**H**) *(arrows)*. (From Otsuka F, Joner M, Prati F, et al: Clinical classification of plaque morphology in coronary disease. *Nat Rev Cardiol* 11:379-389, 2014.)

thrombus in healing states at higher frequencies than those with plaque rupture.[37]

Plaque rupture is the most frequent substrate for ACS, and its precursor lesion, TCFA, is considered the hallmark of high-risk VPs (Fig. 61-8).[38] The classic histologic patterns of TCFA include (1) a large plaque burden (>70%) associated with rapid growth (i.e., expansion hypothesis); (2) a thin, fibrous cap with an increased stress-strain relationship; (3) a large necrotic core with an increased ratio of free cholesterol to esterified cholesterol; (4) increased plaque inflammation; (5) positive vascular remodeling; (6) increased vasa vasorum neovascularization; and (7) intraplaque hemorrhage.[39]

LARGE PLAQUE BURDEN AND THE EXPANSION HYPOTHESIS

The PROSPECT trial identified large plaque burden (>70%) as the most powerful predictor of future coronary events. The plaque expansion hypothesis, which refers to the correlation between plaque volume

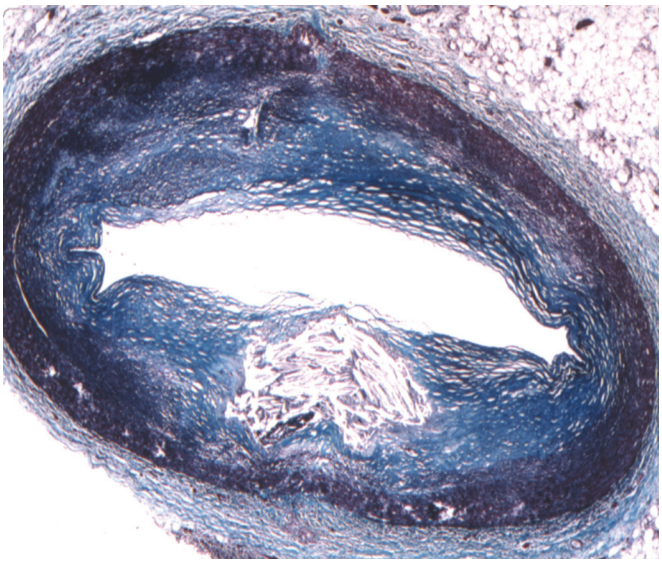


FIGURE 61-8 Thin-cap fibroatheroma is characterized by a very thin fibrous cap and a large necrotic core (trichrome stain). (Courtesy Dr. K. Raman Purushothaman, Mount Sinai Hospital, New York, NY.)

and plaque vulnerability, explains the significant differences in plaque volume between ruptured coronary and aortic plaques and TCFAs (see Figs. 61-6 and 61-7). The plaque expansion hypothesis also reconciles differences in percent diameter stenosis of ruptured plaques of ACS and nonobstructive TCFAs.

The hypothesis that larger plaque volume is associated with more vulnerable phenotypes was postulated by Narula and colleagues after detailed analysis of 295 coronary plaques from patients who had died suddenly.[40] The investigators reported that 70% of culprit lesions with plaque rupture were determined to be obstructive by angiography, with a percent diameter stenosis greater than 75%, whereas this was observed in only 40% of the specimens classified as TCFAs. Less obstructive plaques with 50% to 75% stenosis were seen in 25% of the ruptured plaques and in 50% of the TCFAs. Only 5% of the specimens in the plaque rupture group and 10% in the TCFA group had less than 50% stenosis (Fig. 61-9) The larger percent diameter stenosis documented in ruptured plaques suggests that TCFAs undergo a significant expansion of the plaque burden before rupture.[41] Recurrent cycles of plaque rupture and healing lead to increased plaque volume.[42] These data support the transition from vulnerable (nonobstructive) to thrombosed (severely obstructed), ruptured plaques[43] and the use of physiologic testing such as fractional flow reserve (FFR).[44,45]

PLAQUE PATHOLOGY

Stress-Strain Relationships

Autopsy studies have shown that ruptured plaques are characterized by a mean fibrous cap thickness of only 23 ± 19 μm. In one study, 95% of ruptured caps measured 64 μm thick or less in the coronary and 60 μm thick or less in the aorta.[46] An important histologic feature of TCFAs is a fibrous cap 65 μm thick or less.

Thin caps are unable to withstand the circumferential tensile stress applied by the oscillations of arterial blood pressure. The ratio of the circumferential tensile stress to the radial strain of the fibrous cap equals the stiffness of the tissue.[47] Soft (fatty) tissue is more strained than stiff (fibrous) tissue when equally stressed. As caps become thinner, the stress increases exponentially (Fig. 61-10). Stress also increases as lipid pools become larger.

The strength of a fibrous cap is as important as its thickness. This was confirmed in an elegant study by Stone and coworkers.[48] They demonstrated that a large plaque burden and low local endothelial shear stress predict plaque progression and luminal narrowing by profiling vascular segments with coronary angiography and IVUS in 506 patients undergoing prospective evaluation of clinical events at 1 year.[48]

Microcalcificatons are common features of the fibrous caps of human atheromas. They increase plaque vulnerability by concentrating stress, which facilitates cap rupture.[49] Research techniques such as intravascular palpography are being used for assessment of a vulnerable plaque with a radial resolution of less than 65 μm and for quantifying the stress-strain relationship of fibrous caps, but these methods have not been validated in clinical practice.[50]

Increased Ratio of Free Cholesterol to Esterified Cholesterol

Oxidized low-density lipoprotein (oxLDL) cholesterol is avidly taken up by macrophages by means of scavenger receptors, producing a cytoplasm overloaded with lipid droplets. Continuous inflow of oxLDL leads to extracellular lipid accumulation in the matrix of the plaque and cell death. Distribution of oxLDL plays a pivotal role in plaque growth according to mathematical models based on physical laws.[51] Similarly, preclinical experimentation has demonstrated how oxLDL isoforms are associated with plaque vulnerability depending on the predominant type of molecule and that they mostly induce macrophage apoptotisis.[52] The necrotic core is formed by apoptosis of lipid-laden macrophages, foam cells, and erythrocytes. Active collagen dissolution by metalloproteinases contributes to core expansion, which plays a major role in plaque vulnerability.

In the aorta, TCFAs exhibit necrotic core areas of 40% and ruptured plaques up to 50% of the total plaque area.[53] However, other studies of coronary arteries show necrotic areas of as little as 24% and 34% in TCFAs and ruptured plaques, respectively.[19] Core composition may influence the propensity for plaque rupture and thrombosis. An increased ratio of free cholesterol to esterified cholesterol with oxidized cholesterol increases the likelihood of thrombosis by interacting with the oxidized low-density lipoprotein (lectin-like) receptor 1 (OLR1), a cell surface receptor for oxLDL, and enhancing the expression of tissue factor.[38-40,54,55]

Increased Plaque Inflammation

Macrophages and T cells can degrade the extracellular matrix by secretion of proteolytic enzymes such as plasminogen activators and matrix metalloproteinases (MMPs), including collagenases, elastases, gelatinases, and stromelysins. The enzymes weaken the already thin fibrous cap and predispose it to rupture.[56] This process was confirmed by Suzuki and colleagues, who found increased levels of MMP1, MMP13, and interleukin-6 (IL-6) in the coronary vessels of patients who had AMIs, supporting the role of MMPs in plaque rupture leading to clinical events.[57]

Among the many MMPs that have roles in atherosclerosis, two subtypes, MMP7 and MMP12, seem to be selectively localized in specific subsets of macrophages; especially those located in the necrotic core that have low arginase 1 expression, representing a marker of activation and enhanced inflammation.[58-60] The aim of continuous entry, survival, and replication of monocytes or macrophages in plaques is to remove oxLDL and reduce oxidation and generation of reactive oxygen species. When the macrophage scavenger capacity becomes overloaded, cell death is activated by apoptosis, releasing MMPs and tissue factor.[61] This link among inflammation, apoptosis, and thrombosis was elegantly documented by Hutter and coworkers in human and murine atherosclerotic lesions,[62] confirming plaque inflammation as a pivotal feature of plaque vulnerability.[63]

Two subclasses of monocytes or macrophages have been identified in atheromas.[64] The first type, classically known as activated macrophages (M1), promote inflammation. The second type (M2) appears to be antiinflammatory. The ratio between M1 and M2 macrophages affects atherosclerosis progression and plaque regression. Factors that shift the ratio toward increased M2 cell content include increased

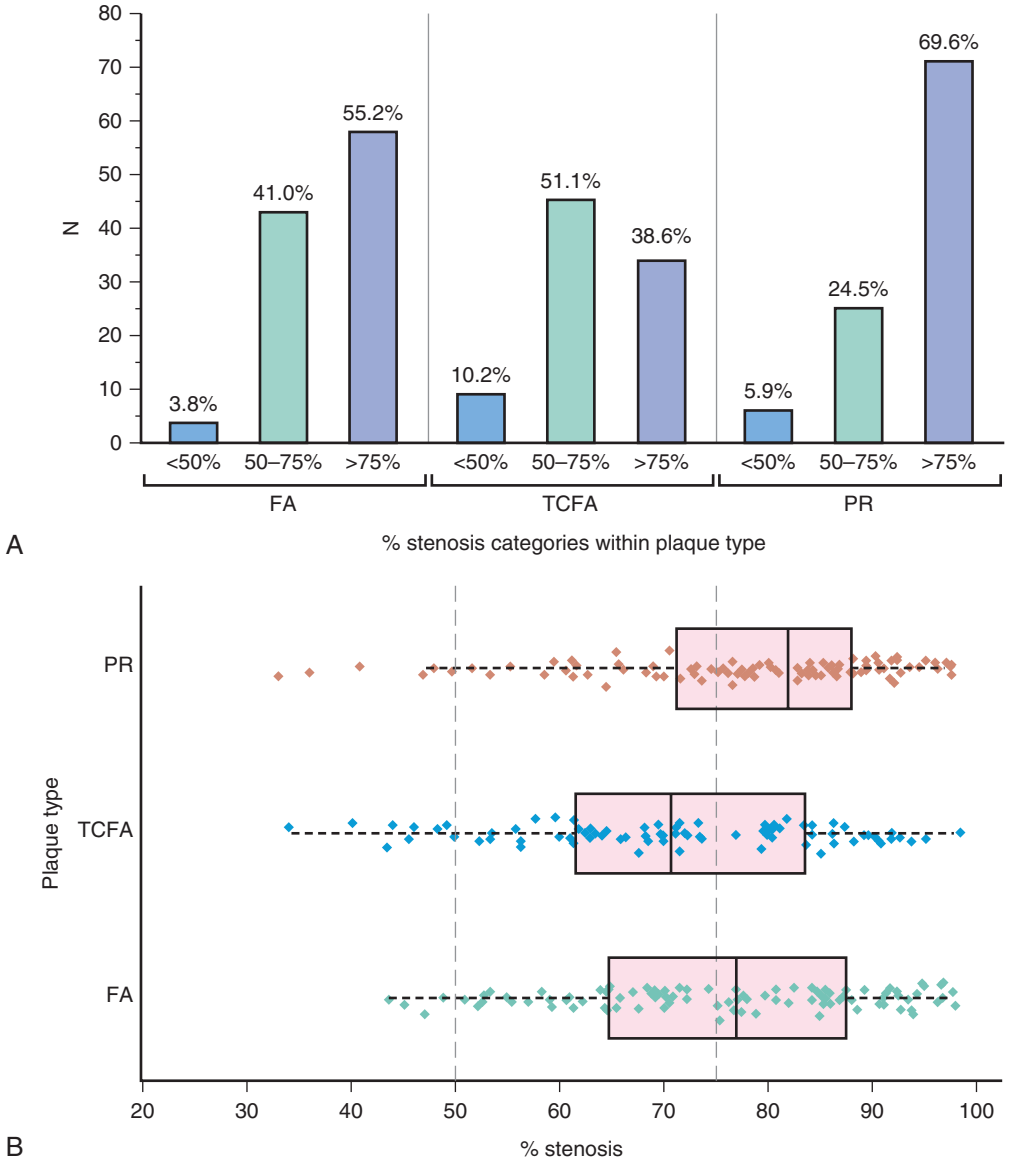


FIGURE 61-9 Luminal obstruction in cases of fibroatheroma (FA), thin-cap fibroatheroma (TCFA), and plaque rupture (PR) with various degrees of percent diameter stenosis. The bar graph (**A**) and plot diagram (**B**) show a greater than 50% cross-sectional vascular area stenosis in most PRs and TCFAs. The distribution indicates that TCFAs may further enlarge before plaque rupture. The plot diagram shows numeric data through the lower, median, and upper quartiles. The whiskers represent the sample minimum and sample maximum observations. The pink boxes and their divisions indicate indicate median and interquartile range (lower and upper quartiles).

numbers of helper T-cell–secreted molecules (e.g., IL-4, IL-13), peroxisome proliferator-activated receptor δ (PPARδ), and the lipid sphingosine 1-phosphate (S1P).[65,66]

M2 macrophages are also responsible for efferocytosis, or the removal of short-lived apoptotic bodies from the atheroma. Defective efferocytosis leads to secondary necrosis, a process linked to advanced disease. The failure of macrophage efflux, prothrombotic factors, inflammatory chemokines, and collagenases increase the size of the necrotic core, leading to plaque rupture and thrombosis.[67]

The macrophage scavenger receptor CD163 is a key mediator in plaque stabilization. It promotes defensive pathways involving the metabolism of hemoglobin released by intraplaque hemorrhage (discussed later).[68-71] Other novel inflammatory markers such as pentraxin have been linked to plaque vulnerability,[72,73] as have leukocyte-derived microparticles, but their application in clinical practice awaits more research.[72-74]

Vascular Remodeling

As a defense mechanism, the vessel wall can expand significantly to harbor large atheromas without obstructing the lumen (Fig. 61-11). Also known as *remodeling*, this process is linked to high-risk atherosclerosis. The remodeling process promotes higher stress at the level of the fibrous cap, which makes plaques more prone to rupture and clinical events. Cilla and associates[75] compared the geometric and physical properties of the different types of plaque remodeling (Fig. 61-12). The mechanisms responsible for remodeling involve an inflammatory process at the base of the plaque at the intimomedial junction, which leads to digestion of the internal elastic lamina and compromise of the tunica media and adventitia. Several studies have shown increased expression of MMPs in the intimomedial interface of remodeled plaques.[67,76,77] Disruption of the internal elastic lamina is associated with medial and adventitial inflammation, and evidence suggests that

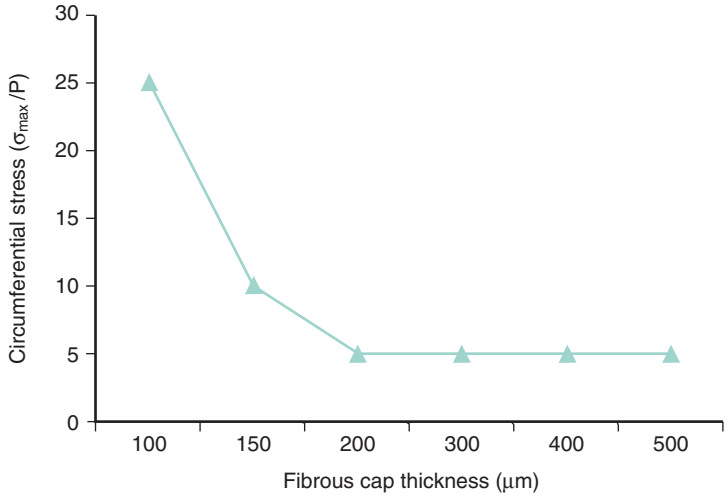


FIGURE 61-10 Relationship between circumferential stress *(vertical axis)* and fibrous cap thickness *(horizontal axis)*. Notice the exponential increase in circumferential stress when cap thickness is reduced to less than 200 μm. (Modified from Loree HM, Kamm RD, Stringfellow RG, Lee RT: Effects of fibrous cap thickness on peak circumferential stress in model atherosclerotic vessels. *Circ Res* 71:850-858, 1992.)

FIGURE 61-11 Large human thrombotic plaque in the left main coronary artery shows extensive remodeling and a large necrotic core. (Courtesy Dr. K. Raman Purushothaman, Mount Sinai Hospital, New York, NY.)

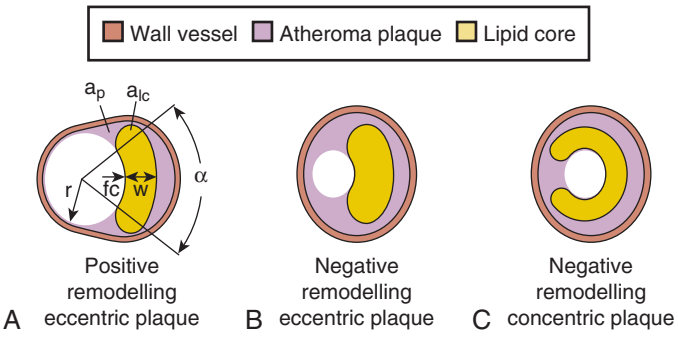
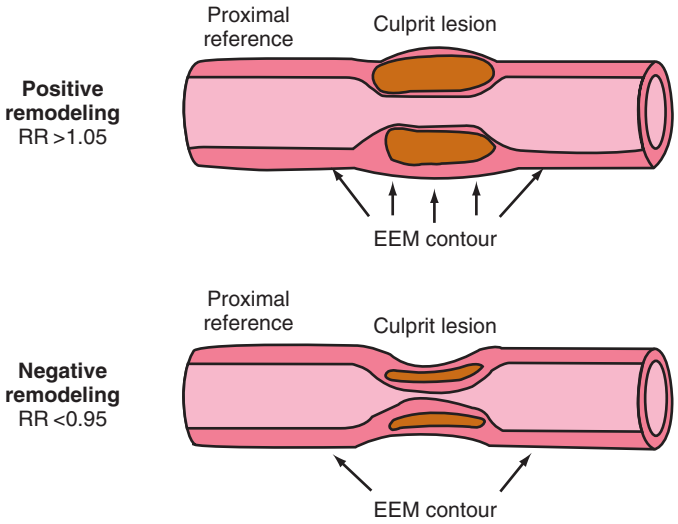


FIGURE 61-12 Idealized cross-sectional models and geometric parameters: fibrous cap thickness (*fc*), lumen radius (*r*), lipid core area (a_{lc}), lipid core width (*w*), lipid core angle (α), and atheroma plaque area (a_p). **A,** Positive arterial remodeling. **B,** Negative arterial remodeling with an eccentric atheroma plaque. **C,** Negative arterial remodeling with a concentric atheroma plaque. (From Cilla M, Pena E, Martinez MA, Kelly DJ: Comparison of the vulnerability risk for positive versus negative atheroma plaque morphology. *J Biomech* 46:1248-1254, 2013.)



Remodeling ratio (RR) = EEM area lesion / EEM area proximal reference

FIGURE 61-13 Diagram explains the direction of positive and negative remodeling. *EEM,* External elastic membrane. (Modified from Schoenhagen P, Ziada KM, Kapadia SR, et al: Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: an intravascular ultrasound study. *Circulation* 101:598-603, 2000.)

MMP10 plays a regulatory role in atherosclerosis progression by influencing plaque inflammation and vascular remodeling.[78] Burke and colleagues also demonstrated that marked expansion of the internal elastic lamina occurred in plaque hemorrhage with or without rupture.[79]

The clinical relevance of remodeling was pioneered by Schoenhagen and coworkers, who studied 85 patients with unstable coronary syndromes and 46 patients with stable coronary syndromes by using IVUS before PCI.[80] The remodeling ratio (RR) is the area of the external elastic membrane at the lesion divided by the same area at the proximal reference site. Positive remodeling was defined as an RR value greater than 1.05, and negative remodeling was defined as an RR value less than 0.95 (Fig. 61-13). The RR was higher at target lesions in patients with ACS than in patients with stable angina. Positive

remodeling was more common in ACS cases (51.8% vs. 19.6%), whereas negative remodeling was more common in chronic stable angina cases (56.5% vs. 31.8%), confirming the histopathologic associations between plaque remodeling and vulnerability.[80]

Newer technologies to detect TCFAs should yield exact measurements that quantify the degree of vascular remodeling. The method appears to provide an appropriate correlation between invasive and noninvasive approaches.[81]

Corti and associates were the first to document the eccentric pattern of plaque regression after aggressive lipid therapy.[82] Many studies have confirmed this observation (Fig. 61-14).[83,84] Lipid is the main plaque component that can be reversed with therapy, and the eccentric pattern of plaque regression suggests an effective reverse lipid transport system through the deeper layers of the vessel wall, which is probably mediated by vasa vasorum neovascularization.[85]

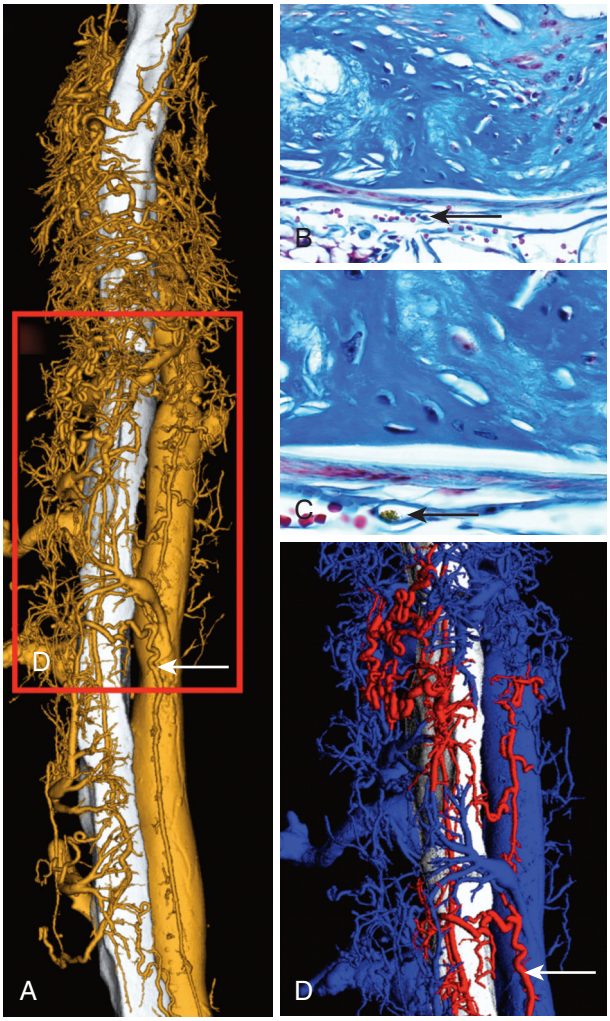


FIGURE 61-14 **A,** Volume-rendered high-resolution, three-dimensional micro-computed tomography (micro-CT) image of the descending aorta vasa vasorum. **B** and **C,** histologic cross-sections demonstrate atherosclerotic lesions in the inferior vena cava *(black arrows)*. **D,** Highlighted differentiated arterial *(red)* and venous *(blue)* vessels of the vasa vasorum (area corresponding to box in **A)**. (Masson trichrome stain, bar 500 microns). (From Langheinrich AC, Michniewicz A, Sedding DG, et al: Correlation of vasa vasorum neovascularization and plaque progression in aortas of apolipoprotein E(–/–)/low-density lipoprotein(–/–) double knockout mice. *Arterioscler Thromb Vasc Biol* 26:347-352, 2006.)

Vasa Vasorum Neovascularization

Atherosclerotic neovascularization evolves early in atherogenesis as a defense mechanism against hypoxia and oxLDL deposition in the tunica intima.[86] In advanced disease, the neovessels may play a defensive role, allowing lipid removal from the plaque through the adventitia and leading to plaque regression as described earlier. The adventitial vasa vasorum is the main source of neovascularization in atherosclerotic lesions (Fig. 61-15).

Neovascularization, elegantly delineated by Barger and colleagues with cinematography (Fig. 61-16), is distributed from the epicardial fat to the plaque throughout vessel wall, although some originates directly from the vessel lumen.[87] Neovessels from the adventitial vasa were 28 times more numerous (96.5%) compared with those from the luminal side (3.5%).[68] Neovessels from the adventitial vasa were characteristic of severely stenotic lesions and correlated with the extent of inflammatory cell infiltration and lipid core size. Conversely, neovessels from the lumen were found in plaques with 40% to 50% stenosis and were associated more often with intraplaque hemorrhage or hemosiderin deposits.[88]

Neovessels can serve as a pathway for leukocyte recruitment to high-risk areas of the plaque, including the cap and the shoulder. Expression of vascular cell adhesion molecule 1 (VCAM-1), intracellular adhesion molecule 1 (ICAM-1), and E-selectin is twofold to threefold higher in neovessels compared with the arterial luminal endothelium, confirming the pivotal role of neovessels as a pathway for leukocyte recruitment in human coronary plaques.[89]

Angiogenesis is stimulated by inflammatory cells. For instance, apoptotic microvesicles at the submicrometer level found in atherosclerosis plaques are highly proangiogenic by regulating CD40L and are produced mostly by macrophages.[90] Histologic evidence has documented atherosclerotic neovascularization as a pathway for macrophage infiltration in advanced, lipid-rich plaques (Fig. 61-17).[91] Neovessel content was significantly increased in plaques with severe inflammation associated with increased macrophage and T-lymphocyte infiltration.[92] Ruptured plaques exhibited the highest degree of neovascularization.[93] Further analysis of plaque angiogenesis in DM documented a complex morphology, including sprouting, red blood cell (RBC) extravasation, and perivascular inflammation.[94]

Neovascularization may increase calcification, as demonstrated by the close link between immature endothelial cells and osteoblasts in atherosclerotic plaques and in cellular tissue expressing vascular calcification–associated factor (VCAF).[95] Using micro-CT imaging, studies have shown increased vasa vasorum density and iron and glycophorin A content in nonstenotic, noncalcified plaques. The calcium content was inversely proportional to neovessel content.[96] Detection of TCFAs should quantify vasa vasorum neovascularization in the adventitia, tunica media, and atherosclerotic plaque.

In summary, plaque neovascularization is initially a defense mechanism to provide oxygen and to remove lipid from the plaque. It may eventually fail, leading to extravasation of RBCs, perivascular inflammation, and intraplaque hemorrhage.

Intraplaque Hemorrhage

Neovessel leakage leads to extravasation of plasma and RBCs into the plaque, which is known as *intraplaque hemorrhage*. Leakage of RBCs from immature neovessels is mediated by various growth factors and chemokines that are expressed in VPs.[97] Compared with nonhemorrhagic atheromas, hemorrhagic plaques have lower levels of epidermal growth factor (EGF), placental growth factor (PGF), and angiopoietin 1 and increased levels of vascular endothelial growth factor (VEGF).[97,98] RBC lysis contributes to lipid deposition and the plaque homeostasis dictated by the balance between proatherogenic factors and defense mechanisms.[99] Extracorpuscular hemoglobin can induce oxidative

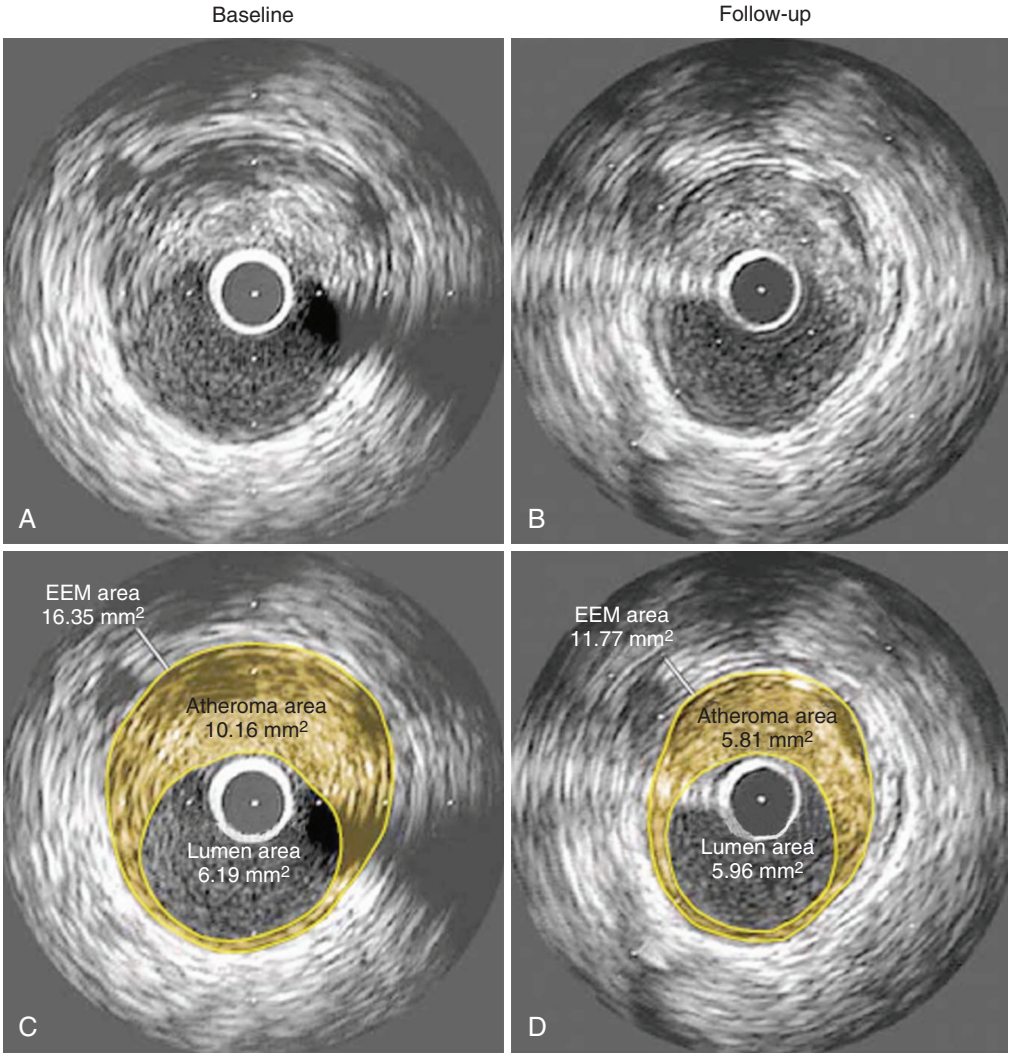


FIGURE 61-15 **A** and **B**, Baseline and follow-up intravascular ultrasound images of a single coronary cross section after 24 months of rosuvastatin treatment. **C** and **D**, Measurements superimposed on the same cross sections demonstrate the reduction in atheroma area. *EEM,* External elastic membrane. (From Nissen SE, Nicholls SJ, Sipahi I, et al: Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 295: 1556-1565, 2006.)

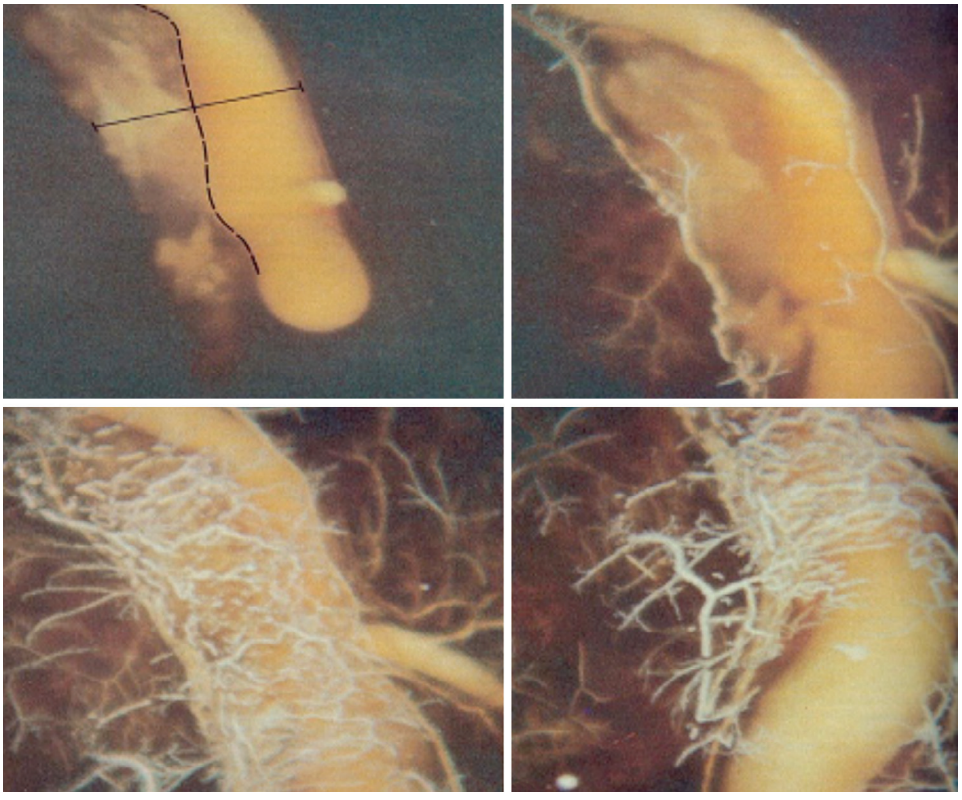


FIGURE 61-16 Color images obtained during the injection of silicone polymer into the coronary arteries of the cleared left anterior descending coronary artery demonstrate regions of vessels with abundant neovascularization. The positive regions are composed of networks of small-caliber vessels coming from the adventitia and penetrating the tunica media into the atherosclerotic plaque. (From Barger AC, Beeuwkes R 3rd, Lainey LL, Silverman KJ: Hypothesis: vasa vasorum and neovascularization of human coronary arteries, a possible role in the pathophysiology of atherosclerosis. *N Engl J Med* 310:175-177, 1984.)

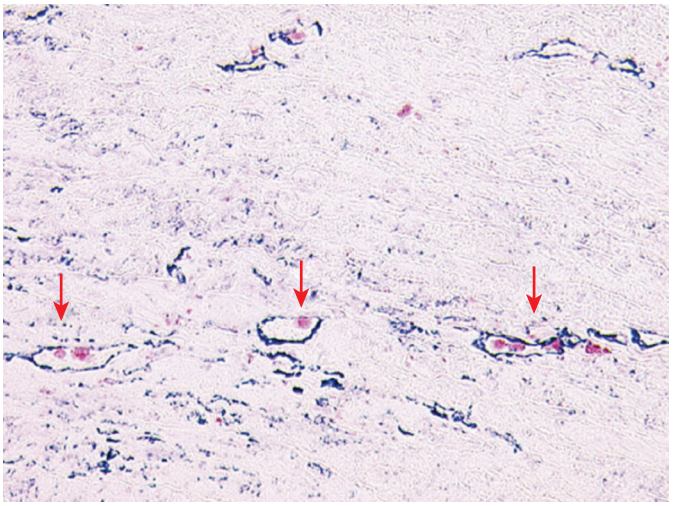


FIGURE 61-17 Histologic evidence of atherosclerotic neovascularization as a pathway for macrophage infiltration in human aortic plaques obtained at autopsy. Bicolor, contrasting immunohistochemical technique reveals microvessels in cross sections *(arrows)*, identified with the monoclonal endothelial cell marker CD34 linked to a blue chromogen, and inflammatory cells, identified with a combined macrophage and T-cell marker (CD68-CD3) linked to a red chromogen. (From Fuster VM, Fayad PR, Corti ZA, Badimon JJ: Atherothrombosis and high-risk plaque, part I: evolving concepts. *J Am Coll Cardiol* 46:937-954, 2005.)

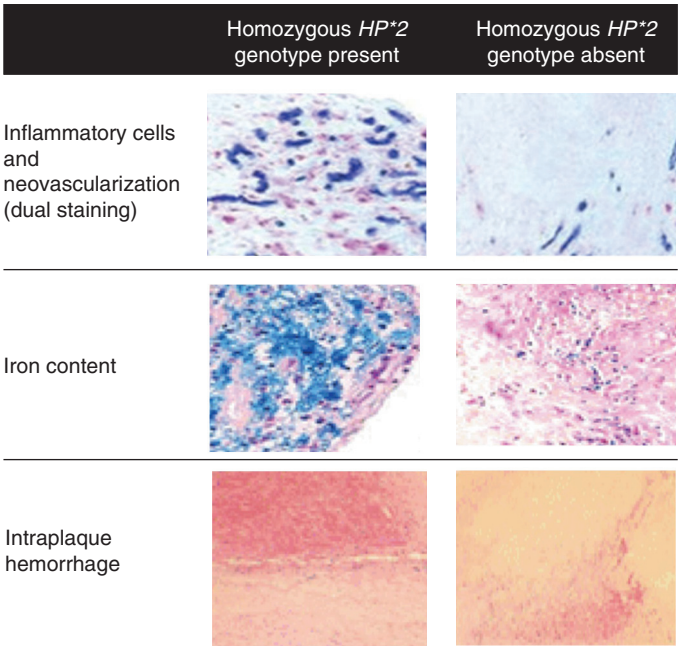


FIGURE 61-18 Histologic analysis of plaques from diabetic patients homozygous for the *HP*2* allele *(left)* were compared with control plaques *(right)*. *HP*2* plaques had a higher inflammatory cell content, higher degree of neovascularization, and higher level of intraplaque hemorrhage. (Courtesy Dr. K. Raman Purushothaman, Mount Sinai Hospital, New York, NY.)

tissue damage by its heme iron, with subsequent production of reactive oxygen species. Similarly, hemoglobin inside the atheroma can trigger macrophage differentiation.[69]

The defense mechanism against free hemoglobin is haptoglobin, which irreversibly binds to free hemoglobin, forming a haptoglobin-hemoglobin complex. The haptoglobin gene *(HP)* has two codominant alleles (*HP*1* and *HP*2*), The haptoglobin gene cluster resides at chromosome 16q22. The protein products of the two *HP* alleles are structurally different, and the cardiovascular effects of the polymorphisms play a major role in patients with DM.[100] Multiple independent epidemiologic studies examining incident cardiovascular disease have demonstrated that individuals with DM who are homozygous for the *HP*2* allele have a risk of cardiovascular events four to five times higher than those who are homozygous for the *HP*1* allele.

The mechanism by which the homozygous *HP*2* genotype regulates inflammation and enhances plaque vulnerability is decreased haptoglobin clearance. This is explained in part by a defective CD163 receptor in macrophages, which is the receptor in charge of removing the haptoglobin-hemoglobin complex from an atheroma.[101] Similarly, persons homozygous for the *HP*2* allele have a higher inflammatory cell content, greater level of neovascularization, and higher MMP levels in the atheroma (Fig. 61-18).[102,103] Detection of TCFAs should include identification of intraplaque hemorrhage, iron deposition, RBC membranes, and hemosiderin deposits in macrophages. In patients with DM, genotyping may offer additional prognostic value.

In summary, atherosclerotic lesions at high risk for plaque rupture and thrombosis are composed of a large lipid core, a thin fibrous cap subject to increased shear stress, macrophage infiltration, positive remodeling, vasa vasorum neovascularization, and increased intraplaque hemorrhage. Plaques at risk for erosion and thrombosis do not exhibit specific morphologic features that can be detected by imaging techniques. Although this limits the lesion-oriented approach to high-risk VPs, clinical events can be significantly reduced by identifying and treating TCFAs.

PLAQUE IMAGING

Invasive Techniques

Coronary angiography can delineate the coronary lumen, but it does not provide information about the vessel wall. It is therefore not appropriate for the detection of VPs.

Many intracoronary imaging techniques have been proposed to identify TCFAs. Every imaging technique should have appropriate validation using histology as the standard for identifying key histomorphologic components. Because most atherosclerotic plaques (i.e., TCFAs and non-TCFAs) have some degree of fibrous cap thickness, shear stress pattern, necrotic core area, macrophage area, positive remodeling, and vasa vasorum neovascularization, the sensitivity and specificity of these features alone is not enough for identification.

Proper histologic validation must include accurate assessment of the degree of the histomorphologic components, which involves linear regression analysis. The validation process should be confirmed in animal models of TCFA before being applied in human coronary arteries.[104] The ultimate test should be a natural history study of all techniques to determine whether specific plaque components have prognostic implications.

Intracoronary techniques for detecting TCFAs include IVUS, virtual histology, intravascular OCT, elastography, angioscopy, spectroscopy, and modalities such as thermography, intravascular palpography, and intravascular magnetic resonance imaging (MRI) that have been studied in research settings but have not found substantial use in clinical practice. Table 61-1 summarizes these techniques, the component detected, and their resolution or accuracy. The interventionalist must understand the potential and discern the limitations of these techniques before considering them for clinical use.

TABLE 61-1 Summary of Current Invasive Detection Technologies

Technology	Component Detected	Resolution/Accuracy (μm)
IVUS	Remodeling, calcium	100-250
IVUS with virtual histology	Necrotic core, calcium, collagen	480
Optical coherence tomography	Necrotic core, fibrous cap thickness, macrophages	5-20
IVUS elastography	Plaque strain	100-250
Intravascular magnetic resonance imaging	Necrotic core	250
Angioscopy	Surface appearance of the plaque	NA
Spectroscopy	Necrotic core	NA
Thermography	Metabolic activity of the plaque	0.05° C accurate

IVUS, Intravascular ultrasound; *NA,* not applicable.

Intravascular Ultrasound

Unlike angiography, IVUS allows visualization of the disease in the vessel wall and provides cross-sectional and longitudinal images of atherosclerotic plaques in vivo.[105] IVUS is based on transmitting and receiving high-frequency sound waves from tissue through a low-profile catheter (≈1 mm), reaching a radial resolution between 100 to 250 μm. IVUS is safe, quick, and easy.

IVUS allows identification of hemodynamically significant lesions that may be underestimated by angiography, particularly in nonoccclusive plaques with positive remodeling. IVUS delineates the degree of calcification, plaque burden, and arterial remodeling. It uses the amplitude of the backscattered ultrasound signal to differentiate highly echogenic components such as calcium and dense fibrous tissue from echolucent tissue such as lipid and necrotic core. However, it cannot clearly differentiate between fibrous and fatty plaques.[106] Gray-scale IVUS as an isolated technology is not capable of distinguishing plaque types.

The application of other imaging protocols and algorithms to IVUS, including integrated backscatter IVUS analysis and IVUS-VH, may contribute to better identification of the various plaque components. Researchers have studied backscatter analysis, which extracts frequency components of a signal buried in the original IVUS signal. The imaging signal from a small volume of tissue creates an integrated backscatter pattern.[107]

Several studies have reported the IVUS characteristics of culprit lesions and the presence of multiple ruptured plaques in patients with acute coronary events.[105,108] One study evaluated the long-term outcomes of VPs arbitrarily defined as plaques with rupture, lipid core, dissection, or thrombus by conventional IVUS during ACS in culprit and nonculprit locations. Multiplicity of VPs in the nontarget vessels (HR = 2.2; 95% confidence interval [CI], 1.4 to 3.4, $P = .001$) was the only independent predictor of long-term critical events. DM and ACS were significantly associated with the multiplicity of VPs.[109]

IVUS can be used to identify several features of TCFAs, including fibrous cap thickness, necrotic core area, plaque inflammation, degree of positive remodeling, plaque neovascularization, and calcified nodules. Because the IVUS resolution is lower than that needed to detect TCFAs, efforts at quantifying cap thickness with IVUS always overestimate the values compared with those provided by histology. With IVUS, ruptured plaques show thinner caps than nonruptured plaques (Fig. 61-19).[110] However, when ruptured plaques are histologically evaluated, the mean cap thickness is about 8 to 10 times lower than the resolution of IVUS (23 ± 19 μm in the coronary and 34 ± 16 μm in the aorta).[111] The significant overestimation of cap thickness is related to poor axial resolution, which means that no IVUS-related technology can detect TCFAs, the most common form of VPs.[110] IVUS can detect the necrotic core with a sensitivity of 46% and a specificity of 97%. Several studies using an integrated backscatter approach have attempted to improve these results.[112] A prospective study demonstrated that 93% of clinical events were associated with plaques with large echolucent areas, a surrogate of the necrotic core, suggesting a prognostic value for IVUS.[113] Similarly, some studies have proposed the attenuation of the echo signal inside the plaque as being indicative of large necrotic cores, but no histologic validation has corroborated this finding.[114] Although IVUS provides useful information about plaque echogenicity, we conclude that the exact sensitivity and accuracy needed to identify necrotic cores is unclear, and the resolution may not be sufficient to properly quantify this important feature of plaque vulnerability.[106]

Detection of plaque inflammation in the fibrous cap requires a resolution of 10 to 20 μm to identify macrophages. Because IVUS resolution is 10 to 20 times lower, it cannot detect macrophages in atherosclerotic plaques.

IVUS is an excellent tool for detecting remodeling, a major feature of plaque vulnerability, in contrast to detection of other features of plaque composition.[115] IVUS-identified arterial remodeling helped to understand the paradox of lumen and plaque size in VP (i.e., large plaques can appear to be nonobstructive on angiography), leading to the realization that ruptured plaques are larger than nonruptured plaques.[108] Because no other imaging modality can show remodeling better than IVUS, it is considered the standard for detecting remodeling in vivo.[115]

IVUS can detect flow within the plaque and identify neovascularization (i.e., functional neovessels). Whereas real-time IVUS is limited to evaluating plaque perfusion, advances with the use of contrast agents have dramatically improved the quality of Doppler ultrasound. Intravascular injection of microbubbles (i.e., small, encapsulated air or gas bubbles or albumin microspheres) can boost the Doppler signal from blood vessels. Microbubbles can help in visualizing flow in smaller vessels, even at the capillary level, as has been shown by contrast-enhanced echocardiography (CEE).[116] Direct visualization of atherosclerotic plaque microvessels using CEE was successfully done by Staub et al in carotid plaques. This has been validated with histology in animal models and in humans.[117,118] In coronary arteries, IVUS-CEE has successfully identified plaque neovessels with spatiotemporal changes and enhancement-detection techniques (Fig. 61-20).[119]

To improve resolution, an IVUS prototype using harmonic imaging with transmission of ultrasound at 20 MHz (fundamental) and detection of contrast signals at 40 MHz (second harmonic) was developed to identify adventitial neovessels in rabbit models.[120] However, vasa vasorum detection of coronary atherosclerosis with IVUS imaging is still evolving for clinical use.

Another important feature of atheromatous lesions that are prone to rupture and that can be properly identified with IVUS is the finding of high-risk calcifications such as *calcified nodules*. This was demonstrated by Lee and colleagues by analyzing sequential pathologic specimens in 856 sections from 29 coronary arteries from autopsies.[121] They carefully matched each segment with ex vivo IVUS images every 2 mm. IVUS quantified the degree of calcification in 285 frames; 94% consisted of nonnodular calcium, and 6% were calcified nodules.

The investigators found that calcified nodules had several features that distinguished them from nonnodular calcifications: a convex shape of the luminal surface of calcium (100% vs. 16.0%, $P < .001$), protrusion with a convex shape of the luminal surface (94.1% vs. 9.7%, $P < .0.001$), irregular luminal surface (64.7% vs 11.6%, $P < 0.001$), and irregular leading edge of calcium (88.2% vs. 19.0%, $P < .001$). The calcium nodules can protrude through and rupture the fibrous cap, becoming thrombogenic and leading to ACS as reported by autopsy data.[6]

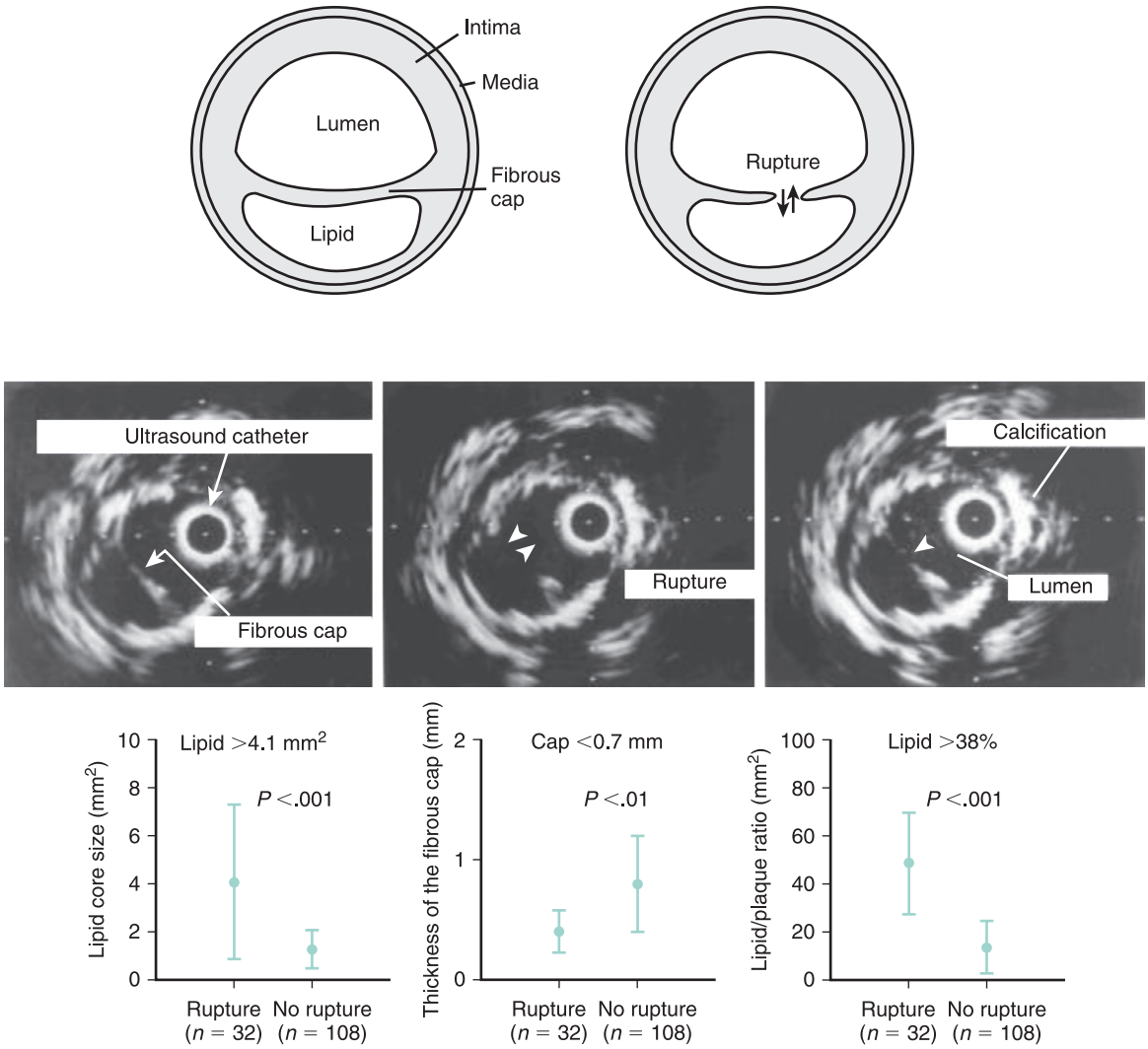


FIGURE 61-19 Diagrams show nonruptured and ruptured plaques. intravascular ultrasound images highlight the fibrous cap and a large echolucent area under the cap, suggesting a large necrotic core. The graphs describe lipid area, cap thickness, and lipid percent area in ruptured versus nonruptured plaques. (Modified from Ge J, Chirillo F, Schwedtmann J, et al: Screening of ruptured plaques in patients with coronary artery disease by intravascular ultrasound. *Heart* 81:621-627, 1999.)

IVUS data about calcified nodules can provide useful prognostic information. This was shown by Xu and colleagues by performing a subgroup analysis of the PROSPECT study that included 699 patients with ACS.[122] Of these patients, 314 had nonculprit calcific nodules after imaging the three major coronary arteries. When correlated with coronary angiography, heavy calcification was seen in only three cases, whereas 35 and 19 had moderate calcification and hazy calcification, respectively. No calcification was seen in 257 patients. Characteristics of patients with nonculprit lesions and calcific nodules included older age, higher incidence of hypertension, and chronic kidney disease. Calcific nodules were located superficially in 91% of the patients and proximally in 55%, and one third of the patients had at least one calcific nodule. Calcified nodules in nonculprit coronary segments in patients with ACS were prevalent, and their distribution correlated with areas associated with thrombotic events, but the rates of MACEs were lower for lesions with calcified nodules than those without them during 3 years of follow-up.

Virtual Histology

Considering the significant limitations of IVUS, Nair and Vince at the Cleveland Clinic studied the ultrasound scattered reflection wave as an alternative to improve tissue characterization.[107,123] The backscattered reflection wave is received by the transducer and converted into voltage. This voltage is known as backscattered radiofrequency data.

Using a combination of previously identified spectral parameters of the backscattered ultrasound signal, the researchers developed a color-coded classification scheme and constructed an algorithm to determine plaque composition in vivo. A color was assigned to each component was displayed on the IVUS image (Fig. 61-21). Four major plaque components were tested: fibrotic tissue (dark green), fibrofatty tissue (yellow-green), calcific-necrotic core (red), and dense calcium (white). The Movat pentachrome–stained histologic images identified homogeneous regions representing each of the four plaque components (Fig. 61-22).

The unit of analysis (i.e., *box*) was initially composed of 64 backscattered radiofrequency data samples 480 μm long.[123] The algorithm developed was then validated ex vivo, with sensitivities and specificities between 79% and 93% for the four plaque components.[123] The initial studies were performed in ex vivo human coronary specimens with a 30-MHz, 2.9-Fr, and mechanically rotating IVUS catheter (Boston Scientific, Natick, MA). The initial catheter approved by the U.S. Food and Drug Administration (FDA) was a 20-MHz device (Eagle Eye Gold,

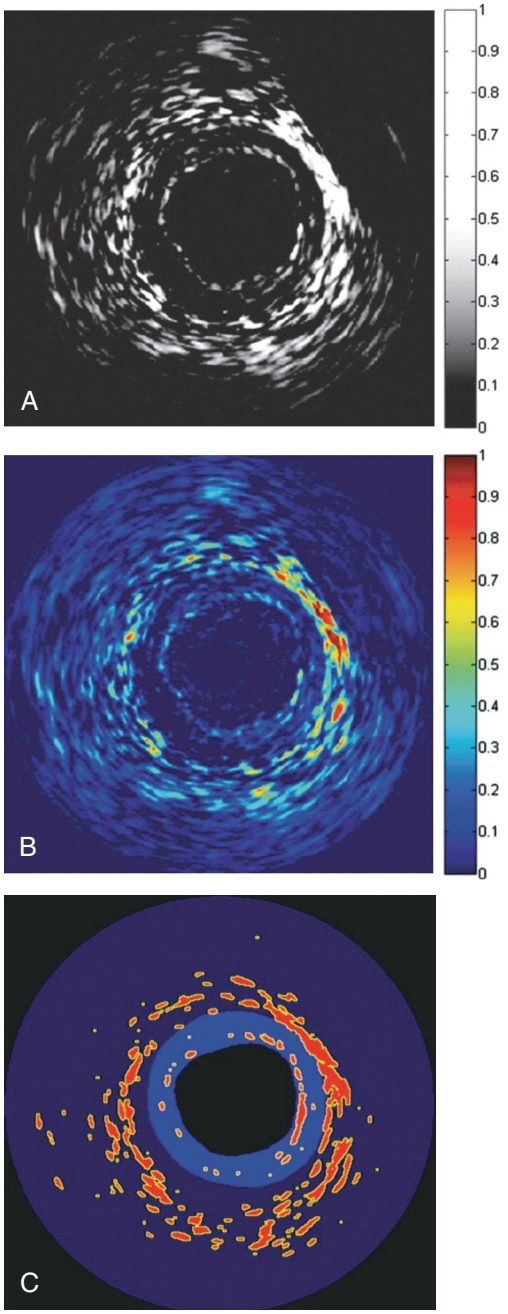


FIGURE 61-20 Differential intravascular ultrasound images identify the vasa vasorum and show the postinjection signals subtracted from the baseline signals. **A,** Black and white image (signal intensity of Fig. 61-1, *A* through *C*). **B,** Color-coded version of **A**. **C,** Threshold needed to show most significant areas of enhancement. (Modified from Vavuranakis M, Kakadiaris IA, O'Malley SM, et al: Images in cardiovascular medicine. Detection of luminal-intimal border and coronary wall enhancement in intravascular ultrasound imaging after injection of microbubbles and simultaneous sonication with transthoracic echocardiography. *Circulation* 112:e1-e2, 2005.)

Volcano, San Diego, CA). The catheter was upgraded with a 45-MHz transducer that is available for clinical practice. In vivo validation studies have shown positive results.[124]

VH gained significant attention with the PROSPECT trial.[18] IVUS-VH–derived TCFAs were associated with increased adverse cardiac events (HR = 3.35, $P < .001$). Most important, the highest-risk lesions (HR = 11.05, $P < .001$) were a conglomerate of several features, including a greater than 70% plaque burden, low minimal luminal area, and TCFA morphology. Isolating TCFAs by using VH may not be enough to categorize lesions as VPs. Use of VH also has been questioned by some studies that reported a poor correlation between IVUS-VH findings and histology for certain atheroma features in animal models[125,126] and for VH findings and clinical presentations of patients with ACS.[127]

It would be ideal to perform a prospective study randomizing patients with high-risk plaques documented by VH or other modalities to receive medical or invasive therapies, although the large number of patients needed and the increased costs may limit the ability to test this hypothesis. The PROSPECT ABSORB trial is an investigator-initiated, multicenter, randomized clinical trial that is designed to test the ability of the ABSORB Bioresorbable Vascular Scaffold plus guideline-directed medical treatment to safely increase the luminal diameter of VPs compared with medical treatment alone.

The PROSPECT trial results were reproduced in the VH-IVUS in Vulnerable Atherosclerosis (VIVA) study.[128] The prospective study included 170 patients with stable angina or ACS with elevated cardiac biomarkers who were referred for PCI. They underwent three-vessel IVUS-VH before PCI and after PCI of the culprit vessel and were followed for up to 3 years. The composite primary end point of total MACEs included death, myocardial infarction (MI), and unplanned revascularization, and nonrestenotic MACEs included a combined end point of death, MI, and unplanned revascularization, excluding in-stent, restenosis-driven events.

A total of 30,372 mm of IVUS-VH data were analyzed, including 1096 plaques that were classified by IVUS-VH. From these, 19 lesions resulted in MACEs, including 13 nonculprit lesions and 6 culprit lesions (Fig. 61-23). Whereas the PROSPECT study was based in analyzing and following individual plaques,[18] the VIVA study assessed the association between IVUS-VH–based plaque classification and nonrestenotic MACEs on a whole-patient scale. These studies highlight the association between IVUS-VH–derived TCFAs and MACEs, confirming that this technology can identify plaques likely to cause adverse clinical events. VH also can be used to identify several features of TCFAs, including fibrous cap thickness, necrotic core area, plaque inflammation, and degree of positive remodeling.

Evaluation of cap thickness by IVUS-VH is limited. In their initial publication, Nair and Vince commented on the limitations: "The window size currently applied for selection of regions of interest and eventual tissue map reconstructions is 480 μm in the radial direction. Detection of thin fibrous caps (≤65 μm below the resolution of IVUS) is be compromised, restricting the detection of vulnerable atheromas."[123] As a result, lesions with a fibrous cap thickness greater than 65 μm are incorrectly classified as TCFAs and perhaps overestimated. With an axial resolution of 250 μm, the method is insufficient to determine fibrous cap thickness.

Investigators have proposed a classification of IVUS-VH–derived TCFAs.[129] They have been defined as plaques with a rich necrotic core (>10%), without evident overlying fibrous tissue, and with a percent plaque volume of 40% seen on at least three consecutive images. These histologic features identify TCFAs that are prone to rupture. As also defined by histology, IVUS-VH–derived TCFAs cluster around the proximal segments of the arteries, are more often associated with positive remodeling, and are more frequently found in patients with ACS than those with stable angina.[130,131] Sawada and coworkers evaluated the ability of IVUS-VH and OCT to detect TCFAs in the same coronary lesions. IVUS-VH was very effective in detecting the absence of TCFAs. However, IVUS-VH diagnosed only half of the TCFAs compared with OCT.[132]

An initial concern was about the accuracy of using IVUS-VH–derived TCFAs to serve as surrogates for VPs and the prognostic value they could provide. This concern was mostly addressed by the PROSPECT trial, which highlighted the value of IVUS-VH–derived TCFAs. The concept was reinforced by a publication by Kubo and

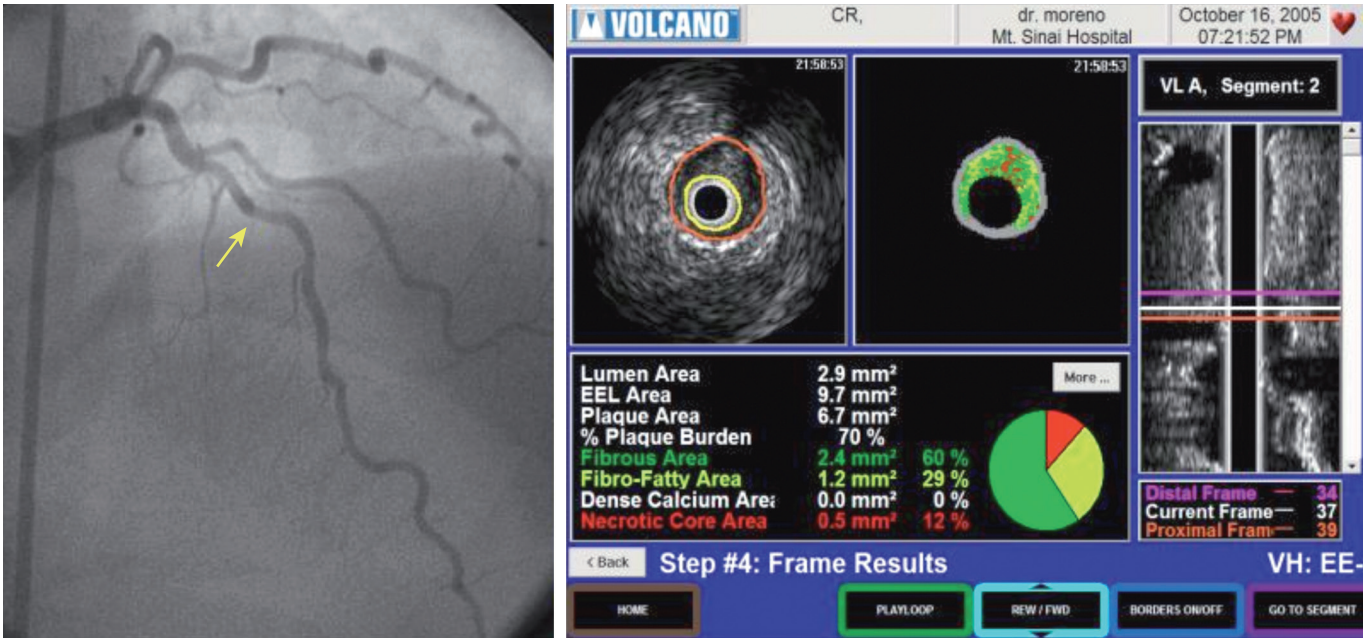


FIGURE 61-21 Color-coded reproduction of virtual histology intravascular ultrasound (IVUS-VH) plaque composition displayed in vivo in the catheter laboratory. Arrow on angiogram indicates the cross section imaged.

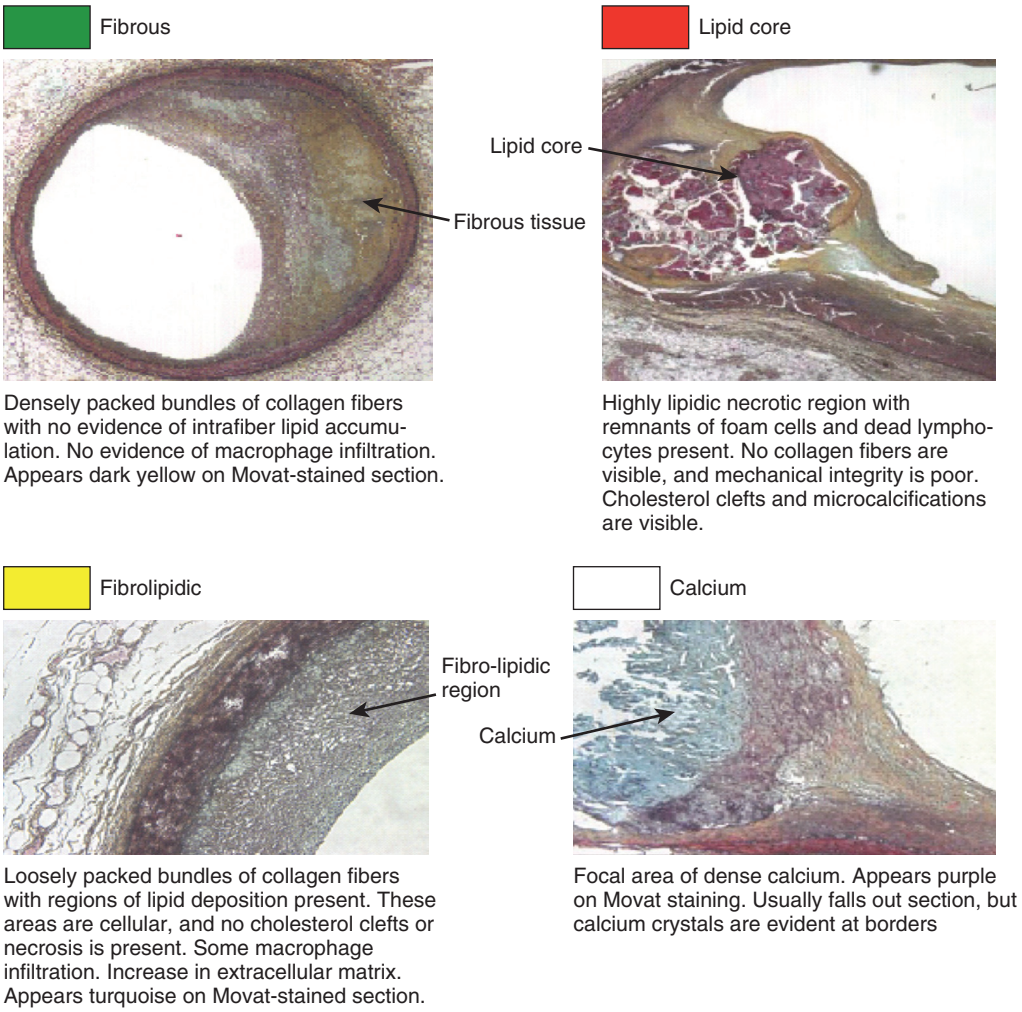


FIGURE 61-22 Definitions of the plaque components visualized with virtual histology intravascular ultrasound. (Courtesy Dr. D.G. Vince, Cleveland Clinic Lerner Research Institute, Cleveland, OH.)

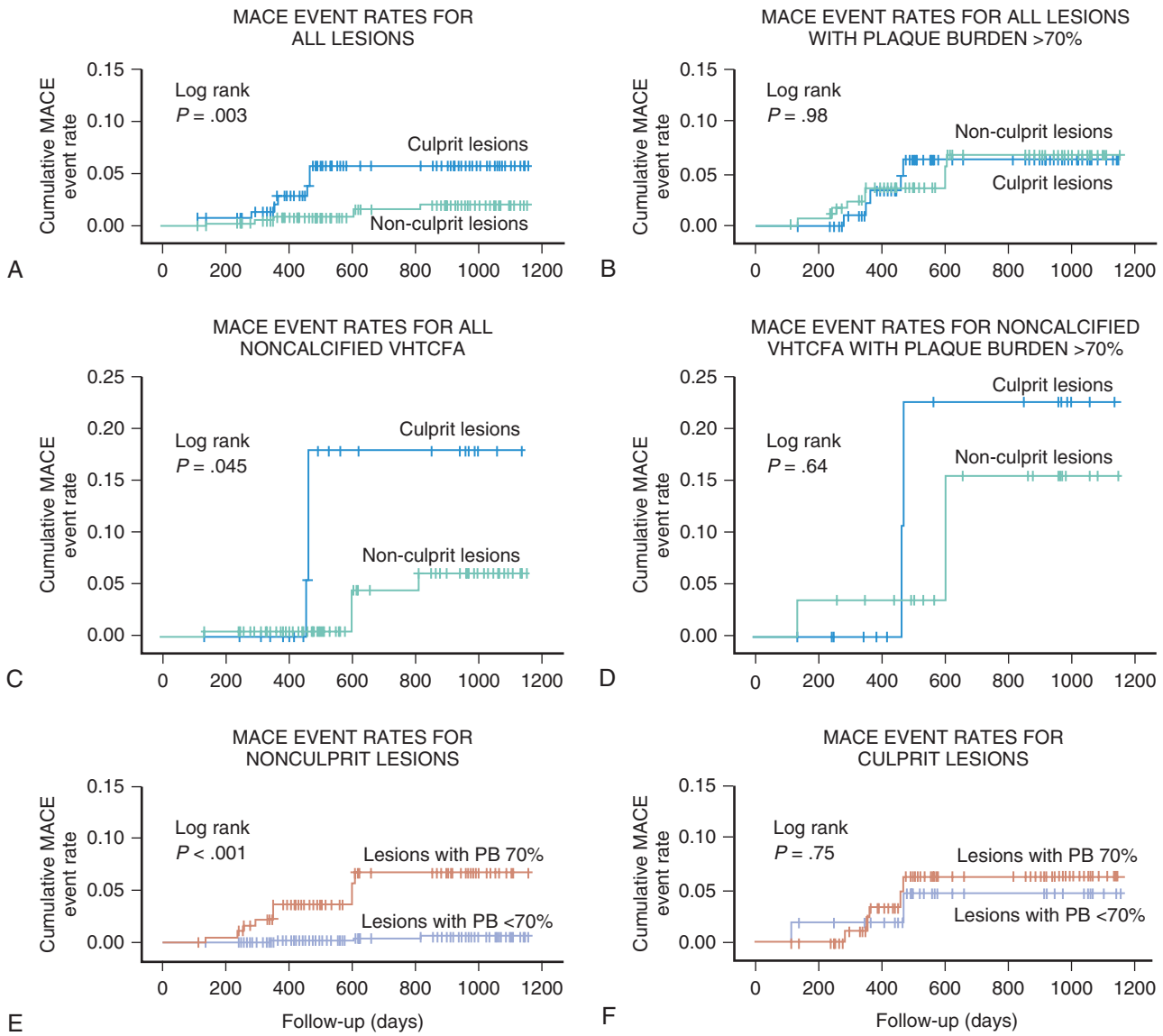


FIGURE 61-23 Kaplan-Meier plot of the cumulative major adverse cardiac event (MACE) rates in the VH-IVUS in Vulnerable Atherosclerosis (VIVA) study. **A,** All lesions. **B,** Lesions with a plaque burden (PB) greater than 70%. **C,** Noncalcified, virtual histology intravascular ultrasound thin-capped fibroatheromas (VHTCFAs). **D,** Noncalcified VHTCFAs with a PB greater than 70%. **E,** Nonculprit lesions. **F,** Culprit lesions.

colleagues, which addressed the natural history of IVUS-VH–derived TCFAs in 99 patients undergoing PCI who were followed for 12 months with serial evaluations of coronary vasculature using IVUS-VH.[133] Of the 20 IVUS-VH–derived TCFAs seen at baseline, 15 (75%) healed: 13 (65%) became thick-cap fibroatheromas, and 2 became fibrotic plaques (10%). Only 5 (25%) remained unchanged. The investigators also reported the occurrence of 12 new IVUS-VH–derived TCFAs that developed during the follow-up period: 6 from pathologic intimal thickening and 6 from TCFAs identified at baseline. No acute coronary events resulting from the initially identified or newly formed IVUS-VH–derived TCFAs occurred during the follow-up period.[133]

IVUS-VH was initially developed to identify calcific necrotic cores. However, the incidence and degree of calcification in necrotic cores varies, and necrotic cores without calcification may not be properly identified.[134] Most advanced atherosclerotic lesions have some degree of necrotic core. IVUS-VH is used to validate the presence or absence of a necrotic core and determine the necrotic core area (mm^2) and percent of total plaque area.[135] A PROSPECT substudy reported that plaques with large areas of attenuation on gray-scale analysis are associated with a large amount of IVUS-VH–detected necrotic core and are markers of fibroatheromas (i.e., TCFAs or thick-capped fibroatheromas).[136]

Despite the cumulative clinical evidence and proposed clinical applications for IVUS-VH, proper validation of necrotic core areas with histology using linear regression analysis has not been performed in humans and probably never will be. Limited studies have attempted to identify the correlations between necrotic core areas by using IVUS-VH with histology in a porcine model, and they demonstrated that IVUS-VH was unreliable in terms of necrotic core assessment.[125,126]

Many pathologic studies have established that necrotic core areas from patients with ACS are larger than those from patients with chronic stable angina.[19] Conversely, fibrous plaque areas (i.e., collagen) were significantly smaller in patients with ACS.[53] Surmely and associates concluded that data on plaque composition obtained by IVUS-VH contradict previously published histopathologic data.[127] However, Rodriguez-Granillo and colleagues identified larger necrotic areas in ruptured plaques and in nonculprit lesions from patients with ACS.[137] Validation with histology in cases of carotid atherosclerosis showed a

diagnostic accuracy of 99.4% for TCFAs, 96.1% for calcified TCFAs, 85.9% for fibroatheromas, 85.5% for fibrocalcific atheromas, 83.4% for pathologic intimal thickening, and 72.4% for calcified fibroatheromas.[138] In a prospective study of 16 patients who underwent PCI, IVUS-VH analysis was correlated with assessment of coronary atherectomy specimens. Correlation coefficients ranged from 0.90 to 0.97 for plaque components.[139]

Detection of macrophages in the fibrous cap requires a resolution of 10 to 20 μm. Because IVUS-VH resolution is at least 10 to 20 times lower, it is impossible for it to detect plaque inflammation in vivo.

IVUS is an excellent tool for detecting positive remodeling, and IVUS-VH should preserve this advantage. Positive remodeling is related to large necrotic core areas, which are more frequently seen in patients with ACS. Conversely, plaques with negative or constrictive remodeling are associated with smaller necrotic core areas, which usually are seen in patients with chronic stable angina. Studies have evaluated IVUS-VH–derived necrotic core areas in plaques with positive and negative remodeling and found smaller necrotic core areas in positively remodeled plaques.[108] However, some investigators have demonstrated contradictory data, with strong correlations between large IVUS-VH–derived necrotic core areas and positive remodeling.[136]

Vasa vasorum neovascularization and intraplaque hemorrhage require highly sophisticated technology and cannot be identified with IVUS-VH. Because of contradictory findings for the identification of necrotic core areas and remodeling, it impossible to determine the value of IVUS-VH–derived plaque composition in clinical practice.

Optical Coherence Tomography

OCT is a high-resolution intravascular imaging technique that is approved for clinical use. Among the invasive modalities, OCT provides the highest resolution (5 to 20 μm).[140] This resolution translates into sensitivity and specificity values between 92% and 100% for all components of TCFAs[141] and produces superb images (Fig. 61-24). Optical frequency domain imaging (OFDI) allows high-speed comprehensive imaging, scanning up to 5 cm with a single saline flush (Fig. 61-25).[142]

As the use of OCT has grown in clinical practice, guidelines have been developed for its application in the identification of plaque rupture, fibrous cap erosion, intracoronary thrombus, and TCFA location.[143-145] OCT can predict the no-reflow phenomenon in patients with large lipid cores who undergo PCI for ACS.[146] OCT can identify several high-risk plaque characteristics, including eccentric plaque distribution, concave lumen shape, intimal laceration, ruptured plaque, microchannels, lipid pools or a large lipid pool covered with a thin fibrous cap, macrophage accumulation, calcium deposition, and luminal thrombus (Fig. 61-26).[147,148]

Figure 61-27 compares OCT with IVUS-VH for the detection of TCFAs. OCT can be used to detect several features of TCFAs, including fibrous cap thickness, necrotic core area, plaque inflammation, degree of positive remodeling, plaque neovascularization, and intraplaque hemorrhage.

OCT is the only imaging tool that can identify a fibrous cap thickness of 65 μm or less. This was demonstrated with histologic studies using proper linear regression analysis ($r = 0.89$) (Fig. 61-28). In vivo studies showed that fibrous cap thickness was lowest in patients with AMI, intermediate in patients with unstable angina, and highest in patients with chronic stable angina (Fig. 61-29).[149] OCT can be used to estimate the incidence of TCFAs according to the clinical syndrome.

OCT has allowed researchers to identify levels of cap thicknesses that are associated with various clinical presentations. For instance, Yonetsu and colleagues demonstrated that the critical cap thickness associated with ACS was lower than 80 μm based on analysis in vivo of 266 lesions from 103 patients with ACS and stable angina.[150] In addition to measuring fibrous cap thickness, OCT can identify plaque rupture, fibrous cap erosion, and thrombosis more accurately than other imaging modalities, including IVUS and angioscopy. This was demonstrated by Kubo and associates, who studied patients with ACS and assessed fibrous cap thickness after statin treatment.[151]

OCT also can identify the mechanisms that lead to plaque thrombosis.[152] It can provide direct evidence of cap discontinuity with a clear cavity created inside the plaque; assess the type of thrombus formation after plaque erosion or rupture, including differentiation between red and white thrombus; and detect calcium in the atheroma as a protruding calcification, calcified nodule, or superficial calcium deposition.[152,153] Figure 61-30 compares intracoronary imaging modalities for assessment of plaque rupture.

The lipid pool and the necrotic core are signal-poor components and are therefore diffusely delineated with respect to the surrounding tissue. The lipid-rich plaque can be recognized by large areas of ill-defined, signal-poor regions that are evident to the naked eye. This lipid pool is quantified by measuring the lipid arc (i.e., maximal degree of lipid pool) or by the number of quadrants involved on a particular cross-sectional OCT image.[154] When the cap is thick and the signal is strong, the operator can tell that the signal is coming from a fibrous plaque mostly composed of collagen. OCT can identify lipid-rich plaques according to the characteristics of the signal described previously. This classification of the plaque moderately correlates with IVUS-VH for necrotic core identification.[151]

Linear correlations of human coronary plaque collagen were performed, and regression plots of OCT and measured collagen showed a correlation value of 0.475 ($P < .002$) and predictive values for collagen between 89% and 93%.[155] Nevertheless, OCT does not validate necrotic core areas as effectively as it does cap thickness and collagen, and further experimentation is warranted to achieve better necrotic and lipid tissue evaluation.[156,141]

Results from a study performed in the Thorax Center, Rotterdam, The Netherlands, demonstrated how vessel wall components, including necrotic cores and macrophages, can be distinguished by their optical properties with good histologic correlation.[157] Another study identified large necrotic cores as predictors of luminal stenosis from nonobstructive lesions when analyzed by OCT.[148]

OCT resolution allows proper identification of plaque inflammation (i.e., macrophage accumulation) in atherosclerotic plaques.[140] The first correlation in vitro was performed by Tearney and coworkers, who identified multiple strong backscatter reflections from caps with abundant macrophage infiltration, resulting in a relatively high OCT signal variance.[158] The signal variance was processed with the use of logarithmic transformation (Fig. 61-31). Linear regression analysis showed correlations for raw and logarithmic OCT-derived and immunostained macrophages of 0.84 ($P < .0001$) and 0.47 ($P < .05$), respectively. In vivo studies showed increased macrophage density in ruptured plaques from patients with ACS (in culprit and nonculprit lesions) compared with nonruptured plaques from patients with chronic stable angina (Fig. 61-32).[159] OCT also can assess the content of macrophages located in the fibrous cap and enabled correlation of this macrophage density with the peripheral white blood cell count.[160]

OCT has limited plaque penetration; the depth is reduced to 2 to 3 mm. It is therefore not possible to image beyond the internal elastic lamina, and OCT cannot assess the diameter of the vessel to calculate the remodeling index. This is a significant limitation of OCT.

OCT is the gold standard for quantifying neovascularization and the effects of novel antiangiogenic therapies in common diseases such as age-related macular degeneration, extrafoveal choroid neovascularization, and proliferative diabetic retinopathy.[161] However, the number of studies specifically assessing atherosclerotic neovascularization or intraplaque hemorrhage is limited.

A study by Kitabata and colleagues proposed the use of OCT to identify intraplaque structures that may represent neovessels. These *microchannels* were defined as no-signal, tubuloluminal structures without a connection to the vessel lumen seen on three consecutive cross-sectional OCT images (Fig. 61-33). The investigators reported that plaques with microchannels displayed characteristics of vulnerability, including plaque rupture, positive remodeling, and thin fibrous caps, compared with plaques without these structures. A later study

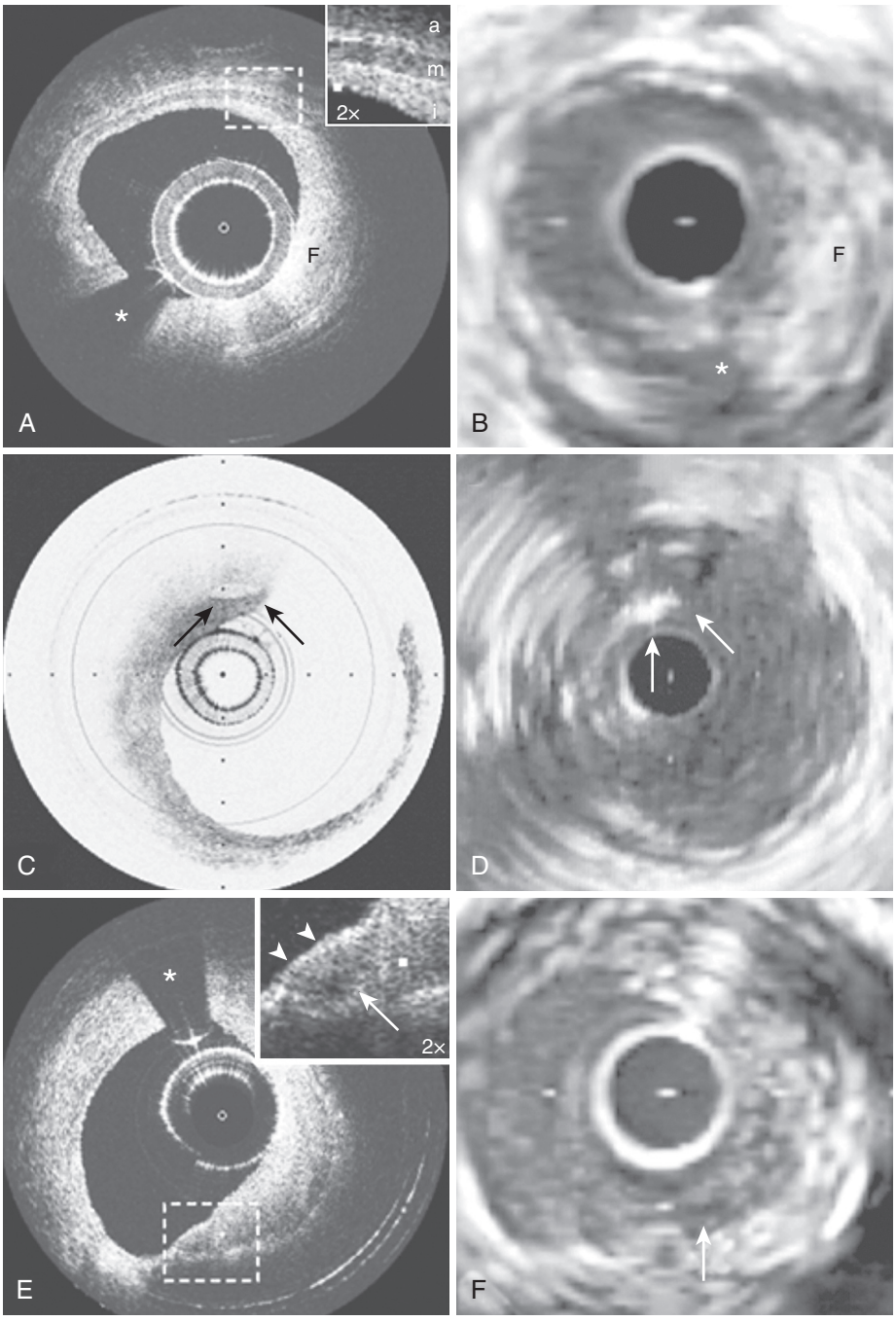


FIGURE 61-24 In vivo optical coherence tomography (OCT) images of various coronary plaque types *(left column)* are compared with corresponding intravascular ultrasound (IVUS) images *(right column)*. **A,** From 9 o'clock to 2 o'clock, the three-layer structure (*a,* adventitia; *i,* intima; *m,* media) of a typical intimal hyperplasia is shown by OCT, along with a magnified area *(inset)*. A homogeneous, signal-rich pattern indicates the fibrous plaque (F), which is partly obscured by a guidewire artifact *(asterisk)*. **B,** Fibrous plaque (F) on the IVUS image corresponds to that shown in **A**. **C,** A signal-poor region surrounded by sharp borders represents calcific plaque *(arrows)*. **D,** On the IVUS image corresponding to **C**, calcium is easily identified, but the strong signal obscures the structure in front of the calcium deposit, and a back-shadow artifact obscures that behind the deposit. **E,** In a lipid-rich plaque, a signal-poor region *(arrow in inset)*, surrounded by diffuse borders and separated by a thin cap *(arrowheads in inset)*, is consistent with a thin-cap fibroatheroma. The *asterisk* indicates a guidewire artifact. **F,** The intravascular ultrasound image corresponding to **E** suggests a superficial echolucent region *(arrow)*. (Modified from Low AF, Tearney GJ, Bouma BE, Jang IK: Technology Insight: optical coherence tomography—current status and future development. *Nat Clin Pract Cardiovasc Med* 3:154-162, quiz 172, 2006.)

reported that the microchannels identified by OCT were markers of progression from nonobstructive to obstructive plaques[148] and that they were associated with unstable clinical syndromes.[162] However, histologic validation of the structures observed with in vivo OCT imaging has not been done.[162,163]

Angioscopy

Direct visualization of atherosclerotic plaques can provide information about plaque composition and has the potential to identify specific plaque components.[164] Angioscopic classification of coronary lesions is performed according to the color of plaques in a bloodless field. White, yellow, and glistening yellow plaques have been studied in patients with CAD. Yellow plaques are associated with high concentrations of cholesterol-laden crystals with or without plaque degeneration, and an intense yellow color indicates a thin fibrous cap overlying a lipid core according to histologic studies.

Uchida and colleagues evaluated the prospective clinical value of the three types of plaques in a prospective, three-vessel angioscopic study that included 157 patients with chronic stable angina.[165] The incidence of ACS was evaluated 12 months later. Most patients (75%) had white plaques, which were associated with a low incidence of ACS (3.3%). The second group of patients (18%) had yellow plaques, which were associated with an intermediate incidence of ACS (7.6%). The third group of patients (8%) had glistening yellow plaques, which were associated with an impressive incidence of ACS (68%) and death in 22% of cases.[165] The investigators also evaluated the fibrous cap thickness of the three types of plaques in autopsy specimens (Fig. 61-34). White plaques were associated with thick caps (400 μm), yellow

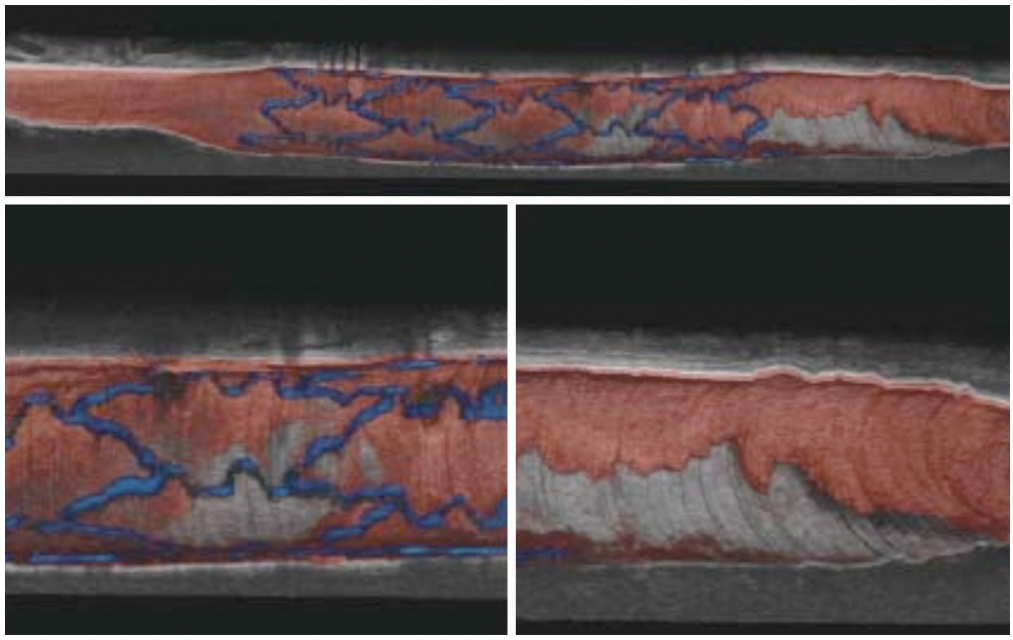


FIGURE 61-25 In vivo optical frequency domain imaging (OFDI) of a coronary stent deployed in a porcine model shows normal endothelium *(red)*, dissections induced by the balloon during stent deployment *(white)*, and stent struts *(blue)*. (From Bouma BE: New insights from OCT, polarization-sensitive OCT, and the emergence of OFDI. Presented at the Transcatheter Therapeutic Intervention [TCT] meeting, Washington, DC, 2006.)

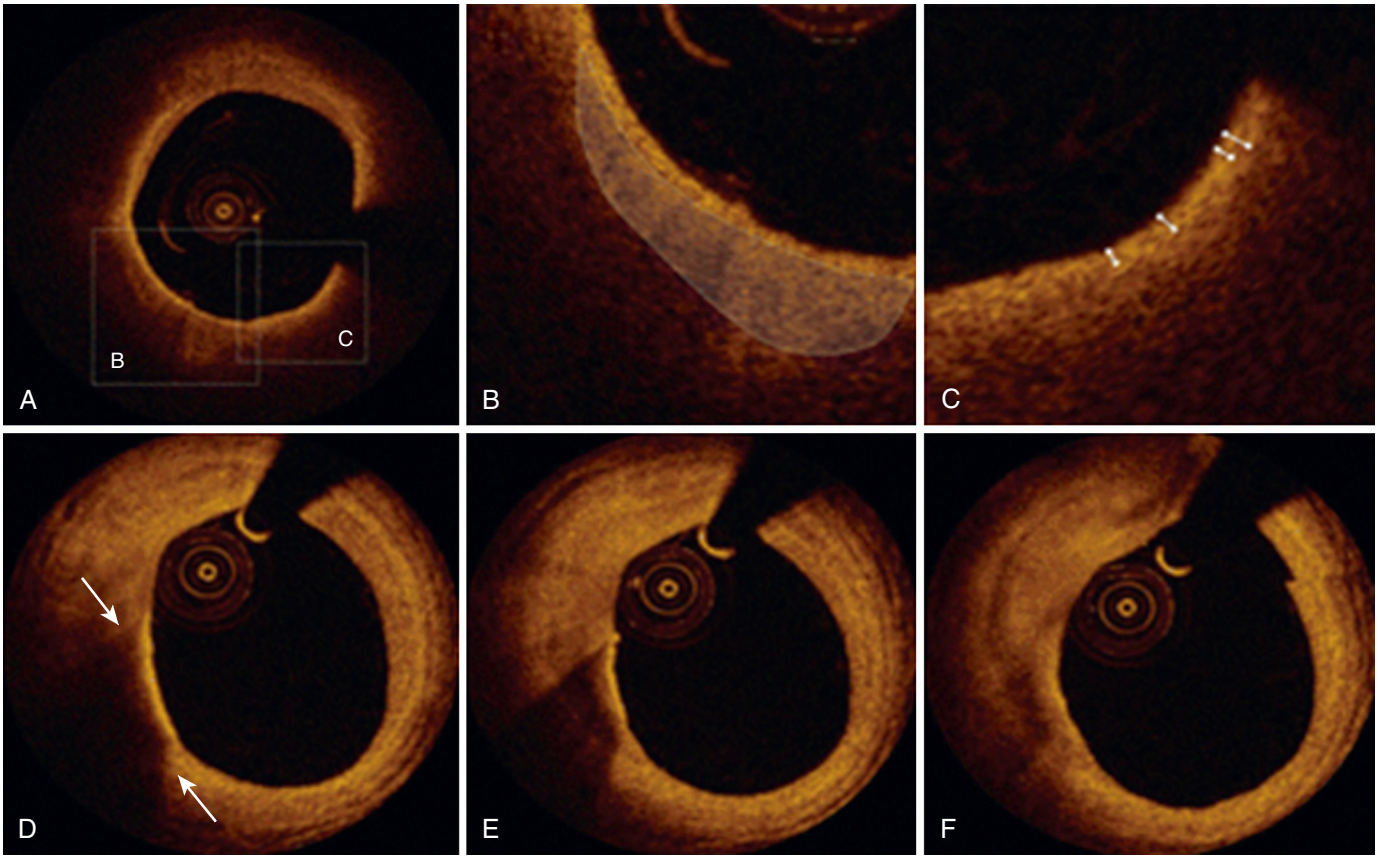


FIGURE 61-26 An optical coherence tomography cross section from a nonculprit vessel of a patient with an ST-elevation myocardial infarction. **A,** From 1 to 11 o'clock, a relatively signal-rich layer is seen covering a signal-poor region. This layer becomes thinner from 4 to 8 o'clock. The underlying signal-poor region is diffusely delineated at 4 to 6 o'clock but is more marked at 6 to 8 o'clock (*shaded area* in the magnification in **B**), suggesting a lipid pool and a calcific pool, respectively, according to criteria by Yabushita and colleagues.[158] **C,** Magnification of the diffusely delineated signal-poor region in **A** illustrates the difficulty in manually measuring the thickness of the overlying fibrous cap *(white traces)*. Measurements from left to right are 60, 80, 70, and 130 μm. If the first measurement is correct, the lesion can be diagnosed as a thin-cap fibroatheroma (TCFA) using the current criteria. **D** through **F,** Three consecutive frames show findings consistent with luminal macrophage accumulation. There is a signal-rich band (**D**) from 7 to 9 o'clock, with strong light attenuation creating an underlying signal-poor region that is relatively sharply demarcated laterally *(arrows)*. The appearance as a whole is reminiscent of a TCFA, but inspection of adjacent frames (**E** and **F,** 0.4 mm apart) suggests that there is no typical lipid pool or necrotic core, which would be expected in a TCFA having a large necrotic core. Instead, the attenuated area becomes somewhat transparent, with even sharper borders in **E,** and it disappears in **F,** revealing a relatively homogeneous, bright tissue composition, consistent with a fibrous plaque. The high light attenuation in **D** can be attributed to shadowing from the luminal signal-rich band, which probably represents macrophage infiltration. (From Radu MD, Falk E: In search of vulnerable features of coronary plaques with optical coherence tomography: is it time to rethink the current methodological concepts? *Eur Heart J* 33:9-12, 2012.)

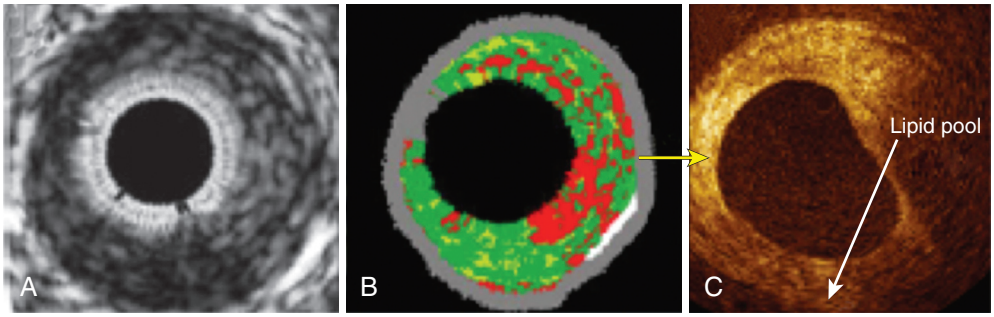
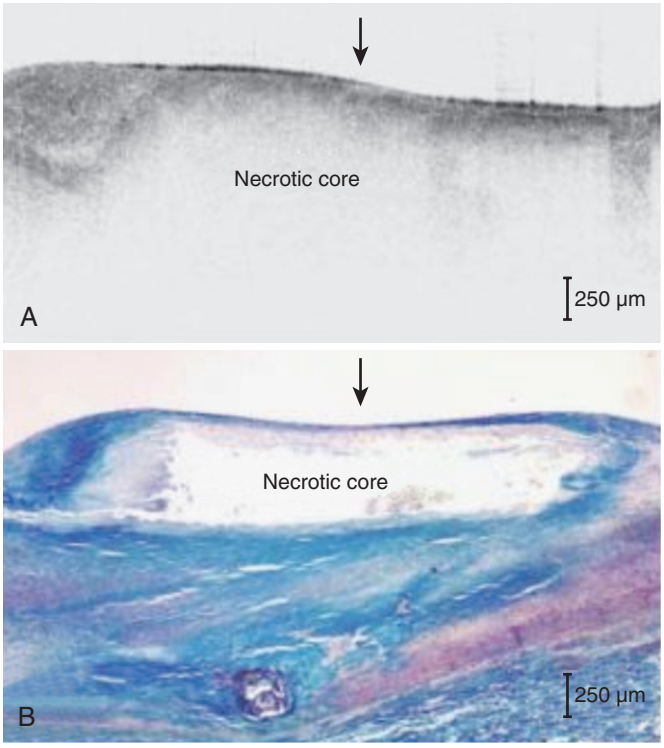


FIGURE 61-27 A thin-cap fibroatheroma is imaged in vivo by three different invasive modalities. **A,** Conventional intravascular ultrasound (IVUS) imaging. **B,** Virtual histology intravascular ultrasound (IVUS-VH). **C,** Optical coherence tomography (OCT). The *yellow arrow* from **B** to **C** corresponds to the matching cross-sectional frame of the same arterial segment by IVUS-VH (**B**) and OCT (**C**). (From Sawada T, Shite J, Garcia-Garcia HM, et al: Feasibility of combined use of intravascular ultrasound radiofrequency data analysis and optical coherence tomography for detecting thin-cap fibroatheroma. *Eur Heart J* 29:1136-1146, 2008.)



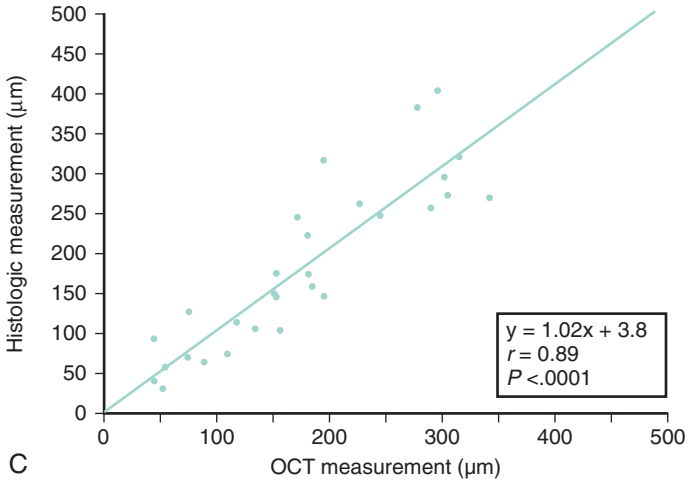


FIGURE 61-28 Optical coherence tomography (OCT) evaluation of fibrous cap thickness. **A,** Minimal fibrous cap thickness was 44.1 μm by OCT *(arrow)*. **B,** Minimal fibrous cap thickness was 40.4 μm by histologic measurement *(arrow)*. The necrotic core is visualized underneath the fibrous cap. **C,** Linear regression analysis shows an excellent correlation between OCT and histologic measurements in 29 human atherosclerotic plaques. (From Jang IK: Optical coherence tomography: studies at MGH. Presented at Transcatheter Cardiovascular Therapeutics (TCT) meeting, Washington, DC, September 24-28, 2002.)

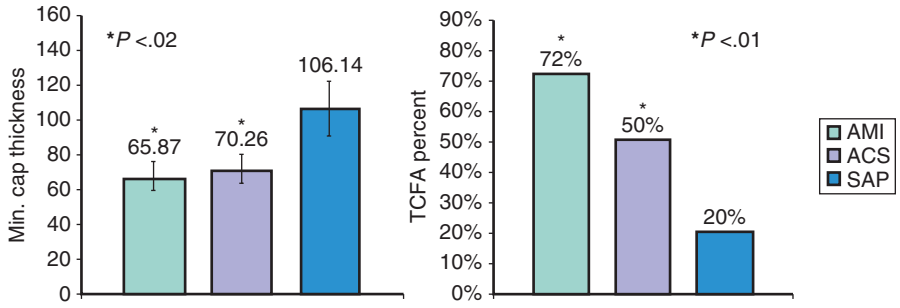


FIGURE 61-29 In vivo quantification of fibrous cap thickness by optical coherence tomography. Cap thickness was lowest in patients with acute myocardial infarction (AMI), intermediate in patients with acute coronary syndrome (ACS; unstable angina and non-ST segment elevation myocardial infarction), and highest in patients with chronic stable angina pectoris (SAP). As a result, the incidence of thin-cap fibroatheroma (TCFA) is highest in those with AMI and lowest in those with SAP. (From Jang IK, Tearney GJ, MacNeill B, et al: In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography. *Circulation* 111:1551-1555, 2005.)

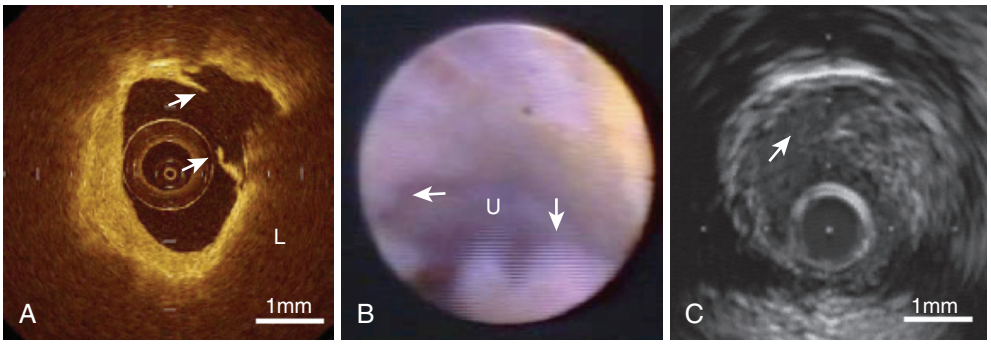


FIGURE 61-30 Fibrous cap rupture during acute coronary syndrome assessed by various invasive modalities. **A,** Optical coherence tomography demonstrates a lipid-rich area (L) and a fibrous cap discontinuation *(arrows)* that protrudes into the lumen. **B,** Angioscopy shows a yellow lesion with cap disruption *(arrows)* and ulceration (U). **C,** Intravascular ultrasound shows an eccentric plaque rupture at the shoulder *(arrow)*. (From Kubo T, Imanishi T, Takarada S, et al: Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angioscopy. *J Am Coll Cardiol* 50:933-939, 2007.)

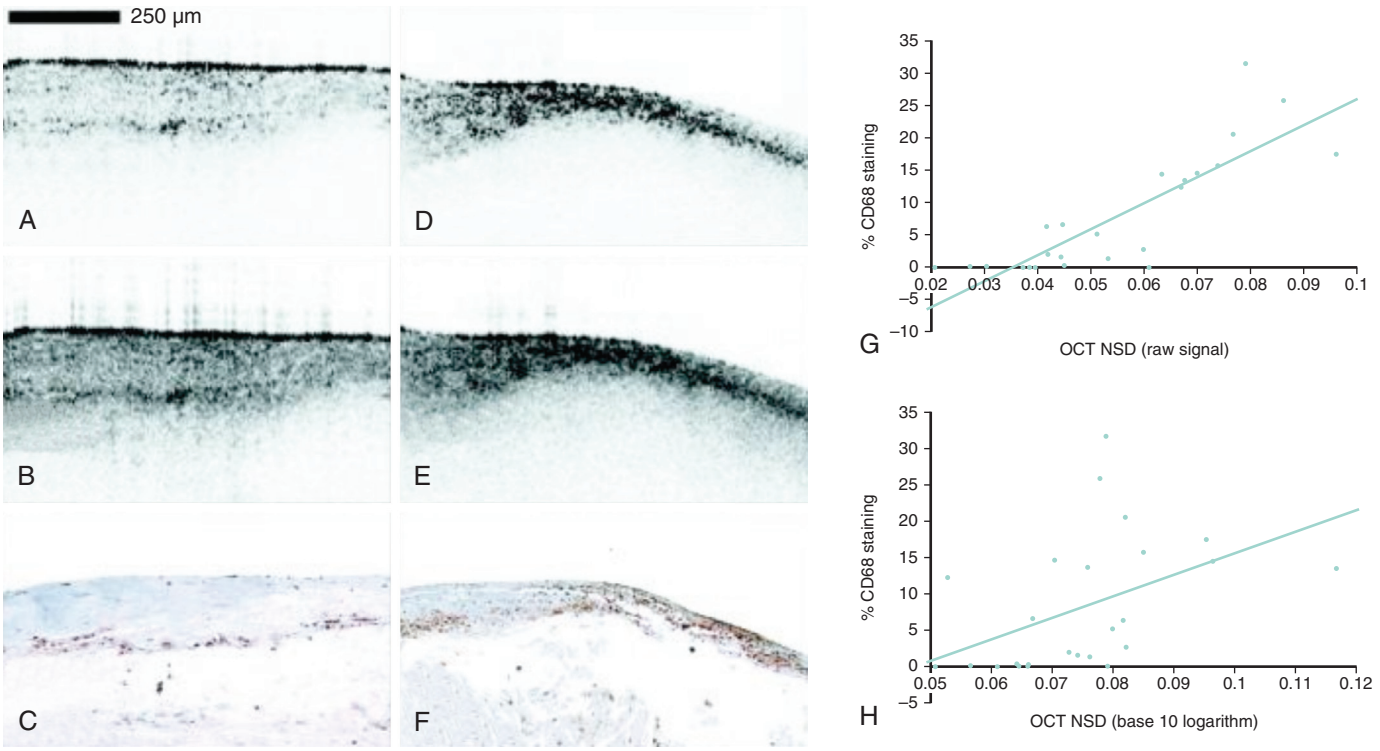


FIGURE 61-31 Raw (**A**) and logarithm base 10 (**B**) optical coherence tomography (OCT) images of a fibroatheroma with a low density of macrophages within the fibrous cap. **C,** Corresponding histology for **A** and **B** (CD68 immunoperoxidase stain, ×100). Raw (**D**) and logarithm base 10 (**E**) OCT images of a fibroatheroma with a high density of macrophages within the fibrous cap. **F,** Corresponding histology for **D** and **E** (CD68 immunoperoxidase stain, ×100). Correlations are shown between the raw (**G**) and logarithm base 10 (**H**) OCT signal (normalized standard deviation [NSD]) and CD68 percent area staining (*diamonds,* NSD data; *solid line,* linear fit). (From Tearney GJ, Yabushita H, Houser SL, et al: Quantification of macrophage content in atherosclerotic plaques by optical coherence tomography. *Circulation* 107:113-119, 2003.)

plaques with thinner caps (80 µm), and glistening yellow plaques with the thinnest caps (10 to 20 µm).

Other angioscopic studies of patients with ACS have shown a higher incidence of yellow plaques. Asakura and coworkers performed three-vessel angioscopy in patients 1 month after AMI.[166] Yellow plaques were detected in 90% of 21 culprit lesions, and the number of these plaques was equally prevalent in the infarct-related and non–infarct-related coronary arteries (3.7 ± 1.6 vs. 3.4 ± 1.8 plaques per artery), suggesting a diffuse rather than a localized process in patients with AMI.

To evaluate the predictive value of yellow plaques in clinical practice, Ohtani and colleagues performed culprit vessel angioscopy in 552 patients with chronic stable angina, ACS, or AMI.[167] Yellow color intensity was graded. The number of yellow plaques varied from zero to five or more (Fig. 61-35). After 5 years, 7.1% of patients had developed ACS. The mean number of yellow plaques was higher in the patients with an ACS event compared with those without the event (3.1 ± 1.8 vs. 2.2 ± 1.5, $P = .008$). However, the yellow color intensity scale was similar and lacked predictive value.

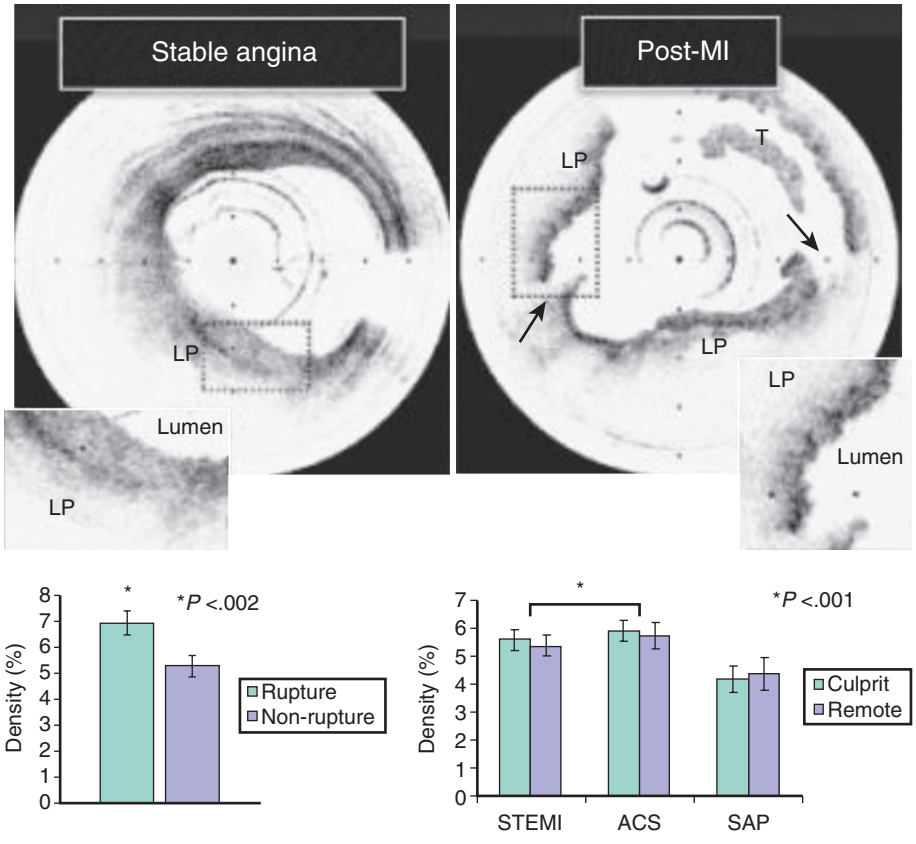


FIGURE 61-32 Optical coherence tomography images of plaques from patients with stable angina *(upper left)* and after myocardial infarction (MI) *(upper right)*. Increased signal area is seen at the fibrous cap after MI *(detail)*, highlighting areas of increased macrophage density. The *black arrows* denote areas of fibrous cap rupture. *Lower left,* Increased macrophage density in ruptured *(green bar)* compared with nonruptured *(purple bar)* plaques. *Lower right,* Macrophage density in culprit *(green bar)* and remote *(purple bar)* plaques from patients with ST-elevation myocardial infarction (STEMI), acute coronary syndrome (ACS), and stable angina pectoris (SAP). Macrophage density is higher in culprit and remote plaques from patients with STEMI and ACS compared with SAP. *LP,* Lipid pool. (From MacNeill BD, Jang IK, Bouma BE, et al: Focal and multi-focal plaque macrophage distributions in patients with acute and stable presentations of coronary artery disease. *J Am Coll Cardiol* 44:972-979, 2004.)

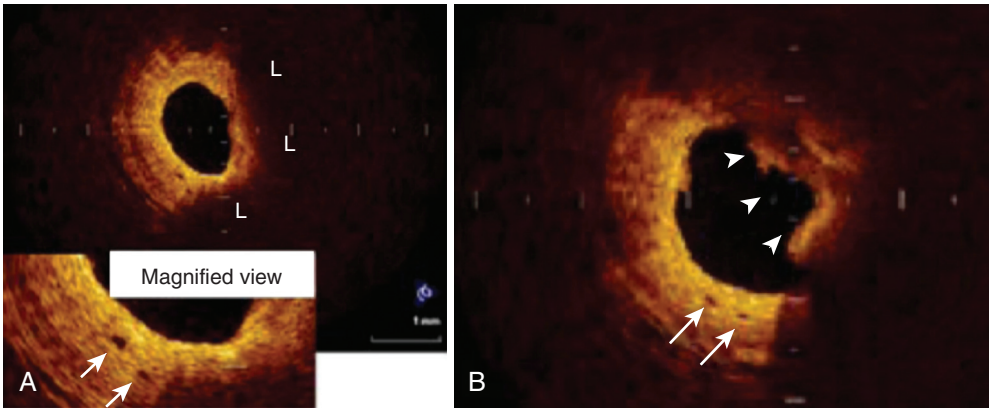


FIGURE 61-33 Microchannels representing plaque neovascularization. **A,** Eccentric, lipid-rich plaque (L) with microchannels *(arrows on inset)*. **B,** Intracoronary thrombus *(arrowheads)* and two additional microchannels *(arrows)*. (Modified from Kitabata H, Tanaka A, Kubo T, et al: Relation of microchannel structure identified by optical coherence tomography to plaque vulnerability in patients with coronary artery disease. *Am J Cardiol* 105:1673-1678, 2010.)

An in vivo study that compared angioscopy with OCT demonstrated that yellow plaques identified by angioscopy had a 98% sensitivity and 96% specificity for the identification of a fibrous cap measuring less than 110 µm thick by OCT.[168] The investigators also found that plaques with angioscopic yellow grade 3 had a mean fibrous cap thickness of 40 ± 14, but they did not specify the sensitivity and the correlation coefficients for plaques with fibrous caps measuring less than 65 µm.[168] Clinically, yellow plaques are seen more commonly at the site of culprit lesions, are more likely to rupture, and carry an increased risk of subsequent coronary events.

Similar to other imaging modalities, angioscopy has been used to demonstrate plaque stabilization with statin therapy, as manifested by decreased yellow intensity that correlates with the plaque volume reduction shown by IVUS.[169] These findings have been reproduced in several studies, especially in diabetic patients for whom the morphologic features of plaques determined by angioscopy can reveal important prognostic information.[170,171]

The main limitation of coronary angioscopy is the need for a blood-free environment to visualize the vessel wall, which requires proximal occlusion with a low-pressure intracoronary balloon. The risk of ischemia and vessel injury is increased with this method. Another option is to flush saline continuously before introducing the angioscope, which transiently displaces blood. Color interpretation is usually subjective and can be affected by the angulation of the catheter.

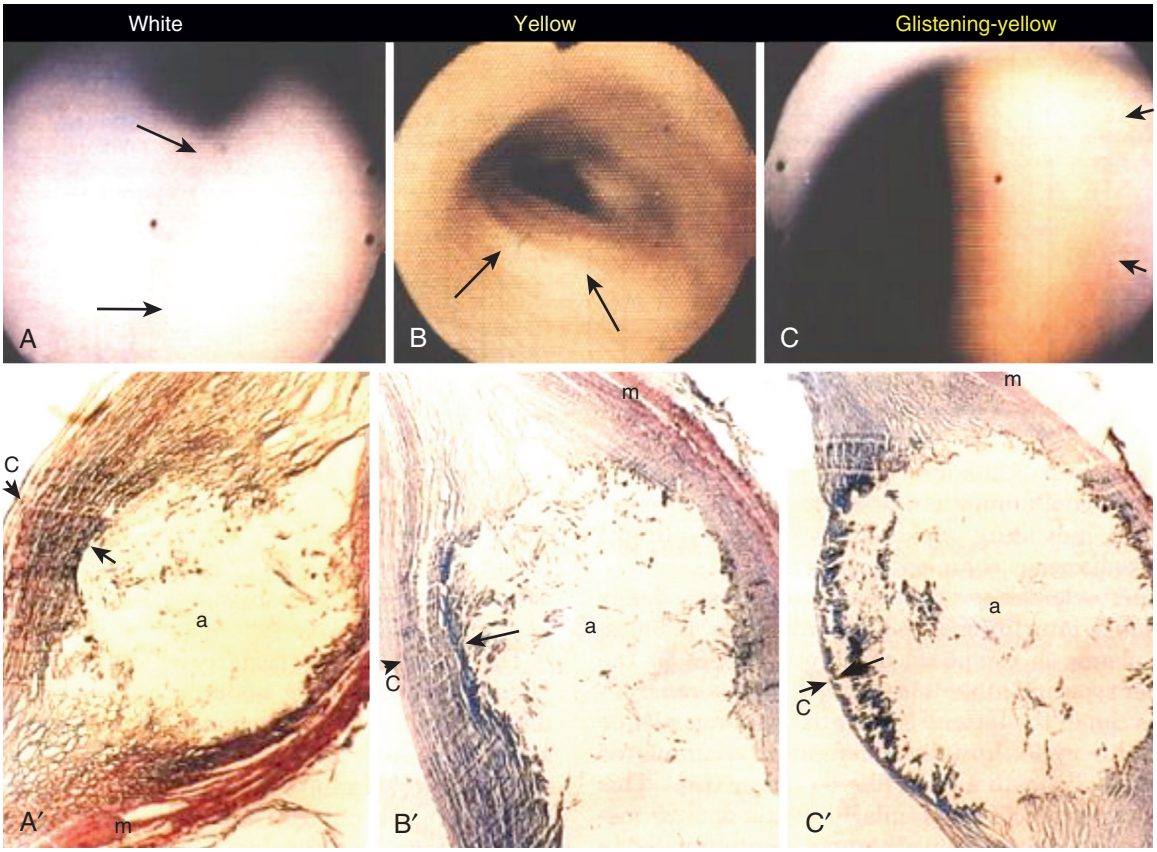


FIGURE 61-34 Correlation between angioscopic appearance *(upper panel)* and histopathologic features of plaques at the time of autopsy *(lower panel)*. The white plaque seen in the *upper* **A** (*arrows* highlight its white appearance) is associated with a thick cap *(black arrows)* in histology as seen in **A′.** Yellow plaque seen in *upper* **B** (yellow color highlighted by arrows in **B**) is associated with a thinner cap as denoted by *arrows* in *lower* **B′.** Glistening yellow plaque as seen in *upper* **C,** where *black arrows* point to the glistering yellow color, is associated with the thinnest cap in histology as pinpointed by the arrows in *lower* **C′.** (From Uchida Y, Nakamura F, Tomaru T, et al: Prediction of acute coronary syndromes by percutaneous coronary angioscopy in patients with stable angina. *Am Heart J* 130:195-203, 1995.)

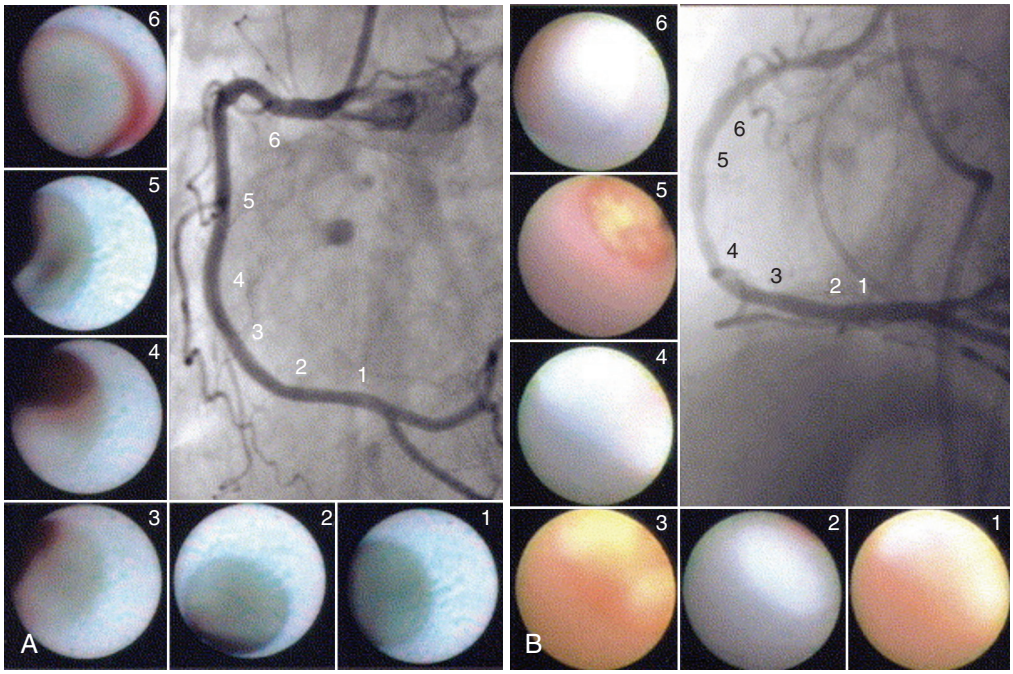


FIGURE 61-35 A representative case with no yellow plaque (**A**) and one with multiple yellow plaques (**B**). In **A**, no yellow plaques were detected in the right coronary artery. In **B,** three yellow plaques were detected in the right coronary artery, and the maximum color grade of yellow plaques was 3. The cross sections are numbered according to their location along the vessel, as shown on the angiographic image. (From Ohtani T, Ueda Y, Mizote I, et al: Number of yellow plaques detected in a coronary artery is associated with future risk of acute coronary syndrome: detection of vulnerable patients by angioscopy. *J Am Coll Cardiol* 47:2194-2200, 2006.)

To overcome these issues, a quantitative colorimetric method was developed.

Ishibashi and colleagues proposed a more accurate grading system for interpretation of coronary angioscopic data using quantitative colorimetric analysis based on the L*a*b* color space and brightness algorithm.[172] Based on this algorithm, plaque disruption in culprit lesions of patients with ACS was found in 79% of those lesions with high yellow color intensity (b* value >23) but only 41% of those with b* values lower than 23 ($P = .007$).[172]

Because angioscopy is only a surface evaluation technique, it cannot provide direct information about plaque composition. Fibrous cap thickness, inflammatory cell infiltration, necrotic core size, and remodeling are mostly considered surrogate parameters based on color coding and correlation coefficients. A prospective study of coronary angioscopy in nonobstructive coronary lesions would help to elucidate the angioscopic factors associated with clinical events.

Spectroscopy

Spectroscopy is a nondestructive optical technology with the ability to analyze the chemical composition of plaque components.[173] After irradiation of tissue with a laser beam, scattered photons are acquired to identify specific features of plaque vulnerability. Plaque components such as calcium and cholesterol have specific absorption and reflectance patterns of light, producing a pattern that is converted into an image. This modality is important for the identification of the necrotic core, fibrous cap, and inflammation.[174]

Two modalities are being evaluated for intravascular detection of high-risk VPs: near-infrared and Raman spectroscopy. Both techniques have good correlations with histologic analyses of coronary and aortic tissue.[175] However, the complexity of signal analysis may force investigators to focus on only one or two features of plaque vulnerability.

The physicochemical characteristics of lipid and calcium and their shift patterns make Raman spectroscopy highly sensitive for plaque detection. However, only a few photons are recruited into the Raman shift, providing poor tissue penetration and a low signal-to-noise ratio. Backscattered noise can also decrease signal quality and limit imaging interpretation. Newer technologies in combination with IVUS have improved image quality by increasing signal acquisition.[176]

Near-infrared spectroscopy (NIRS) measures diffuse reflectance signals with the use of near-infrared light. The spectrometer emits light onto a substance and measures the light that is reflected over a wide range of optical wavelengths, which are processed as a spectrum, applied to an algorithm that predicts the probability of VPs, and displayed on a chemogram. The main objective of NIRS is quantification of the necrotic core. The result is reported on a scale of 1 to 999, called the *lipid core burden index* (LCBI). Because of this feature, NIRS has the potential for becoming the standard for necrotic core evaluation.[177]

The NIRS system was evaluated in 106 patients undergoing PCI in a multicenter study, with encouraging results.[178] The investigators compared in vivo imaging with autopsy NIRS signals by using multivariate analysis. They found that NIRS appropriately identified lipid core–containing plaques in vivo. NIRS can be performed without replacing the blood in the vessel, but it can detect only one characteristic of VPs, offering no input on the superficiality of lipid cores or fibrous cap thickness.

Catheters that combine NIRS with IVUS provide complementary data for evaluation of atherosclerosis by combining assessment of plaque burden, plaque composition, and vascular remodeling.[179] Multiple-imaging technology has shown excellent correlation with adverse cardiac events,[180] similar to that reported by the PROSPECT trial.[18] The combination of a catheter providing IVUS for determining plaque burden and minimal luminal area and NIRS for evaluating necrotic core content offers a more comprehensive assessment of the high-risk lesion.[181] This has been proved by correlating NIRS findings with clinical findings in various clinical scenarios, including ST-elevation myocardial infarction (STEMI),[179] periprocedural MI,[177] and in cardiac arrest survivors.[182]

For patients with STEMI, Madder and colleagues reported a 5.8-fold higher maximum LCBI (4 mm) in culprit lesions compared with nonculprit plaques.[179] Large LCBI scores were reported for 95% of culprit lesions. The investigators identified a threshold (maxLCBI4mm > 400) for detecting culprit segments during STEMI with 85% sensitivity and 98% specificity. Similar results were reported by Erlinge and coworkers at the Transcatheter Cardiovascular Therapeutics meeting in 2013.[183] In patients surviving cardiac arrest, plaques with a large LCBI score were responsible for the clinical event.[182] Accumulated evidence suggests that large necrotic core lesions appear to be most relevant substrate for life-threatening ACS.

Studies have found that plaques with large LCBI scores determined by NIRS are associated with increased risk of periprocedural AMI after PCI.[181,184] Plaques with a very large LCBI scores may benefit from placement of an embolic protection device (e.g., filter) to prevent distal embolization and reduce the incidence of periprocedural MI. This is the rationale of the Coronary Assessment by Near-Infrared of Atherosclerotic Rupture-Prone Yellow (CANARY) trial, and it will soon be known whether spectroscopy is a useful tool in the catheter laboratory for identifying a lipid core plaque that is at high risk of rupturing during therapy and causing complications.

NIRS in combination with IVUS has been shown to accurately detect high-risk plaques compared with OCT.[185] Roleder and associates evaluated 60 patients undergoing coronary angiography. OCT and combined NIRS-IVUS were done on 76 identical coronary segments. When OCT was used to define TCFAs based on a fibrous cap measuring less than 65 μm, the lesions exhibited positive remodeling, a higher plaque burden, a higher plaque volume, a smaller cross-sectional area, and longer plaque lengths, whereas NIRS revealed a greater LCBI score for 2-mm segments. OCT had greater accuracy for identifying TCFAs when an LCBI score higher than 315 and a remodeling index higher than 1.046.[185]

Most clinical data on NIRS come from cross-sectional studies, and there are few studies regarding its application for evaluation of the natural history of VPs with prospective follow-up. Accrued data appear to support the plaque expansion hypothesis, and it would be of great utility to assess the natural history and prognosis of lipid-rich atheromas with greater than 70% plaque burdens because of their potential for increasing MACEs during follow-up.

The ongoing PROSPECT II trial hopes to address these issues.[186] It is an investigator-initiated, multicenter, prospective registry for assessing the ability of intracoronary NIRS to identify non–flow-obstructing VPs that ultimately promote coronary events. This trial is recruiting 900 patients with ACS at 20 hospitals in Sweden, Denmark, and Norway. After patients undergo PCI of all culprit and obstructive lesions, three-vessel IVUS plus NIRS imaging will be performed to assess the proximal 6 to 8 cm of each coronary artery. The follow-up period will be at least 3 years, with assessment of secondary outcomes related to the safety and efficacy of bioabsorbable stents. Patients who have lesions with greater than 70% stenosis will be randomized to bioresorbable stenting plus optimal medical therapy or to optimal medical therapy alone to assess a primary safety end point.

The Lipid-Rich Plaque (LRP) study is an ongoing, multicenter clinical trial that is recruiting 9000 patients with ACS from centers in the United States, Europe, and Japan to evaluate the role of LCBI in predicting future MACEs. The LRP study will test whether a nonobstructive, lipid-rich plaque documented by IVUS plus NIRS is associated with new coronary events within 24 months.[187] These study designs will help to evaluate potential therapies for the prevention of cardiac events in patients with obstructive plaques with high-risk features.

Finally, NIRS can be used to follow patients after therapy. It has documented plaque regression after aggressive medical therapy with statins (Fig. 61-36).[188]

Elastography, Palpography, and Intravascular Thermography

Several additional intravascular imaging modalities have been designed to identify and characterize high-risk plaques. They assess the physical, mechanical, and metabolic features of VPs. Although some data

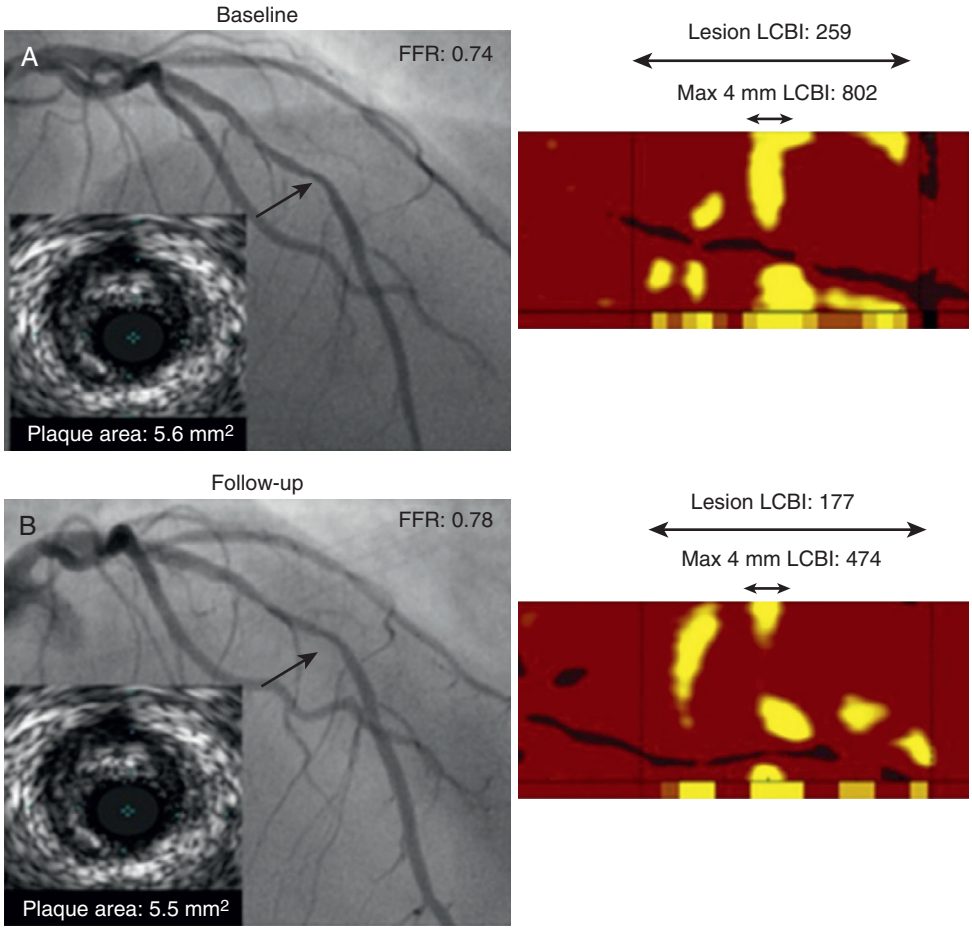


FIGURE 61-36 Angiography, intravascular ultrasound (IVUS, *insets*), fractional flow reserve (FFR), and near-infrared spectroscopy (NIRS) images of a severely obstructive lesion before and after 7 weeks of aggressive lipid-lowering therapy. Significant reductions occurred in the lipid core burden index (LCBI) without angiographic or IVUS changes. (From Kini AS, Baber U, Kovacic JC, et al: Changes in plaque lipid content after short-term intensive versus standard statin therapy: the YELLOW trial (reduction in yellow plaque by aggressive lipid-lowering therapy). *J Am Coll Cardiol* 62:21-29, 2013.)

support their ability to identify high-risk plaques, evidence is lacking for their use in the clinical arena.

Plaque composition affects the response of the vessel wall to pulsatile changes in blood pressure that deform the fibrous cap. The mechanical strain patterns can be measured with elastography or palpography, which uses IVUS to assess the deformation of tissue caused by intraluminal pressure.[127] The stress-strain relationship in coronary lesions determined by elastography or palpography is displayed on a color-coded scale.[128] Purple indicates low strain (i.e., hard, stiff cap), whereas yellow indicates a region of high strain (i.e., soft, deformable cap).[129]

Palpography has high sensitivity and specificity for detecting VPs. Deformation of more than 2% indicates increased macrophage infiltration, reduced smooth muscle cell content, and low collagen content (Fig. 61-37).[129,130] Palpography findings correlate with CRP levels and the likelihood of an STEMI. The limitations in measuring fibrous cap thickness, necrotic core, remodeling, neovascularization, and intraplaque hemorrhage may explain why these features are less applicable to identifying VPs than other methods.

Intravascular thermography has proposed for the assessment of VPs. Macrophage and lymphocyte infiltration of VPs increase the temperature of the vascular wall. By using a catheter-based thermistor, it is possible to assess changes of temperature of 0.05° C with a discrimination of 0.5 mm. Studies evaluating this modality showed by multivariate analysis that a change in temperature was an independent predictor of positive remodeling, plaque rupture, and ACS.[189-191] Despite these findings, the cooling effect of blood and other limitations significantly reduce the use of intravascular thermography in patient care.

Because of the low signal-to-noise ratio of surface MRI, it has been used for intravascular imaging.[152] Conventional MRI resolution is approximately 460 µm, but intravascular MRI resolution is 250 µm, and it may provide valuable information on plaque characterization of coronary lesions. This technology is undergoing aggressive clinical testing in the United States and Europe, with more than 100 patients enrolled. Intravascular MRI has a safe profile at 30-day follow-up as described in the first-in-human study published,[153] but there is no strong evidence supporting its utility in clinical practice.

Noninvasive Imaging Techniques

Many scientific advances in noninvasive imaging have improved the characterization of atherosclerotic plaques and detection of high-risk lesions. Noninvasive imaging techniques used for VP assessment include MRI (previously discussed), CTA, and nuclear imaging.

Computed Tomography Angiography

Advances in the field of CT and the use of newer protocols allow detailed examination of vascular structures and evaluation of coronary atherosclerotic plaques. One study reported that multidetector CT (MDCT) identified some differences in the plaque morphologies of

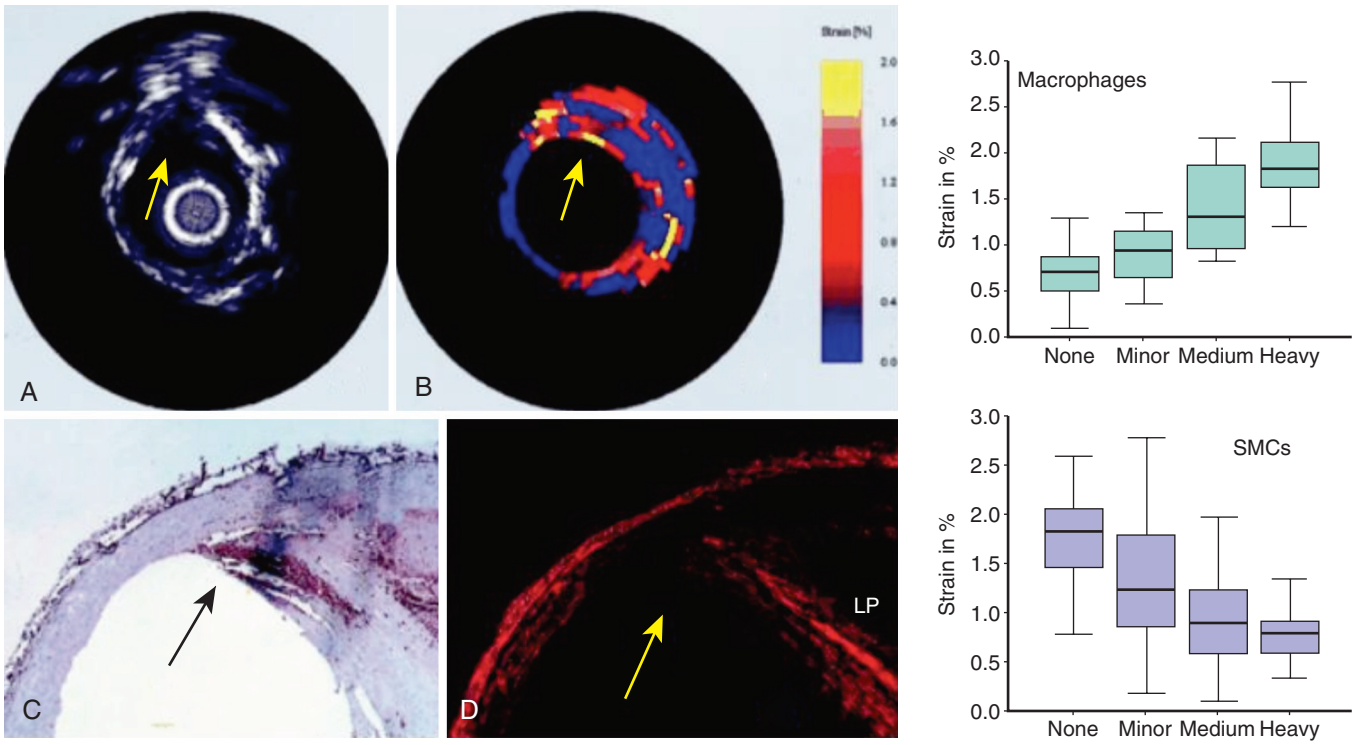


FIGURE 61-37 Vulnerable plaque is identified by intravascular ultrasound (**A**), elastography (**B**), macrophage staining (**C**), and collagen staining (**D**). In the elastogram, a vulnerable plaque *(arrow in **A**)* is indicated by a high strain on the surface *(arrow in **B**)*. The corresponding histology reveals many macrophages *(arrow in **C**)*, as well as a thin cap *(arrow in **D**)* and a lipid pool (LP). Box plots correlate content of macrophages and smooth muscle cells (SMC) with the level of strain. High levels of strain are associated with significant increases in macrophage content and significant decreases in SMC content. (Modified from Schaar JA, De Korte CL, Mastik F, et al: Characterizing vulnerable plaque features with intravascular elastography. *Circulation* 108:2636-2641, 2003.)

TCFAs and non-TCFAs and determined that the ringlike enhancement seen by MDCT indicated a precursor lesion likely to rupture.[192]

The ability of coronary CTA to provide prognostic information according to the type of plaque identified has been validated in two studies.[193] Kristensen and colleagues studied plaque volume in 312 patients with non–ST-segment elevation myocardial infarction undergoing coronary CTA before cardiac catheterization.[194] Twenty-three of the patients had a coronary event during a median follow-up of 16 months. The study authors reported that the volume of nonobstructive, noncalcified plaque measured by coronary CTA acted as a strong predictor of future coronary events, with a hazard ratio of 1.18 per 100 mm^3 of plaque volume increase. Curiously, there was no association between the presence of coronary calcification and occurrence of cardiovascular events.[194]

The second study, which was an exploratory substudy of the PROSPECT trial, enrolled 32 patients who underwent coronary CTA.[195] The investigators found that having a higher total atheroma volume (970 vs. 811 mm^3, $P < .01$) at baseline was associated with the development of cardiac events at a mean follow-up of 39 months.[195]

The main limitation of coronary CTA is the low spatial resolution (≈400 μm) of the CT scanners used in clinical practice, which precludes identifying TCFAs,[196] compared with imaging modalities such as OCT or IVUS-VH that have enhanced resolution and higher diagnostic accuracy. Classically, coronary CTA has been considered useful only for noninvasive evaluation of the calcified and fibrofatty components of plaque because its ability to differentiate high-risk plaques is extremely low.[189,190,192,197] However, some features of high-risk atherosclerotic plaques can be detected by coronary CTA (Table 61-2).

Data suggest that rupture-prone plaques are enlarged in all three dimensions. They have a large necrotic core with a mean length of 8 mm (range, 2 to 17 mm), and more than 80% of plaques measure more than 1.0 mm^2. These dimensions are above the detection threshold for plaque thickness by coronary CTA.[198] Because most TCFAs are located in the proximal segments of the epicardial coronary arteries, coronary CTA can visualize areas where the vessel lumen is the greatest and detect and quantify high-risk atheromas.[19,191]

Newer automated software applications for coronary CTA allow submillimeter isotropic resolution with subsequent attenuation-based tissue characterization. This approach can quantify the total coronary plaque burden and identify some individual plaque components in a way comparable to IVUS[199-202] or OCT.[203] Low attenuation can be used as a marker of lipid-rich plaques,[204,205] and the napkin-ring sign can be used as a surrogate for the necrotic core.[206] This qualitative characteristic of high-risk plaques is a central area of low CT attenuation that is in apparent contact with the lumen and surrounded by a ringlike, higher-attenuation tissue in a noncalcified plaque.[207] This feature has been associated with slow-flow and the no re-flow phenomenon during ACS[208] and was identified as an independent predictor for future ACS events in a prospective study of 895 patients followed for about 2.3 years (HR = 5.6, $P < .001$).[209]

Coronary CTA can identify other features of high-risk atheromas, such as positive remodeling,[81,210] spotty calcifications,[211,212] and plaque rupture, by visualizing contrast dye penetration into the lesion, a feature that correlates with large atheroma volume and low-attenuation imaging.[213] Coronary CTA is also a useful tool for the prospective evaluation of dynamic changes in coronary plaque size and morphology, and it can detect atheroma changes after statin therapy.[214]

Advances in computational fluid dynamics have allowed scientists to design useful algorithms that permit anatomic and physiologic evaluation of the coronary tree. These tools can assess endothelial shear

TABLE 61-2 Computed Tomography Morphologic Features of Vulnerable Plaques

Study	Groups Compared	Follow-Up	Item Measured	Value in ACS or Culprit Plaque	Value in SAP or Stable Plaque	No. of Patients or Plaques
Plaque Burden						
Pflederer et al, 2010[297]	ACS vs. SAP	—	Plaque volume (mm^3)	193 ± 115	104 ± 52	ACS, 55; SAP, 55
Versteylen et al, 2013[298]	ACS vs. SAP	26 ± 10 mo	Total NCP volume (mm^3)	28 (16-59)	4 (0-20)	ACS, 25; SAP, 101
Madder et al, 2011[213]	Disrupted vs. nondisrupted plaques in UAP	—	Plaque volume (mm^3)	313 ± 356	118 ± 93	Disrupted, 133; nondisrupted, 161
Kristensen et al, 201[194]	Prospective ACS or SCD	16 mo	Hazard ratio, 100 mm^3 NCP volume increase	1.18 (1.06-1.31)	—	*N* =312; 19 ACS or SCD
Motoyama et al, 2009[14]	ACS vs. no ACS	27 ± 10 mo	Plaque volume (mm^3)	134.9 ± 14.1	57.8 ± 5.7	ACS, 15; no ACS, 1044
Papadopoulou et al, 2012[195]	MACE vs. no MACE	32 mo	Total plaque volume (mm^3)	970	811	MACE, 8; no MACE, 24
Plaque Composition						
Pflederer et al, 2010[297]	ACS v.s SAP	—	Mean attenuation (HU)	85.6 ± 45.1	143.8 ± 104.1	ACS, 55; SAP, 55
Madder et al, 2011[213]	Disrupted vs. nondisrupted plaques in UAP	—	Low-attenuation (<50 HU) plaque volume (mm^3)	99 ± 161	118 ± 93	Disrupted, 133; nondisrupted, 161
Ferencik et al, 2006[299]	ACS vs. SAP	—	Total <90 HU NCP volume (mm^3)	91 (51-109)	49 (40-75)	ACS, 21; SAP, 13
Motoyama et al, 2007[215]	ACS vs. SAP	—	Low-density (<30 HU) plaques (%)	79	9	ACS, 38; SAP, 33
Ozaki et al, 2011[43]	Culprit ACS vs. stable plaques	—	Low-density (<30 HU) plaques (%)	88	18	Culprit, 25; stable, 22
Ito et al, 2011[203]	TCFA vs. non-TCFA	—	Mean attenuation (HU)	44.9 ± 19.2	78.7 ± 25.0	TCFA, 37; non-TCFA, 85
Kashiwagi et al, 2009[192]	TCFA vs. non-TCFA	—	Mean attenuation (HU)	35.1 ± 32.3	62.0 ± 33.6	TCFA, 25; non-TCFA, 80
Motoyama et al, 2009[14]	ACS vs. no ACS	27 ± 10 mo	Low-attenuation (<30 HU) plaque volume (mm^3)	20.4 ± 3.4	1.1 ± 1.4	ACS, 15; no ACS, 1044
Yamamoto et al, 2013[300]	MACE vs. no MACE	3.3 ± 1.2 yr	Hazard ratio/ low-attenuation (≤34 HU) plaque	8.23 (2.41-37.7)	—	*N*, 453; MACE, 15
Napkin Ring Sign						
Pflederer et al, 2010[297]	ACS vs. SAP	—	Frequency (%) of NRS	14	0	ACS, 55; SAP, 55
Tanaka et al, 2008[301]	Culprit ACS vs. stable plaques	—	Frequency (%) of NRS	41	18	Culprit, 27; stable, 40
Otsuka et al, 2013[209]	ACS vs. no ACS segments	2.3 ± 0.8 yr	Frequency (%) of NRS	41	3	ACS, 24; no ACS, 1150
Kashiwagi et al, 2009[192]	TCFA vs. non-TCFA	—	Frequency (%) of NRS	44	4	TCFA, 25; non-TCFA, 80
Ito et al, 2011[203]	TCFA vs. non-TCFA	—	Frequency (%) of NRS	65	16	TCFA, 37; non-TCFA, 85
Maurovich-Horvat et al, 2012[207]	Histologically advanced vs. early plaques	—	Frequency (%) of NRS	24.4	1.1	Advanced; 132, early, 472
Positive Remodeling						
Madder et al, 2011[213]	Disrupted vs. nondisrupted plaques in UAP	—	RI	1.5 ± 0.4	1.1 ± 0.3	Disrupted, 133; nondisrupted, 161
Ozaki et al, 2011[43]	Culprit ACS vs. stable plaques	—	RI	1.15 ± 0.06	0.99 ± 0.09	Culprit, 25; stable, 22
Kitagawa et al, 2009[189]	Culprit ACS vs. stable plaques	—	RI	1.26 ± 0.16	1.09 ± 0.17	Culprit, 21; stable, 44
Hoffmann et al, 2006[302]	Culprit ACS vs. stable plaques	—	RI	1.4 ± 0.3	1.2 ± 0.3	Culprit, 13; stable, 12
Motoyama et al, 2007[215]	ACS vs. SAP	—	Frequency (%) of RI >1.1	87	12	ACS, 38; SAP, 33
Motoyama et al, 2009[14]	ACS vs. no ACS	27 ± 10 mo	RI	1.27 ± 0.39	1.13 ± 0.16	ACS, 15; no ACS, 1044

TABLE 61-2 Computed Tomography Morphologic Features of Vulnerable Plaques—cont'd

Study	Groups Compared	Follow-Up	Item Measured	Value in ACS or Culprit Plaque	Value in SAP or Stable Plaque	No. of Patients or Plaques
Kim et al, 2010[303]	Culprit ACS vs. stable plaques	—	RI	1.44 ± 0.43	0.90 ± 0.44	Culprit, 35; stable, 36
Ito et al, 2011[203]	TCFA vs. non-TCFA	—	RI	1.14 ± 0.20	0.95 ± 0.16	TCFA, 37; non-TCFA, 85
Kashiwagi et al, 2009[192]	TCFA vs. non-TCFA	—	RI	1.14 ± 0.15	1.02 ± 0.10	TCFA, 25; non-TCFA, 80
Pflederer et al, 2010[297]	ACS vs. SAP	—	RI	1.6 ± 0.4	0.97 ± 0.17	ACS. 55; SAP, 55
Yamamoto et al, 2013[300]	MACE vs. no MACE	3.3 ± 1.2 yr	Hazard ratio/RI ≥ 1.2	8.3 (2.83-26.7)	—	*N*, 453; MACE, 15
Spotty Calcium						
Kitagawa et al, 2009[189]	ACS vs. SAP	—	Frequency (%) of spotty calcium	60	38	ACS, 21; SAP, 80
Motoyama et al, 2007[215]	ACS vs. SAP	—	Frequency (%) of spotty calcium	63	21	ACS, 38; SAP, 33
Kim et al, 2010[303]	Culprit ACS vs. stable plaques	—	Frequency (%) of spotty calcium	95	23	ACS, 35; SAP, 36
Pflederer et al, 2010[297]	ACS vs. SAP	—	Frequency (%) of spotty calcium	20	0	ACS, 55; SAP, 55
Ozaki et al, 2011[43]	Culprit ACS vs. stable plaques	—	Frequency (%) of spotty calcium	26	16	Culprit, 25; stable, 22

ACS, Acute coronary syndrome; *MACE,* major adverse cardiac event; *N,* total number of patients in study; *NCP,* noncalcified plaque; *NRS,* napkin ring sign; *RI,* remodeling index; *SAP,* stable angina pectoris; *SCD,* sudden cardiac death; *TCFA,* thin-cap fibroatheroma; *UAP,* unstable angina pectoris.

stress and FFR, providing information that can help risk-stratify coronary plaques.[216,217] The Prediction of Progression of Coronary Artery Disease and Clinical Outcomes Using Vascular Profiling of Shear Stress and Wall Morphology (PREDICTION) trial enrolled 506 patients who underwent three-vessel IVUS and repeat imaging at the 1-year follow-up. The investigators found that a large plaque burden and low endothelial shear stress were independent predictors of plaques enlargement.[48] Despite promising results, reproducibility demands use of the same automated software for serial measurements.[218]

In summary, coronary CTA can characterize the anatomy of the main epicardial coronary vessels and identify several features of plaque vulnerability, with the exception of fibrous cap measurements and neovascularization. Table 61-2 summarizes the parameters of VPs that can be assessed by coronary CTA.[219] Nanoparticle-contrast–based techniques for coronary CTA have identified inflammatory cell activity in animal studies.[220,221] Large, prospective trials should be performed to confirm the findings from prospective registries and smaller, shorter studies and to assess the role of systemic or local therapies for high-risk lesions in combination with coronary CTA.

Nuclear Imaging

Nuclear imaging using positron emission tomography (PET) and CT has provided useful information for patients with VPs.[222] These techniques address the molecular aspects of atheromas, and when used with dual gating protocols, they can provide images with less motion artifact and image quality appropriate for clinical studies.[223]

Specific tracers are used for the identification of various plaque components. Among the tracers and markers of plaque vulnerability that have been used with nuclear imaging, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is the most studied in preclinical and clinical experiments. Studies have demonstrated that ^{18}F-FDG uptake correlates with plaque macrophage density in animal models and human atherosclerosis and predicts future cardiovascular events.[224,225]

The utility of PET and CT to detect high-risk plaques using ^{18}F-sodium fluoride (^{18}F-NaF) and ^{18}F-FDG has been demonstrated in clinical settings. Joshi and colleagues studied 40 patients with AMI and 40 with stable angina undergoing elective invasive coronary angiography.[226] They reported that ^{18}F-NaF uptake was 34% higher in culprit lesions compared with nonculprit plaques ($P < .0001$) and that 93% of the patients had increased levels of ^{18}F-NaF in culprit plaques. Among patients with stable angina, 45% had plaques with increased ^{18}F-NaF uptake, and they were mostly nonobstructive lesions seen on coronary angiography and displayed more high-risk features on IVUS compared with plaques without ^{18}F-NaF uptake. It is possible that ^{18}F-FDG can help to identify atheroma microcalcification associated with plaque inflammation as a marker of plaque vulnerability.[227]

MMP-rich plaques have been identified in preclinical studies with the use of nuclear radiotracers, LDL receptor 1 with the use of ^{99m}Tc-labeled anti-LOX-1 antibody, apoptotic cells with the use of annexin A5213, and neovascularization with the use of $\alpha\beta_3$-integrin–targeted PET.[228-231] Other promising agents for noninvasive imaging include high-density lipoprotein (HDL) cholesterol–based contrast and gold nanoparticles.[221,232]

Figure 61-38 summarizes the potential targets in VPs that are suitable for identification with nuclear imaging. Despite encouraging results for noninvasive techniques, they are unable to provide accurate plaque localization and anatomic evaluation of the lesions. Further studies with appropriate histologic validation are required to clarify the strengths and weaknesses of these technologies.

The BioImage study, which includes a comprehensive assessment of cardiovascular risk factors, will provide substantial data to discern the role of noninvasive modalities in the identification of atherosclerotic plaque vulnerability. This trial is recruiting more than 6000 asymptomatic patients with moderate to high cardiovascular risk between 50 to 65 years of age who are undergoing three-dimensional vascular ultrasound and other advanced imaging modalities to predict events during a 3-year follow-up. The results will elucidate the natural history of plaques, ultimately leading to better therapeutic and preventive approaches.[233]

Cardiac Magnetic Resonance Imaging

MRI can provide quantification of the atherosclerotic plaque burden and lesion composition.[234] It allows three-dimensional evaluation of vascular structures, with outstanding depiction of components of the atherothrombotic plaque such as lipid, fibrous tissue, calcium, and

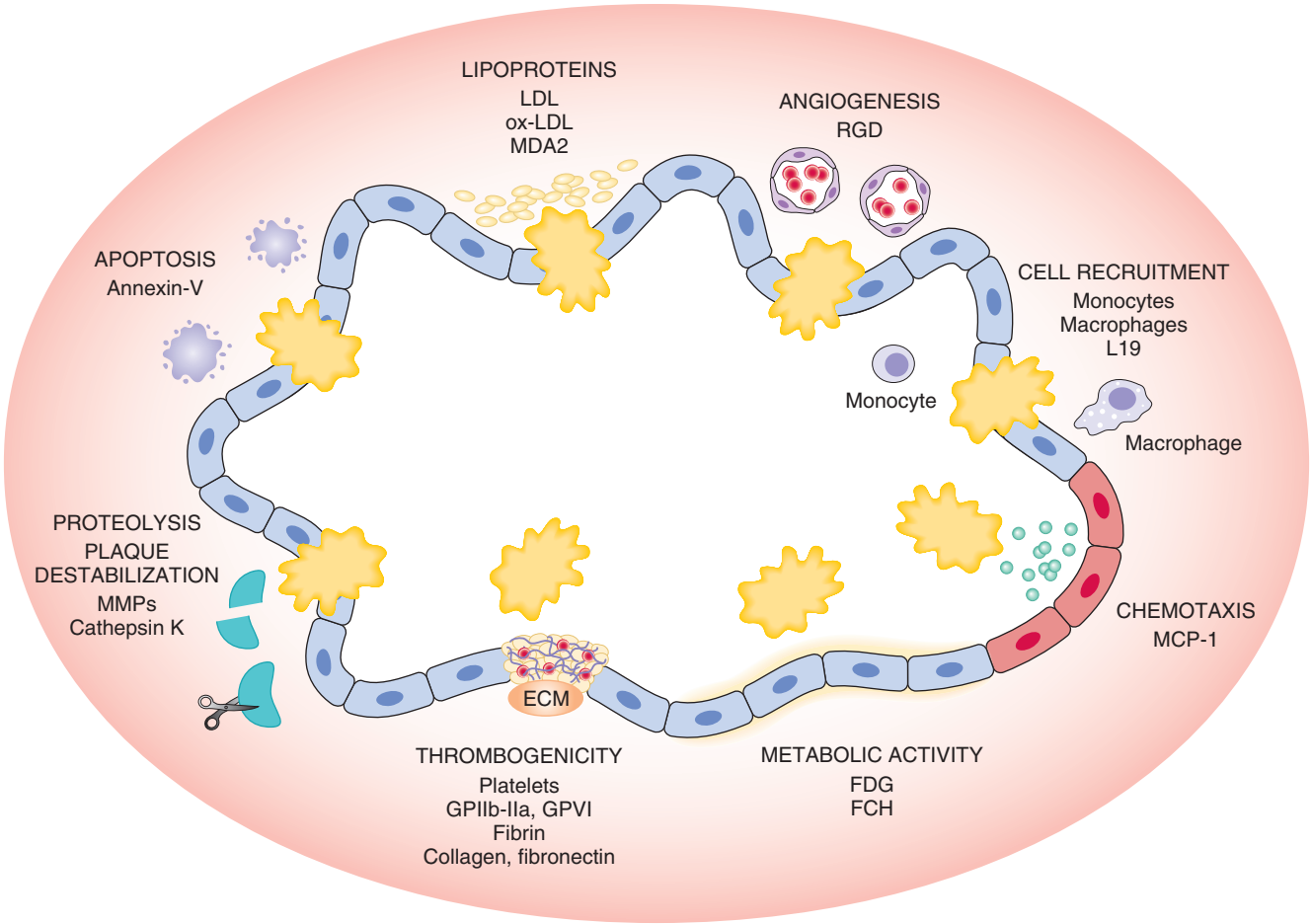


FIGURE 61-38 Targets in the pathophysiologic pathways of atherosclerotic plaque that can be identified by nuclear imaging modalities. *ECM,* Extracellular matrix; *FCH,* fluorocholine; *FDG,* fluorodeoxyglucose; *GP,* glycoprotein; *LDL,* low-density lipoprotein; *L19,* antibody against the extradomain B of fibronectin; *MCP,* monocyte chemoattractant protein; *MDA2,* malondialdehyde epitope on oxidized low-density lipoprotein; *MMPs,* matrix metalloproteinases; *ox-LDL,* oxidized low-density lipoprotein; *RGD,* arginine-glycine-aspartate sequence. (Modified from Langer HF, Haubner R, Pichler BJ, Gawaz M: Radionuclide imaging: a molecular key to the atherosclerotic plaque. *J Am Coll Cardiol* 52:1-12, 2008.)

thrombus.[235] MRI combined with cellular and molecular targeting is providing important data on the biologic activity of high-risk VPs, especially carotid and aortic lesions.[236]

A longitudinal study by Zhao and coworkers demonstrated the ability of MRI to document lipid content reduction in carotid plaques.[237] This work led to the characterization of plaque in coronary vessels by MRI. The task is difficult and image quality is poorer because of limited resolution, the deep intrathoracic position of coronary arteries (4 to 10 cm from the surface), the smaller dimensions, and the tortuous and irregular course of these vessels under continuous movement.[238] Despite these limitations, several studies have demonstrated comparable coronary plaque assessment by MRI and IVUS, including features such as vascular remodeling,[239] intracoronary thrombus,[240] and coronary wall thickness[241] and distensibility[242] (Fig. 61-39).[243] MRI can detect edema in the coronary wall of the culprit lesions in patients with acute vascular injury and ACS.[244]

Animal studies using contrast-enhanced MRI have been able to detect high-risks plaques.[245] Preclinical studies have employed molecular imaging techniques that target various VP components and assess inflammatory, lipid, reparative, thrombotic, and neovascularization pathways.[246]

A comprehensive approach to invasive therapy is becoming mandatory for the interventionist interested in the prevention of recurrent coronary events. Because each technology can provide information about different aspects of VP, imaging, physiologic tests, and serum or genetic markers should be combined to enhance VP detection. Although individual imaging modalities have reached a certain degree of technologic sophistication, a combination, such as OCT with backscattered IVUS and IVUS with Raman spectroscopy, may offer a better future.

The PROSPECT trial, which assessed three-vessel coronary imaging in patients with ACS, has provided prognostic information about invasive plaque imaging in CAD. If the adverse event rate at follow-up is higher than expected with pharmacologic therapy, the scientific community will need to consider additional strategies.

Nanotechnology in multimodality imaging, including cardiac MRI and nuclear imaging with PET, is being applied to the evaluation of high-risk plaques. Lipid-encapsulated perfluorocarbon nanoparticles have been used to target pathways involved in VP formation in preclinical models with promising results.[247]

THERAPY

Systemic Therapy

The treatment of high-risk VPs relies on aggressive medical therapy, which can reduce coronary events and improve survival. Systemic therapy is the cornerstone of plaque stabilization, with documented

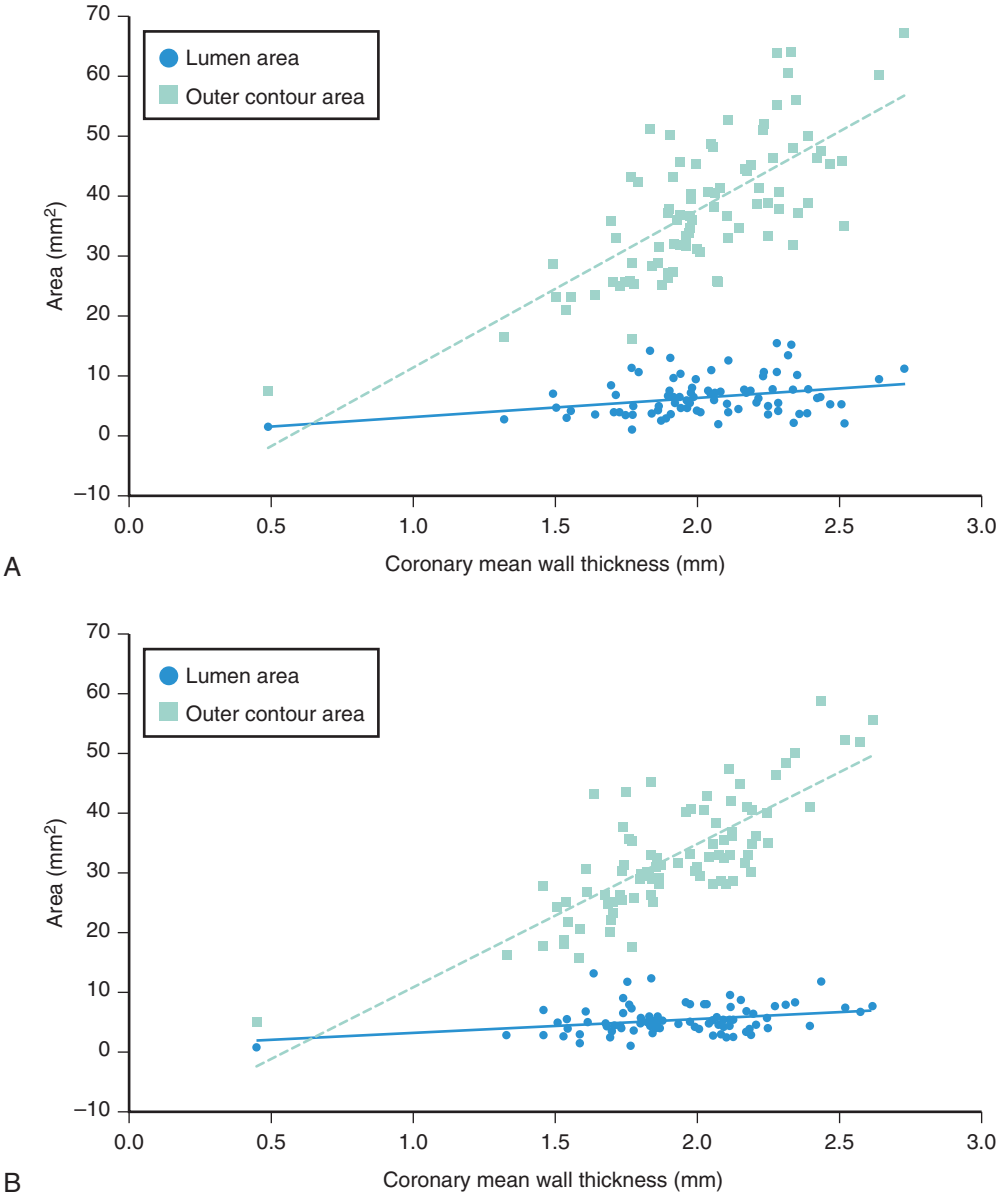


FIGURE 61-39 Coronary artery cross-sectional area (i.e., outer contour area) and lumen area compared with mean wall thickness for men (**A**) and women (**B**). The outer contour area and the lumen area were positively correlated with mean wall thickness: for men, $r = 0.53$ ($P < .0001$) and $r = 0.09$ ($P < .05$), respectively; for women, $r = 0.62$ ($P < .0001$) and $r = 0.09$ ($P < .05$), respectively. However, the slope of the outer contour area increase was significantly greater than that of the lumen area increase ($P < .0001$ for both men and women). (From Kelle S, Hays AG, Hirsch GA, et al: Coronary artery distensibility assessed by 3.0 Tesla coronary magnetic resonance imaging in subjects with and without coronary artery disease. *Am J Cardiol* 108:491-497, 2011.)

reductions in lipid content, inflammation, and vasa vasorum neovascularization.[248]

Intensive statin therapy has produced a significant decrease in coronary events in patients with stable disease (i.e., Trending to New Targets [TNT] and Incremental Decrease in Events Through Aggressive Lipid Lowering [IDEAL] trials) and in patients with ACS (i.e., Aggrastat to Zocor [A to Z] and Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 [PROVE IT–TIMI 22] trials). Statins have reduced the incidence of coronary death, AMI, and heart failure, independent of recurrent infarction.[249,250] Early intensive statin therapy for ACS was associated with clinical benefits that became evident after 4 to 12 months, including a decrease in serum VEGF levels, which probably represents an attenuation of plaque angiogenesis.[251,252] In the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) trial, aggressive therapy with rosuvastatin led to an absolute regression of atheroma volume (Fig. 61-40).[84]

Another potent antiatherogenic therapy involves increasing HDL levels. Studies using bezafibrate, a peroxisome proliferator-activated receptor α (PPARα) agonist, and fenofibrate have demonstrated reduced events and plaque regression, respectively.[253,254] These beneficial effects may be caused by HDL augmentation and reverse cholesterol transport and by recruitment of endothelial progenitor cells into the damaged endothelium.[255]

The beneficial effects of statin therapy on VPs in terms of plaque regression and stabilization have been documented many times with

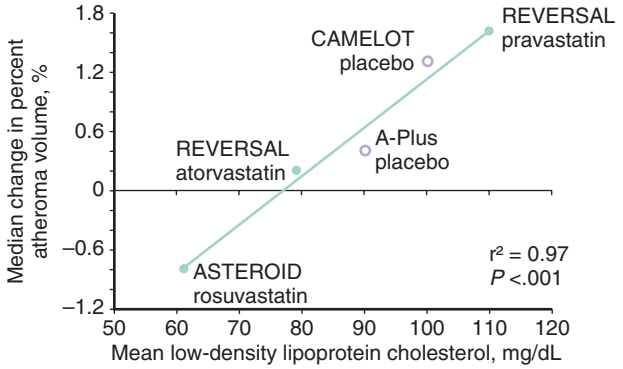


FIGURE 61-40 Relationship between mean low-density lipoprotein cholesterol levels and median change in percent atheroma volume for several intravascular ultrasound trials.

OCT, angioscopy, MRI, and IVUS-VH.[82,256] In addition to high-dose statin therapy, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and aspirin have reduced the rates of death and AMI and are therefore mandatory to achieve stabilization of high-risk VPs.[248]

Several interventions improve endothelial function by increasing endothelial progenitor cell regeneration, mobilization, and release into the circulation, contributing to the passivation of the inflammatory environment. These interventions include exercise, statins, angiotensin receptor blockers, ACE inhibitors, and some peroxisome proliferator-activated receptor agonists.[257,258]

The n-3 fatty polyunsaturated acids provide a stabilizing effect through regulation of adhesion molecule expression, proinflammatory and proangiogenic growth factors secreted by the endothelium, and attenuation of the nuclear factor-κB system.[259] Nishio and coworkers studied 49 nonculprit TCFAs from 30 patients with dyslipidemia who were not receiving treatment.[260] The patients were randomized to receive 1800 mg/day of eicosapentaenoic acid (EPA) plus a statin or a statin only. The statin dose was adjusted to achieve an LDL target of less than 70 mg/dL. Post-PCI assessment and OCT were performed at the 9-month follow-up. The investigators reported features of plaque stabilization such as a higher increase in plaque thickness and greater decrease in lipid arch and lipid pool by OCT in patients receiving EPA plus a statin compared with those receiving a statin alone.

Another method to achieve plaque stabilization is reversal of the cholesterol transport system. This therapeutic alternative has been proposed to promote cholesterol efflux from macrophages by activation of the ATP-binding cassette transporters ABCA1 and ABCG1. Studies are ongoing.[86,261]

In the search for systemic therapies, other approaches are being studied. For instance, preclinical data have demonstrated that vaccination against endothelial tyrosine kinase (TEK, formerly called TIE2), the angiopoietin receptor, promotes the formation of smaller atherosclerotic plaques with a more stable phenotype.[262] Similarly, both animal and human experiments have demonstrated that the selective inhibition of lipoprotein-associated phospholipase A_2 reduces its plasma activity and is associated with a decrease in plaque and necrotic core areas.[24,263]

Despite the tremendous value of systemic therapy, patients have a 22% recurrent event rate within 2 years and demonstrate resistance to systemic therapy, as confirmed in the PROVE IT trial.[264] Even the best combination of systemic therapies does not successfully prevent all episodes of plaque rupture and thrombosis. Nonetheless, intravascular imaging studies have demonstrated significant plaque regression with statin use.

One study included 1039 patients with coronary disease who underwent IVUS at baseline and after 104 weeks. They were randomized to atorvastatin (80 mg) or rosuvastatin (40 mg).[265] At 104 weeks, the percent atheroma volume (PAV) decreased by 0.99% (95% confidence interval [CI], −1.19 to −0.63) in the atorvastatin group and by 1.22% (95% CI, −1.52 to −0.90) in the rosuvastatin group ($P = .17$). The normalized total atheroma volume (TAV) was more favorable for patients receiving rosuvastatin compared with those on atorvastatin: −6.39 mm^3 (95% CI, −7.52 to −5.12) compared with −4.42 mm^3 (95% CI, −5.98 to −3.26) ($P = .01$). Plaque regression was induced in most patients in both groups: 63.2% of the patients receiving atorvastatin and 68.5% of the patients receiving rosuvastatin for PAV ($P = 0.07$) and 64.7% and 71.3%, respectively, for TAV ($P = .02$).

A similar study with a smaller sample size and shorter follow-up period (7 weeks) reported similar findings using combinations of intravascular modalities, including FFR, NIRS, and IVUS.[188] Statin therapy can also decrease atheroma size and plaque morphology,[214] and it can induce reductions in the lipid content of obstructive lesions.[266]

Other therapies targeting pathways involved in TCFA formation include inhibition of MMP activity by doxycycline, which appeared to be as effective as simvastatin in reducing the incidence of plaque rupture in a cholesterol-fed rabbit model of atherosclerosis.[267] Similarly, the use of beta-blockers decreased shear stress and the plaque vulnerability index seen in transgenic models of atherosclerosis.[268]

Despite the encouraging results from animal studies, some of these concepts await validation in humans. The strongest clinical evidence obtained for systemic therapy for VPs comes from statin studies. However, it is not clear whether the plaque regression in atheromas seen by serial imaging during follow-up was responsible for the lower rates of coronary events among patients in the statin trials. Newer systemic therapies are urgently needed for high-risk patients.

Regional Therapy

Regional therapy is intravascular treatment of coronary segments using pharmacologic agents and physicochemical treatment to stabilize high-risk VPs. Regional therapies include photodynamic therapy (PDT), endoluminal phototherapy, and cryotherapy.[269-271] PDT, which has gained attention in recent years, uses photosensitizing (light-sensitive) drugs, light, and tissue oxygenation to treat targeted diseases, mostly in the field of oncology.[272]

Photosensitizing agents (i.e., porphyrins) are administered locally or parentally. They are selectively absorbed and retained in tissues, enabling targeted therapy when the tissues are exposed to light at an appropriate wavelength. The surrounding normal tissue does not absorb the photosensitizer and is spared therapeutic injury. Activation of the photosensitizer in tissue generates free radicals and cytotoxic effects, mostly apoptosis (i.e., DNA fragmentation) or delayed necrosis.

The application of PDT to atherosclerotic plaques was successfully performed in vivo by Waksman and associates in hypercholesterolemic rabbits.[273] PDT induced a significant reduction (92% ± 6%) in the population of nuclei of all cell types in plaques relative to controls ($P < .01$). This effect partly resulted from a reduction in smooth muscle cells (i.e., antibody staining for α-actin) and macrophages (i.e., RAM11 staining) (Fig. 61-41). The results suggest that PDT can almost eliminate macrophages from atherosclerotic plaques and may provide a therapeutic alternative for high-risk VPs refractory to aggressive systemic therapy.

Endoluminal phototherapy and cryotherapy are being investigated, but experience with them is limited. Publications about PDT, endoluminal phototherapy, and cryotherapy during the past few years have been limited.

Local Therapy

Coronary stents can stabilize high-risk VPs by thickening the fibrous cap through the formation of neointimal hyperplasia. As predicted by Peter Libby and highlighted by Patrick Serruys in 2006, "If we could identify potentially unstable atheromas before they are evident, we might contemplate angioplasty on nonsignificant stenosis to induce smooth muscle cell proliferation and reinforce the plaque fibrous

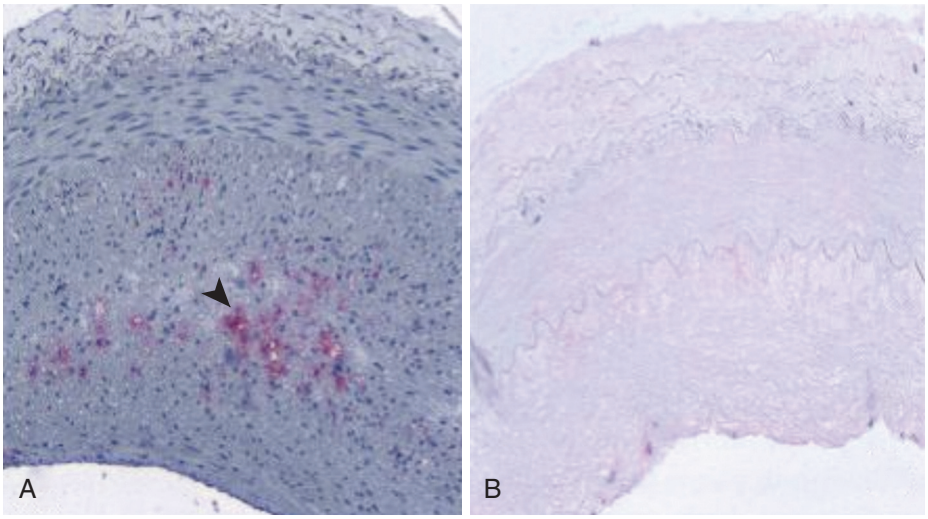


FIGURE 61-41 Histologic images show the effects of photodynamic therapy on atherosclerotic plaques from hypercholesterolemic rabbits. **A,** Macrophages *(arrowhead)* in the untreated control. **B,** Seven days after photodynamic therapy. (From Waksman R: *Photodynamic therapy,* New York and London, 2004, Taylor & Francis.)

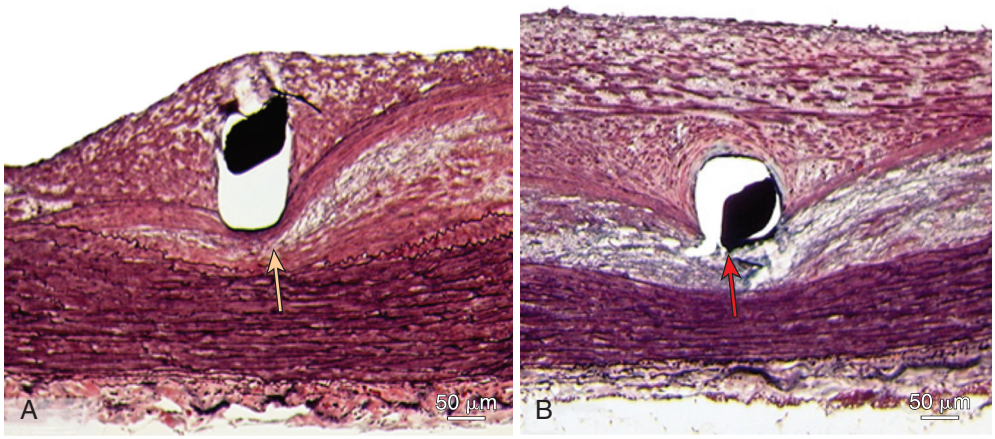


FIGURE 61-42 Histologic section illustrates the various components of a thin-cap fibroatheroma 28 days after stent deployment. **A,** The strut compresses the old, thin fibrous cap *(arrow)*. **B,** A cellular neointimal layer has been laid down, creating a new, thick fibrous cap *(arrow)* (elastic tissue trichrome stain; ×20).

cap."[274] In an editorial, Michael Davies wrote, "The time for prophylactic angioplasty has not come yet, but it may."[275]

In an editorial entitled "Locking the Barn Door Before the Horse Is Stolen," Eugene Brauwald addressed the concept of prophylactic stenting: "The clinical application of VPs at risk of future rupture require the development of measures for the prevention of plaque rupture that are more potent than those currently employed in what we refer to as intensive prevention. Perhaps stenting or surgically bypassing these plaques could be considered in some patients."[9] However, stenting VPs is highly controversial, and the risk-benefit ratio must be evaluated in animal models because stenting may increase the risk of periprocedural AMI.

To evaluate these parameters, we developed an animal model of spontaneous VPs in New Zealand hypercholesterolemic rabbits that were followed for 4 years. The animals were randomized to three groups: metallic stents, drug-eluting stents (DESs), and controls ($N = 16$).[276] Only stent struts deployed into VPs were evaluated. Fibrous cap thickness, stent-induced fibrous cap rupture (Fig. 61-42), and peristrut healing (Fig. 61-43) were evaluated, including peristrut inflammation (see Fig. 61-43, *A*), fibrin deposition (see Fig. 61-43, *B*), hemorrhage (see Fig. 61-43, *C*), and strut endothelialization (see Fig. 61-43, *D*). Metallic stents, β-estradiol–eluting stents, and everolimus-eluting stents increased fibrous cap thickness by 396%, 322%, and 270%, respectively ($P < .0001$ for all comparisons) (Table 61-3). Stent-induced fibrous cap rupture was identified in 63% of stented lesions. Peristrut inflammation, fibrin deposition, and hemorrhage increased, and endothelialization decreased in DESs compared with metallic stents ($P < .05$) (Table 61-4). These effects were obtained at the cost of increased cap damage and potentially iatrogenic, peristrut healing patterns, including increased inflammation, fibrin deposition, hemorrhage, and decreased endothelialization.

Newer self-expanding devices with very thin struts and with low-pressure expanding profiles have been successfully tested in a large animal model of localized atherosclerosis and produced promising results.[277] Evidence from clinical settings has supported the use of this approach, published first as a case report.[278] Later, a small clinical registry that included 29 patients demonstrated that the implantation of a self-expanding shield in noncomplex coronary lesions of intermediate severity was a safe and feasible strategy, with encouraging angiographic and IVUS results reported during a follow-up period of 9 months.[279]

The vShield Evaluated at Cardiac Hospital in Rotterdam for Investigation and Treatment of TCFA (SECRITT) trial evaluated a self-expanding endovascular device (vShield [Prescient Medical, Inc.,

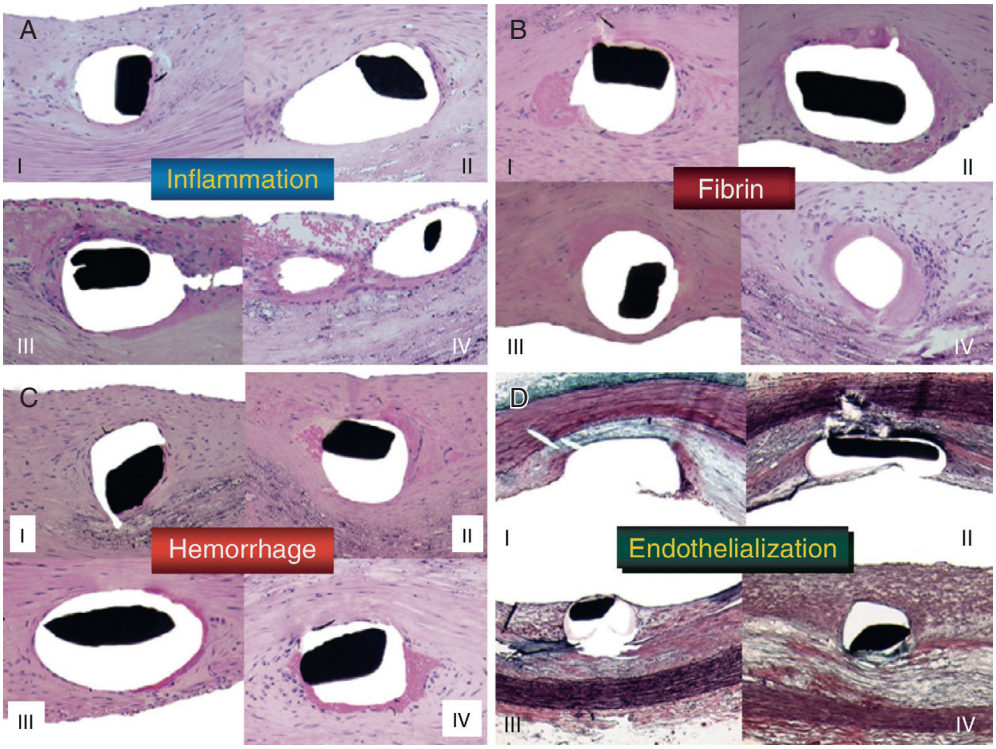


FIGURE 61-43 Micrographs display examples of numeric scoring (on a scale of I to IV) applied to four categories of strut-related healing patterns at 28 days after stent deployment: **A,** inflammation; **B,** fibrin deposition; **C,** hemorrhage; **D,** endothelialization. Score criteria for categories A, B, and C assessed the extent of the perimeter of each strut affected as follows: I, up to one quadrant around the strut (25%); II, up to two quadrants (50%); III, up to three quadrants (75%); and IV, up to four quadrants (100%). Scores for endothelialization (category D) were as follows: I, up to 25% endothelial coverage; II, up to 75% endothelial coverage; III, up to 100% endothelial coverage; and IV, complete coverage with neointimal tissue.

TABLE 61-3 Planimetric Data on Fibrous Cap Thickness for Stented and Nonstented Thin-Cap Fibroatheromas

Fibrous Cap Area (μm^2)	Metallic Stents ($n = 127$)	β-Estradiol–Eluting Stents ($n = 46$)	Everolimus-Eluting Stents ($n = 41$)	Controls ($n = 122$)
Before stenting	26 ± 3.9	24.4 ± 1.7	23 ± 1.9	27 ± 1.3
Four years after stenting	107 ± 6.5*	87.6 ± 6.7*†	72.8 ± 3.9*†	27 ± 1.3

*$P < .0001$ compared with the control group.
†$P < .05$ compared with the metallic stent group.

TABLE 61-4 Planimetric Data on Iatrogenic Peristrut Healing Patterns for Metallic and Drug-Eluting Stents in Thin-Cap Fibroatheromas

Vascular Healing	Metallic Stents ($n = 127$)	β-Estradiol–Eluting Stents ($n = 46$)	Everolimus-Eluting Stents ($n = 41$)
Inflammation score	0.9 ± 0.1	1.1 ± 0.1*	1.1 ± 0.1*
Fibrin score	0.6 ± 0.1	1.1 ± 0.1*	1.1 ± 0.2*
Hemorrhage score	0.1 ± 0.0	0.1 ± 0.0	0.2 ± 0.1*
Endothelization score	3.7 ± 0.1	3.2 ± 0.2*	3.6 ± 0.1

*$P < .05$ compared with metallic stent group.

Doylestown, PA]) in a pilot study that included 23 patients from a larger trial currently taking place in Europe.[280] This study identified IVUS-VH–derived TCFAs with thin caps by using diagnostic modalities that included angiography, FFR, IVUS-VH, and OCT. Patients were randomized to optimal medical therapy or vShield implantation. After 6 months, the percent diameter stenosis decreased, FFR remained stable, and no increase in MACEs was seen in the vShield group. The results suggested that implanting a self-expandable vShield prosthesis in a TCFA with the purpose of producing plaque passivation and cap sealing is feasible and safe. The long-term results of this ongoing trial should answer several questions about the local treatment of TCFAs with implantation of intravascular devices.[280]

Local therapeutic options include blocking proangiogenic factors.[281] Stents coated with the VEGF-specific antibody bevacizumab demonstrated encouraging results in terms of angiogenesis control in small studies.[282,283] However, it is not known whether local antiangiogenic therapy with stent-based or non–stent-based modalities will require a single-dose or multiple-dose approach. Evidence from experiments treating nonatherosclerotic angiogenesis favors repeated dosing. A controlled-release delivery system may ensure a sustained inhibitory effect on proangiogenic factors.[284] Other local therapies, including blocking molecular pathways or specific genes related to plaque vulnerability, have been tested.[285] Further studies are needed to elucidate the clinical applications of this approach.

One study highlighted the potential implications of thrombus aspiration without stenting in 31 patients with ACS when assessing plaque

integrity by OCT.[286] Prati and associates demonstrated that aspiration thrombectomy, when yielding an excellent angiographic result, is enough and does not require stent implantation if there is no evidence of plaque rupture by OCT. These patients remained asymptomatic after 2 years of follow-up, and successful angiographic results were documented. This suggests that documenting the integrity of the fibrous cap with OCT after thrombectomy may have clinical implications for the treatment of plaques associated with ACS.

Targeted molecular therapy such as gene silencing has been tested. Monocyte infiltration into the arterial wall is promoted by monocyte chemoattractant protein 1 (MCP1), a chemokine implicated in the development of atherosclerosis. Blockade of the MCP1 pathway can reduce new atheroma formation and limit progression and destabilization of established atherosclerosis. For example, in apolipoprotein E–knockout (ApoE−/−) mice fed a high-fat diet, local RNA interference of MCP1 by site-specific delivery of adenovirus-mediated small hairpin RNA enhanced plaque stability and prevented plaque disruption, and it was associated with lower inflammatory levels and lower MMP activity.[287]

Because of the diffuse pattern of the disease, local therapy to reinforce VPs is subject to controversy, and the risk of late stent thrombosis only adds to the controversy.[288] However, proponents of stenting argue that the clinical event rate associated with high-risk TCFAs (18% at 3 years in the PROSPECT trial) may be higher than the clinical event rate associated with stenting (4% to 6% for the first year and 1% to 2% per year thereafter). New stent designs, including biodegradable materials, and self-expanding delivery systems may reduce the long-term risk of stent thrombosis, preserving the integrity of the fibrous cap with neointimal tissue.[289,290] The Absorb bioresorbable vascular scaffold (Abbott Vascular, Santa Clara, CA) demonstrated good results 6 months after implantation compared with a cobalt-chromium everolimus-eluting stent for the treatment of coronary lesions.[291]

The treatment of high-risk TCFAs resistant to aggressive medical therapy remains controversial, but it also offers opportunities for interventional cardiologists. Prospective, randomized clinical trials are needed to elucidate this issue.

FUTURE DIRECTIONS

Despite more than 2 decades of study and treatment of high-risk VPs, they continue to cause AMI and premature death. Identification of the main factors associated with plaque instability has not ensured prediction of rupture and thrombosis, and the search for effective early diagnosis and treatment to prevent catastrophic consequences goes on.

Extensive research with invasive and noninvasive imaging, clinical trials, biomarker assessment, and focal, regional, and systemic therapies has shown that VPs are not responsible for an increased incidence of future events. The incidence of death and AMI in the PROSPECT trial was only 4.9% at 3.4 years, highlighting the excellent contemporary outcomes of aggressive medical therapy in secondary prevention. Moreover, a TCFA by itself is not sufficient to characterize a VP. The current definition of a VP includes a thin fibrous cap, large plaque burden, and reduced lumen determined by IVUS.[8]

The details of plaque stabilization or regression, or both, in response to medical and interventional therapies are still unclear. Issues of early detection and prevention must be addressed. Most patients with high-risk TCFAs first come to attention because of sudden cardiac death or AMI, and efforts should be made to identify them sooner and treat them accordingly.

The data from ongoing studies support noninvasive imaging as an effective tool to identify subclinical atherosclerosis.[292] Methods include assessment of flow-mediated brachial artery vasodilation, coronary calcium score, and intimomedial thickness, as in the Multi-Ethnic Study in Atherosclerosis (MESA) trial[293]; three-dimensional vascular ultrasound imaging and other modalities, as in the BioImage study[233]; and carotid and femoral two- or three-dimensional ultrasound, abdominal aortic two-dimensional ultrasound, noncontrast CT, and combined ^{18}FDG-PET and MRI in younger patients (40 to 54 years old), as in the Progression and Early Detection of Subclinical Atherosclerosis (PESA) study.[294] Invasive imaging, including coronary angiography, continues to play a role in risk stratification based on data demonstrating that the plaque burden may predict outcomes such as MACEs better than ischemia evaluation.[295]

Aggressive pharmacologic treatment has reduced the rate of secondary events, but there is a role for other systemic therapies to decrease clinical events by targeting inflammation, cholesterol homeostasis, and neovascularization pathways. Interventional therapy is an option for high-risk TCFAs refractory to medical therapy. Ongoing studies of intracoronary imaging and bioabsorbable stents may provide alternative approaches for diagnosis and therapy that reduce the burden of cardiovascular events.[296] Randomized clinical trials are needed to elucidate the risk-benefit ratios of all VP therapies.

REFERENCES

1. Ford ES, Li C, Zhao G, et al: Trends in the prevalence of low risk factor burden for cardiovascular disease among United States adults. *Circulation* 120:1181–1188, 2009.
2. Yeh RW, Sidney S, Chandra M, et al: Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med* 362:2155–2165, 2010.
3. Go AS, Mozaffarian D, Roger VL, et al: Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation* 129:e28–e292, 2014.
4. Laslett LJ, Alagona P, Jr, Clark BA, 3rd, et al: The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology. *J Am Coll Cardiol* 60:S1–S49, 2012.
5. World Health Organization: Cardiovascular diseases (CVDs): fact sheet no. 317. Available at <http://www.who.int/mediacentre/factsheets/fs317/en/>, (Accessed February 27, 2015).
6. Virmani R, Kolodgie FD, Burke AP, et al: Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 20:1262–1275, 2000.
7. Fuster V, Moreno PR, Fayad ZA, et al: Atherothrombosis and high-risk plaque: part I: evolving concepts. *J Am Coll Cardiol* 46:937–954, 2005.
8. Moreno PR: The high-risk thin-cap fibroatheroma: a new kid on the block. *Circ Cardiovasc Interv* 2:500–502, 2009.
9. Braunwald E: Noninvasive detection of vulnerable coronary plaques: locking the barn door before the horse is stolen. *J Am Coll Cardiol* 54:58–59, 2009.
10. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al: Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol* 12:56–62, 1988.
11. Rdzanek A, Kochman J, Pietrasik A, et al: The prevalence of potentially unstable coronary lesions in patients with coronary artery disease—virtual histology study. *Kardiol Pol* 66:244–250, discussion 51–52, 2008.
12. Cutlip DE, Chhabra AG, Baim DS, et al: Beyond restenosis: five-year clinical outcomes from second-generation coronary stent trials. *Circulation* 110:1226–1230, 2004.
13. Glaser R, Selzer F, Faxon DP, et al: Clinical progression of incidental, asymptomatic lesions discovered during culprit vessel coronary intervention. *Circulation* 111:143–149, 2005.
14. Motoyama S, Sarai M, Harigaya H, et al: Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol* 54:49–57, 2009.
15. Tanaka A, Imanishi T, Kitabata H, et al: Distribution and frequency of thin-capped fibroatheromas and ruptured plaques in the entire culprit coronary artery in patients with acute coronary syndrome as determined by optical coherence tomography. *Am J Cardiol* 102:975–979, 2008.
16. Cheruvu PK, Finn AV, Gardner C, et al: Frequency and distribution of thin-cap fibroatheroma and ruptured plaques in human coronary arteries: a pathologic study. *J Am Coll Cardiol* 50:940–949, 2007.
17. Lee WS, Kim SW, Ryu WS: Progression and observational frequency of atheromatous plaques in autopsied coronary arteries. *Korean Circ J* 39:399–407, 2009.
18. Stone GW, Maehara A, Lansky AJ, et al: A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 364:226–235, 2011.
19. Virmani R, Burke AP, Farb A, Kolodgie FD: Pathology of the vulnerable plaque. *J Am Coll Cardiol* 47:C13–C18, 2006.
20. Marso SP, House JA, Klauss V, et al: Diabetes mellitus is associated with plaque classified as thin cap fibroatheroma: an intravascular ultrasound study. *Diab Vasc Dis Res* 7:14–19, 2010.
21. Lindsey JB, House JA, Kennedy KF, Marso SP: Diabetes duration is associated with increased thin-cap fibroatheroma detected by intravascular ultrasound with virtual histology. *Circ Cardiovasc Interv* 2:543–548, 2009.
22. Wong ND, Gransar H, Narula J, et al: Myeloperoxidase, subclinical atherosclerosis, and cardiovascular disease events. *JACC Cardiovasc Imaging* 2:1093–1099, 2009.
23. Meuwese MC, Stroes ES, Hazen SL, et al: Serum myeloperoxidase levels are associated with the future risk of coronary artery disease in apparently healthy individuals: the EPIC-Norfolk Prospective Population Study. *J Am Coll Cardiol* 50:159–165, 2007.
24. Serruys PW, Garcia-Garcia HM, Buszman P, et al: Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque. *Circulation* 118:1172–1182, 2008.
25. Li QX, Fu QQ, Shi SW, et al: Relationship between plasma inflammatory markers and plaque fibrous cap thickness determined by intravascular optical coherence tomography. *Heart* 96:196–201, 2010.
26. Turu MM, Slevin M, Matou S, et al: C-reactive protein exerts angiogenic effects on vascular endothelial cells and modulates associated signalling pathways and gene expression. *BMC Cell Biol* 9:47, 2008.
27. Wang TJ, Gona P, Larson MG, et al: Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med* 355:2631–2639, 2006.
28. Koenig W, Khuseyinova N: Biomarkers of atherosclerotic plaque instability and rupture. *Arterioscler Thromb Vasc Biol* 27:15–26, 2007.
29. Zethelius B, Berglund L, Sundstrom J, et al: Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med* 358:2107–2116, 2008.
30. Deddens JC, Colijn JM, Oerlemans MI, et al: Circulating microRNAs as novel biomarkers for the early diagnosis of acute coronary syndrome. *J Cardiovasc Transl Res* 6:884–898, 2013.

31. Wang JC, Normand SL, Mauri L, Kuntz RE: Coronary artery spatial distribution of acute myocardial infarction occlusions. *Circulation* 110:278–284, 2004.
32. Valgimigli M, Rodriguez-Granillo GA, Garcia-Garcia HM, et al: Distance from the ostium as an independent determinant of coronary plaque composition in vivo: an intravascular ultrasound study based radiofrequency data analysis in humans. *Eur Heart J* 27:655–663, 2006.
33. Fujii K, Kawasaki D, Masutani M, et al: OCT assessment of thin-cap fibroatheroma distribution in native coronary arteries. *JACC Cardiovasc Imaging* 3:168–175, 2010.
34. Gonzalo N, Garcia-Garcia HM, Regar E, et al: In vivo assessment of high-risk coronary plaques at bifurcations with combined intravascular ultrasound and optical coherence tomography. *JACC Cardiovasc Imaging* 2:473–482, 2009.
35. Bentzon JF, Otsuka F, Virmani R, Falk EL: Mechanisms of plaque formation and rupture. *Circ Res* 114:1852–1866, 2014.
36. Otsuka F, Joner M, Prati F, et al: Clinical classification of plaque morphology in coronary disease. *Nat Rev Cardiol* 11:379–389, 2014.
37. Kramer MC, Rittersma SZ, de Winter RJ, et al: Relationship of thrombus healing to underlying plaque morphology in sudden coronary death. *J Am Coll Cardiol* 55:122–132, 2010.
38. Virmani R, Burke AP, Kolodgie FD, Farb A: Pathology of the thin-cap fibroatheroma: a type of vulnerable plaque. *J Interv Cardiol* 16:267–272, 2003.
39. Moreno PR: Vulnerable plaque: definition, diagnosis, and treatment. *Cardiol Clin* 28:1–30, 2010.
40. Narula J, Nakano M, Virmani R, et al: Histopathologic characteristics of atherosclerotic coronary disease and implications of the findings for the invasive and noninvasive detection of vulnerable plaques. *J Am Coll Cardiol* 61:1041–1051, 2013.
41. Fearon WF: Is a myocardial infarction more likely to result from a mild coronary lesion or an ischemia-producing one? *Circ Cardiovasc Interv* 4:539–541, 2011.
42. Burke AP, Kolodgie FD, Farb A, et al: Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. *Circulation* 103:934–940, 2001.
43. Ozaki Y, Okumura M, Ismail TF, et al: Coronary CT angiographic characteristics of culprit lesions in acute coronary syndromes not related to plaque rupture as defined by optical coherence tomography and angioscopy. *Eur Heart J* 32:2814–2823, 2011.
44. Moreno PR, Narula J: Thinking outside the lumen: fractional flow reserve versus intravascular imaging for major adverse cardiac event prediction. *J Am Coll Cardiol* 63:1141–1144, 2014.
45. Puri R, Nicholls SJ, Ellis SG, et al: High-risk coronary atheroma: the interplay between ischemia, plaque burden, and disease progression. *J Am Coll Cardiol* 63:1134–1140, 2014.
46. Moreno PR, Purushothaman KR, Fuster V, O'Connor WN: Intimomedial interface damage and adventitial inflammation is increased beneath disrupted atherosclerosis in the aorta: implications for plaque vulnerability. *Circulation* 105:2504–2511, 2002.
47. Tang D, Teng Z, Canton G, et al: Local critical stress correlates better than global maximum stress with plaque morphological features linked to atherosclerotic plaque vulnerability: an in vivo multi-patient study. *Biomed Eng Online* 8:15, 2009.
48. Stone PH, Saito S, Takahashi S, et al: Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION study. *Circulation* 126:172–181, 2012.
49. Cardoso L, Kelly-Arnold A, Maldonado N, et al: Effect of tissue properties, shape and orientation of microcalcifications on vulnerable cap stability using different hyperelastic constitutive models. *J Biomech* 47:870–877, 2014.
50. Schaar JA, van der Steen AF, Mastik F, et al: Intravascular palpography for vulnerable plaque assessment. *J Am Coll Cardiol* 47(Suppl):C86–C91, 2006.
51. Fok PW: Growth of necrotic cores in atherosclerotic plaque. *Math Med Biol* 29:301–327, 2012.
52. Shang YY, Wang ZH, Zhang LP, et al: TRB3, upregulated by ox-LDL, mediates human monocyte-derived macrophage apoptosis. *FEBS J* 276:2752–2761, 2009.
53. Moreno PR, Bernardi VH, Lopez-Cuellar VH, et al: Macrophages, smooth muscle cells, and tissue factor in unstable angina. Implications for cell-mediated thrombogenicity in acute coronary syndromes. *Circulation* 94:3090–3097, 1996.
54. Kuge Y, Kume N, Ishino S, et al: Prominent lectin-like oxidized low density lipoprotein (LDL) receptor-1 (LOX-1) expression in atherosclerotic lesions is associated with tissue factor expression and apoptosis in hypercholesterolemic rabbits. *Biol Pharm Bull* 31:1475–1482, 2008.
55. Reininger AJ, Bernlochner I, Penz SM, et al: A 2-step mechanism of arterial thrombus formation induced by human atherosclerotic plaques. *J Am Coll Cardiol* 55:1147–1158, 2010.
56. Shah PK, Galis ZS: Matrix metalloproteinase hypothesis of plaque rupture: players keep piling up but questions remain. *Circulation* 104:1878–1880, 2001.
57. Suzuki H, Kusuyama T, Sato R, et al: Elevation of matrix metalloproteinases and interleukin-6 in the culprit coronary artery of myocardial infarction. *Eur J Clin Invest* 38:166–173, 2008.
58. Newby AC: Metalloproteinases and vulnerable atherosclerotic plaques. *Trends Cardiovasc Med* 17:253–258, 2007.
59. Thomas AC, Sala-Newby GB, Ismail Y, et al: Genomics of foam cells and nonfoamy macrophages from rabbits identifies arginase-I as a differential regulator of nitric oxide production. *Arterioscler Thromb Vasc Biol* 27:571–577, 2007.
60. Newby AC, George SJ, Ismail Y, et al: Vulnerable atherosclerotic plaque metalloproteinases and foam cell phenotypes. *Thromb Haemost* 101:1006–1011, 2009.
61. Seshiah PN, Kereiakes DJ, Vasudevan SS, et al: Activated monocytes induce smooth muscle cell death: role of macrophage colony-stimulating factor and cell contact. *Circulation* 105:174–180, 2002.
62. Hutter R, Valdiviezo C, Sauter BV, et al: Caspase-3 and tissue factor expression in lipid-rich plaque macrophages: evidence for apoptosis as link between inflammation and atherothrombosis. *Circulation* 109:2001–2008, 2004.
63. Libby P: Inflammation and cardiovascular disease mechanisms. *Am J Clin Nutr* 83:456S–460S, 2006.
64. Tabas I: Macrophage death and defective inflammation resolution in atherosclerosis. *Nat Rev Immunol* 10:36–46, 2010.
65. Odegaard JI, Ricardo-Gonzalez RR, Goforth MH, et al: Macrophage-specific PPARgamma controls alternative activation and improves insulin resistance. *Nature* 447:1116–1120, 2007.
66. Nofer JR, Bot M, Brodde M, et al: FTY720, a synthetic sphingosine 1 phosphate analogue, inhibits development of atherosclerosis in low-density lipoprotein receptor-deficient mice. *Circulation* 115:501–508, 2007.
67. Tabas I: Consequences and therapeutic implications of macrophage apoptosis in atherosclerosis: the importance of lesion stage and phagocytic efficiency. *Arterioscler Thromb Vasc Biol* 25:2255–2264, 2005.
68. Philippidis P, Mason JC, Evans BJ, et al: Hemoglobin scavenger receptor CD163 mediates interleukin-10 release and heme oxygenase-1 synthesis: antiinflammatory monocyte-macrophage responses in vitro, in resolving skin blisters in vivo, and after cardiopulmonary bypass surgery. *Circ Res* 94:119–126, 2004.
69. Finn AV, Nakano M, Polavarapu R, et al: Hemoglobin directs macrophage differentiation and prevents foam cell formation in human atherosclerotic plaques. *J Am Coll Cardiol* 59:166–177, 2012.
70. Levy AP, Purushothaman KR, Levy NS, et al: Downregulation of the hemoglobin scavenger receptor in individuals with diabetes and the Hp 2-2 genotype: implications for the response to intraplaque hemorrhage and plaque vulnerability. *Circ Res* 101:106–110, 2007.
71. Van Gorp H, Delputte PL, Nauwynck HJ: Scavenger receptor CD163, a Jack-of-all-trades and potential target for cell-directed therapy. *Mol Immunol* 47:1650–1660, 2010.
72. Yasunaga T, Ikeda S, Koga S, et al: Plasma pentraxin 3 is a more potent predictor of endothelial dysfunction than high-sensitive C-reactive protein. *Int Heart J* 55:160–164, 2014.
73. Koga S, Ikeda S, Yoshida T, et al: Elevated levels of systemic pentraxin 3 are associated with thin-cap fibroatheroma in coronary culprit lesions: assessment by optical coherence tomography and intravascular ultrasound. *JACC Cardiovasc Interv* 6:945–954, 2013.
74. Angelillo-Scherrer A: Leukocyte-derived microparticles in vascular homeostasis. *Circ Res* 110:356–369, 2012.
75. Cilla M, Pena E, Martinez MA, Kelly DJ: Comparison of the vulnerability risk for positive versus negative atheroma plaque morphology. *J Biomech* 46:1248–1254, 2013.
76. Back M, Ketelhuth DF, Agewall S: Matrix metalloproteinases in atherothrombosis. *Prog Cardiovasc Dis* 52:410–428, 2010.
77. Page-McCaw A, Ewald AJ, Werb Z: Matrix metalloproteinases and the regulation of tissue remodelling. *Nat Rev Mol Cell Biol* 8:221–233, 2007.
78. Rodriguez JA, Orbe J, Martinez de Lizarrondo S, et al: Metalloproteinases and atherothrombosis: MMP-10 mediates vascular remodeling promoted by inflammatory stimuli. *Front Biosci* 13:2916–2921, 2008.
79. Burke AP, Kolodgie FD, Farb A, et al: Morphological predictors of arterial remodeling in coronary atherosclerosis. *Circulation* 105:297–303, 2002.
80. Schoenhagen P, Ziada KM, Kapadia SR, et al: Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: an intravascular ultrasound study. *Circulation* 101:598–603, 2000.
81. Kroner ES, van Velzen JE, Boogers MJ, et al: Positive remodeling on coronary computed tomography as a marker for plaque vulnerability on virtual histology intravascular ultrasound. *Am J Cardiol* 107:1725–1729, 2011.
82. Corti R, Fayad ZA, Fuster V, et al: Effects of lipid-lowering by simvastatin on human atherosclerotic lesions: a longitudinal study by high-resolution, noninvasive magnetic resonance imaging. *Circulation* 104:249–252, 2001.
83. Schoenhagen P, Tuzcu EM, Apperson-Hansen C, et al: Determinants of arterial wall remodeling during lipid-lowering therapy: serial intravascular ultrasound observations from the Reversal of Atherosclerosis With Aggressive Lipid Lowering Therapy (REVERSAL) trial. *Circulation* 113:2826–2834, 2006.
84. Nissen SE, Nicholls SJ, Sipahi I, et al: Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 295:1556–1565, 2006.
85. Moreno PR, Purushothaman KR, Sirol M, et al: Neovascularization in human atherosclerosis. *Circulation* 113:2245–2252, 2006.
86. Moreno PR, Sanz J, Fuster V: Promoting mechanisms of vascular health: circulating progenitor cells, angiogenesis, and reverse cholesterol transport. *J Am Coll Cardiol* 53:2315–2323, 2009.
87. Barger AC, Beeuwkes R, 3rd, Lainey LL, Silverman KJ: Hypothesis: vasa vasorum and neovascularization of human coronary arteries: a possible role in the pathophysiology of atherosclerosis. *N Engl J Med* 310:175–177, 1984.
88. Kumamoto M, Nakashima Y, Sueishi K: Intimal neovascularization in human coronary atherosclerosis: its origin and pathophysiological significance. *Hum Pathol* 26:450–456, 1995.
89. O'Brien KD, McDonald TO, Chait A, et al: Neovascular expression of E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 in human atherosclerosis and their relation to intimal leukocyte content. *Circulation* 93:672–682, 1996.
90. Leroyer AS, Rautou PE, Silvestre JS, et al: CD40 ligand+ microparticles from human atherosclerotic plaques stimulate endothelial proliferation and angiogenesis a potential mechanism for intraplaque neovascularization. *J Am Coll Cardiol* 52:1302–1311, 2008.
91. Moreno PR, Fuster V: New aspects in the pathogenesis of diabetic atherothrombosis. *J Am Coll Cardiol* 44:2293–2300, 2004.
92. Purushothaman KR, Fuster V, Levy AP, et al: Atherosclerotic neovascularization in diabetes mellitus is related to plaque inflammation expressed as increased macrophage and T-cell lymphocyte infiltration. *Atherosclerosis* 8:P9–P259, 2007.
93. Moreno PR, Purushothaman KR, Fuster V, et al: Plaque neovascularization is increased in ruptured atherosclerotic lesions of human aorta: implications for plaque vulnerability. *Circulation* 110:2032–2038, 2004.
94. Moreno PR, Purushothaman K, O'Connor WN, et al: Microvessel sprouting, red blood cell extravasation, and peri-vascular inflammation is increased in plaques from patients with diabetes mellitus. *J Am Coll Cardiol* 45:430A, 2005.
95. Wilkinson FL, Liu Y, Rucka AK, et al: Contribution of VCAF-positive cells to neovascularization and calcification in atherosclerotic plaque development. *J Pathol* 211:362–369, 2007.
96. Gossl M, Versari D, Hildebrandt HA, et al: Segmental heterogeneity of vasa vasorum neovascularization in human coronary atherosclerosis. *JACC Cardiovasc Imaging* 3:32–40, 2010.
97. Le Dall J, Ho-Tin-Noe B, Louedec L, et al: Immaturity of microvessels in haemorrhagic plaques is associated with proteolytic degradation of angiogenic factors. *Cardiovasc Res* 85:184–193, 2010.
98. Post S, Peeters W, Busser E, et al: Balance between angiopoietin-1 and angiopoietin-2 is in favor of angiopoietin-2 in atherosclerotic plaques with high microvessel density. *J Vasc Res* 45:244–250, 2008.
99. Moreno PR, Purushothaman M, Purushothaman KR: Plaque neovascularization: defense mechanisms, betrayal, or a war in progress. *Ann N Y Acad Sci* 1254:7–17, 2012.
100. Asleh R, Guetta J, Kalet-Litman S, et al: Haptoglobin genotype- and diabetes-dependent differences in iron-mediated oxidative stress in vitro and in vivo. *Circ Res* 96:435–441, 2005.
101. Kalet-Litman S, Moreno PR, Levy AP: The haptoglobin 2-2 genotype is associated with increased redox active hemoglobin derived iron in the atherosclerotic plaque. *Atherosclerosis* 209:28–31, 2010.
102. Purushothaman M, Krishnan P, Purushothaman KR, et al: Genotype-dependent impairment of hemoglobin clearance increases oxidative and inflammatory response in human diabetic atherosclerosis. *Arterioscler Thromb Vasc Biol* 32:2769–2775, 2012.
103. Cahill LE, Levy AP, Chiuve SE, et al: Haptoglobin genotype is a consistent marker of coronary heart disease risk among individuals with elevated glycosylated hemoglobin. *J Am Coll Cardiol* 61:728–737, 2013.
104. Granada JF, Kaluza GL, Wilensky RL, et al: Porcine models of coronary atherosclerosis and vulnerable plaque for imaging and interventional research. *EuroIntervention* 5:140–148, 2009.
105. DeMaria AN, Narula J, Mahmud E, Tsimikas S: Imaging vulnerable plaque by ultrasound. *J Am Coll Cardiol* 47:C32–C39, 2006.
106. Low AF, Kawase Y, Chan YH, et al: In vivo characterisation of coronary plaques with conventional grey-scale intravascular ultrasound: correlation with optical coherence tomography. *EuroIntervention* 4:626–632, 2009.
107. Okubo M, Kawasaki M, Ishihara Y, et al: Tissue characterization of coronary plaques: comparison of integrated backscatter intravascular ultrasound with virtual histology intravascular ultrasound. *Circ J* 72:1631–1639, 2008.
108. Fujii K, Mintz GS, Carlier SG, et al: Intravascular ultrasound profile analysis of ruptured coronary plaques. *Am J Cardiol* 98:429–435, 2006.
109. Kim SH, Hong MK, Park DW, et al: Impact of plaque characteristics analyzed by intravascular ultrasound on long-term clinical outcomes. *Am J Cardiol* 103:1221–1226, 2009.
110. Konig A, Bleie O, Rieber J, et al: Intravascular ultrasound radiofrequency analysis of the lesion segment profile in ACS patients. *Clin Res Cardiol* 99:83–91, 2010.
111. Moreno PR, Purushothaman KR, Fuster V, O'Connor WN: Intimomedial interface damage and adventitial inflammation is increased beneath disrupted atherosclerosis in the aorta: implications for plaque vulnerability. *Circulation* 105:2504–2511, 2002.
112. Sano K, Kawasaki M, Ishihara Y, et al: Assessment of vulnerable plaques causing acute coronary syndrome using integrated backscatter intravascular ultrasound. *J Am Coll Cardiol* 47:734–741, 2006.

113. Yamagishi M, Terashima M, Awano K, et al: Morphology of vulnerable coronary plaque: insights from follow-up of patients examined by intravascular ultrasound before an acute coronary syndrome. *J Am Coll Cardiol* 35:106–111, 2000.
114. Bayturan O, Tuzcu EM, Nicholls SJ, et al: Attenuated plaque at nonculprit lesions in patients enrolled in intravascular ultrasound atherosclerosis progression trials. *JACC Cardiovasc Interv* 2:672–678, 2009.
115. Raffel OC, Merchant FM, Tearney GJ, et al: In vivo association between positive coronary artery remodelling and coronary plaque characteristics assessed by intravascular optical coherence tomography. *Eur Heart J* 29:1721–1728, 2008.
116. Kaul S, Ito H: Microvasculature in acute myocardial ischemia: part II: evolving concepts in pathophysiology, diagnosis, and treatment. *Circulation* 109:310–315, 2004.
117. Staub D, Schinkel AF, Coll B, et al: Contrast-enhanced ultrasound imaging of the vasa vasorum: from early atherosclerosis to the identification of unstable plaques. *JACC Cardiovasc Imaging* 3:761–771, 2010.
118. Moguillansky D, Leng X, Carson A, et al: Quantification of plaque neovascularization using contrast ultrasound: a histologic validation. *Eur Heart J* 32:646–653, 2011.
119. Carlier S, Kakadiaris IA, Dib N, et al: Vasa vasorum imaging: a new window to the clinical detection of vulnerable atherosclerotic plaques. *Curr Atheroscler Rep* 7:164–169, 2005.
120. Vavuranakis M, Kakadiaris IA, O'Malley SM, et al: A new method for assessment of plaque vulnerability based on vasa vasorum imaging, by using contrast-enhanced intravascular ultrasound and differential image analysis. *Int J Cardiol* 130:23–29, 2008.
121. Lee JB, Mintz GS, Lisauskas JB, et al: Histopathologic validation of the intravascular ultrasound diagnosis of calcified coronary artery nodules. *Am J Cardiol* 108:1547–1551, 2011.
122. Xu Y, Mintz GS, Tam A, et al: Prevalence, distribution, predictors, and outcomes of patients with calcified nodules in native coronary arteries: a 3-vessel intravascular ultrasound analysis from Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT). *Circulation* 126:537–545, 2012.
123. Nair A, Kuban BD, Tuzcu EM, et al: Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. *Circulation* 106:2200–2206, 2002.
124. Van Herck J, De Meyer G, Ennekens G, et al: Validation of in vivo plaque characterisation by virtual histology in a rabbit model of atherosclerosis. *EuroIntervention* 5:149–156, 2009.
125. Thim T, Hagensen MK, Wallace-Bradley D, et al: Unreliable assessment of necrotic core by virtual histology intravascular ultrasound in porcine coronary artery disease. *Circ Cardiovasc Imaging* 3:384–391, 2010.
126. Granada JF, Wallace-Bradley D, Win HK, et al: In vivo plaque characterization using intravascular ultrasound-virtual histology in a porcine model of complex coronary lesions. *Arterioscler Thromb Vasc Biol* 27:387–393, 2007.
127. Surmely JF, Nasu K, Fujita H, et al: Coronary plaque composition of culprit/target lesions according to the clinical presentation: a virtual histology intravascular ultrasound analysis. *Eur Heart J* 27:2939–2944, 2006.
128. Calvert PA, Obaid DR, O'Sullivan M, et al: Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) study. *JACC Cardiovasc Imaging* 4:894–901, 2011.
129. Rodriguez-Granillo GA, Garcia-Garcia HM, Mc Fadden EP, et al: In vivo intravascular ultrasound-derived thin-cap fibroatheroma detection using ultrasound radiofrequency data analysis. *J Am Coll Cardiol* 46:2038–2042, 2005.
130. Hong MK, Mintz GS, Lee CW, et al: Comparison of virtual histology to intravascular ultrasound of culprit coronary lesions in acute coronary syndrome and target coronary lesions in stable angina pectoris. *Am J Cardiol* 100:953–959, 2007.
131. Nakamura T, Kubo N, Funayama H, et al: Plaque characteristics of the coronary segment proximal to the culprit lesion in stable and unstable patients. *Clin Cardiol* 32:E9–E12, 2009.
132. Sawada T, Shite J, Garcia-Garcia HM, et al: Feasibility of combined use of intravascular ultrasound radiofrequency data analysis and optical coherence tomography for detecting thin-cap fibroatheroma. *Eur Heart J* 29:1136–1146, 2008.
133. Kubo T, Maehara A, Mintz GS, et al: The dynamic nature of coronary artery lesion morphology assessed by serial virtual histology intravascular ultrasound tissue characterization. *J Am Coll Cardiol* 55:1590–1597, 2010.
134. Burke AP, Joner M, Virmani R: IVUS-VH: a predictor of plaque morphology? *Eur Heart J* 27:1889–1890, 2006.
135. Nasu K, Tsuchikane E, Katoh O, et al: Accuracy of in vivo coronary plaque morphology assessment: a validation study of in vivo virtual histology compared with in vitro histopathology. *J Am Coll Cardiol* 47:2405–2412, 2006.
136. Wu X, Maehara A, Mintz GS, et al: Virtual histology intravascular ultrasound analysis of non-culprit attenuated plaques detected by grayscale intravascular ultrasound in patients with acute coronary syndromes. *Am J Cardiol* 105:48–53, 2010.
137. Rodriguez-Granillo GA, McFadden EP, Valgimigli M, et al: Coronary plaque composition of nonculprit lesions, assessed by in vivo intracoronary ultrasound radio frequency data analysis, is related to clinical presentation. *Am Heart J* 151:1020–1024, 2006.
138. Diethrich EB, Pauliina Margolis M, Reid DB, et al: Virtual histology intravascular ultrasound assessment of carotid artery disease: the Carotid Artery Plaque Virtual Histology Evaluation (CAPITAL) study. *J Endovasc Ther* 14:676–686, 2007.
139. Prasad A, Cipher DJ, Mohandas A, et al: Reproducibility of intravascular ultrasound virtual histology analysis. *Cardiovasc Revasc Med* 9:71–77, 2008.
140. Low AF, Tearney GJ, Bouma BE, Jang IK: Technology Insight: optical coherence tomography—current status and future development. *Nat Clin Pract Cardiovasc Med* 3:154–162, quiz 72, 2006.
141. Di Vito L, Yoon JH, Kato K, et al: Comprehensive overview of definitions for optical coherence tomography-based plaque and stent analyses. *Coron Artery Dis* 25:172–185, 2014.
142. Gutierrez-Chico JL, Alegria-Barrero E, Teijeiro-Mestre R, et al: Optical coherence tomography: from research to practice. *Eur Heart J Cardiovasc Imaging* 13:370–384, 2012.
143. Tearney GJ, Regar E, Akasaka T, et al: Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol* 59:1058–1072, 2012.
144. Prati F, Guagliumi G, Mintz GS, et al: Expert review document part 2: methodology, terminology and clinical applications of optical coherence tomography for the assessment of interventional procedures. *Eur Heart J* 33:2513–2520, 2012.
145. Regar E, van Soest G, Bruining N, et al: Optical coherence tomography in patients with acute coronary syndrome. *EuroIntervention* 6(Suppl G):G154–G160, 2010.
146. Tanaka A, Imanishi T, Kitabata H, et al: Lipid-rich plaque and myocardial perfusion after successful stenting in patients with non-ST-segment elevation acute coronary syndrome: an optical coherence tomography study. *Eur Heart J* 30:1348–1355, 2009.
147. Radu MD, Falk E: In search of vulnerable features of coronary plaques with optical coherence tomography: is it time to rethink the current methodological concepts? *Eur Heart J* 33:9–12, 2012.
148. Uemura S, Ishigami K, Soeda T, et al: Thin-cap fibroatheroma and microchannel findings in optical coherence tomography correlate with subsequent progression of coronary atheromatous plaques. *Eur Heart J* 33:78–85, 2012.
149. Jang IK, Tearney GJ, MacNeill B, et al: In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography. *Circulation* 111:1551–1555, 2005.
150. Yonetsu T, Kakuta T, Lee T, et al: In vivo critical fibrous cap thickness for rupture-prone coronary plaques assessed by optical coherence tomography. *Eur Heart J* 32:1251–1259, 2011.
151. Kubo T, Imanishi T, Takarada S, et al: Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angioscopy. *J Am Coll Cardiol* 50:933–939, 2007.
152. Jia H, Abtahian F, Aguirre AD, et al: In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. *J Am Coll Cardiol* 62:1748–1758, 2013.
153. Hu S, Yonetsu T, Jia H, et al: Residual thrombus pattern in patients with ST-segment elevation myocardial infarction caused by plaque erosion versus plaque rupture after successful fibrinolysis: an optical coherence tomography study. *J Am Coll Cardiol* 63:1336–1338, 2014.
154. Lee T, Kakuta T, Yonetsu T, et al: Assessment of echo-attenuated plaque by optical coherence tomography and its impact on post-procedural creatine kinase-myocardial band elevation in elective stent implantation. *JACC Cardiovasc Interv* 4:483–491, 2011.
155. Giattina SD, Courtney BK, Herz PR, et al: Assessment of coronary plaque collagen with polarization sensitive optical coherence tomography (PS-OCT). *Int J Cardiol* 107:400–409, 2006.
156. Manfrini O, Mont E, Leone O, et al: Sources of error and interpretation of plaque morphology by optical coherence tomography. *Am J Cardiol* 98:156–159, 2006.
157. van Soest G, Goderie T, Regar E, et al: Atherosclerotic tissue characterization in vivo by optical coherence tomography attenuation imaging. *J Biomed Opt* 15:011105, 2010.
158. Tearney GJ, Yabushita H, Houser SL, et al: Quantification of macrophage content in atherosclerotic plaques by optical coherence tomography. *Circulation* 107:113–119, 2003.
159. MacNeill BD, Jang IK, Bouma BE, et al: Focal and multi-focal plaque macrophage distributions in patients with acute and stable presentations of coronary artery disease. *J Am Coll Cardiol* 44:972–979, 2004.
160. Raffel OC, Tearney GJ, Gauthier DD, et al: Relationship between a systemic inflammatory marker, plaque inflammation, and plaque characteristics determined by intravascular optical coherence tomography. *Arterioscler Thromb Vasc Biol* 27:1820–1827, 2007.
161. Avery RL, Pieramici DJ, Rabena MD, et al: Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 113:363e5–372e5, 2006.
162. Tian J, Hou J, Xing L, et al: Significance of intraplaque neovascularisation for vulnerability: optical coherence tomography study. *Heart* 98:1504–1509, 2012.
163. Kitabata H, Tanaka A, Kubo T, et al: Relation of microchannel structure identified by optical coherence tomography to plaque vulnerability in patients with coronary artery disease. *Am J Cardiol* 105:1673–1678, 2010.
164. Uchida Y, Kawai S, Kanamaru R, et al: Detection of vulnerable coronary plaques by color fluorescent angioscopy. *JACC Cardiovasc Imaging* 3:398–408, 2010.
165. Uchida Y, Nakamura F, Tomaru T, et al: Prediction of acute coronary syndromes by percutaneous coronary angioscopy in patients with stable angina. *Am Heart J* 130:195–203, 1995.
166. Asakura M, Ueda Y, Yamaguchi O, et al: Extensive development of vulnerable plaques as a pan-coronary process in patients with myocardial infarction: an angioscopic study. *J Am Coll Cardiol* 37:1284–1288, 2001.
167. Ohtani T, Ueda Y, Mizote I, et al: Number of yellow plaques detected in a coronary artery is associated with future risk of acute coronary syndrome: detection of vulnerable patients by angioscopy. *J Am Coll Cardiol* 47:2194–2200, 2006.
168. Takano M, Jang IK, Inami S, et al: In vivo comparison of optical coherence tomography and angioscopy for the evaluation of coronary plaque characteristics. *Am J Cardiol* 101:471–476, 2008.
169. Hirayama A, Saito S, Ueda Y, et al: Qualitative and quantitative changes in coronary plaque associated with atorvastatin therapy. *Circ J* 73:718–725, 2009.
170. Takayama T, Hiro T, Ueda Y, et al: Plaque stabilization by intensive LDL-cholesterol lowering therapy with atorvastatin is delayed in type 2 diabetic patients with coronary artery disease-Serial angioscopic and intravascular ultrasound analysis. *J Cardiol* 61:381–386, 2013.
171. Kurihara O, Takano M, Yamamoto M, et al: Impact of prediabetic status on coronary atherosclerosis: a multivessel angioscopic study. *Diabetes Care* 36:729–733, 2013.
172. Ishibashi F, Mizuno K, Kawamura A, et al: High yellow color intensity by angioscopy with quantitative colorimetry to identify high-risk features in culprit lesions of patients with acute coronary syndromes. *Am J Cardiol* 100:1207–1211, 2007.
173. Moreno PR, Muller JE: Detection of high-risk atherosclerotic coronary plaques by intravascular spectroscopy. *J Interv Cardiol* 16:243–252, 2003.
174. Moreno PR, Lodder RA, Purushothaman KR, et al: Detection of lipid pool, thin fibrous cap, and inflammatory cells in human aortic atherosclerotic plaques by near-infrared spectroscopy. *Circulation* 105:923–927, 2002.
175. Gardner CM, Tan H, Hull EL, et al: Detection of lipid core coronary plaques in autopsy specimens with a novel catheter-based near-infrared spectroscopy system. *JACC Cardiovasc Imaging* 1:638–648, 2008.
176. Nazemi JH, Brennan JF: Lipid concentrations in human coronary artery determined with high wavenumber Raman shifted light. *J Biomed Opt* 14:034009, 2009.
177. Goldstein JA, Maini B, Dixon SR, et al: Detection of lipid-core plaques by intracoronary near-infrared spectroscopy identifies high risk of periprocedural myocardial infarction. *Circ Cardiovasc Interv* 4:429–437, 2011.
178. Waxman S, Dixon SR, L'Allier P, et al: In vivo validation of a catheter-based near-infrared spectroscopy system for detection of lipid core coronary plaques: initial results of the SPECTACL study. *JACC Cardiovasc Imaging* 2:858–868, 2009.
179. Madder RD, Goldstein JA, Madden SP, et al: Detection by near-infrared spectroscopy of large lipid core plaques at culprit sites in patients with acute ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv* 6:838–846, 2013.
180. Madder RD, Steinberg DH, Anderson RD: Multimodality direct coronary imaging with combined near-infrared spectroscopy and intravascular ultrasound: initial US experience. *Catheter Cardiovasc Interv* 81:551–557, 2013.
181. Fernandez-Friera L, Garcia-Alvarez A, Romero A, et al: Lipid-rich obstructive coronary lesions is plaque characterization any important? *JACC Cardiovasc Imaging* 3:893–895, 2010.
182. Madder RD, Wohns DH, Muller JE: Detection by intracoronary near-infrared spectroscopy of lipid core plaque at culprit sites in survivors of cardiac arrest. *J Invasive Cardiol* 26:78–79, 2014.
183. Erlinde D: Unravelling the ACS culprit: insights from NIRS-IVUS. Presented at Transcatheter Cardiovascular Therapeutics 25th Annual Scientific Symposium, San Francisco, CA, October 27-November 1, 2013.
184. Goldstein JA, Grines C, Fischell T, et al: Coronary embolization following balloon dilation of lipid-core plaques. *JACC Cardiovasc Imaging* 2:1420–1424, 2009.
185. Roleder T, Kovacic JC, Ali Z, et al: Combined NIRS and IVUS imaging detects vulnerable plaque using a single catheter system: a head-to-head comparison with OCT. *EuroIntervention* 10:303–311, 2014.
186. Press release: CRF and UCR announce initiation of PROSPECT II clinical trial. Available at <http://www.eurekalert.org/pub_releases/2013-10/crf-cau102813.php>, (Accessed February 27, 2015.).
187. Waksman R: The Lipid Rich Plaque (LRP) study. Presented at the Cardiovascular Research Technologies meeting, Washington, DC, February 23–25, 2014.
188. Kini AS, Baber U, Kovacic JC, et al: Changes in plaque lipid content after short-term intensive versus standard statin therapy: the YELLOW trial (reduction in yellow plaque by aggressive lipid-lowering therapy). *J Am Coll Cardiol* 62:21–29, 2013.
189. Kitagawa T, Yamamoto H, Horiguchi J, et al: Characterization of noncalcified coronary plaques and identification of culprit lesions in patients with acute coronary syndrome by 64-slice computed tomography. *JACC Cardiovasc Imaging* 2:153–160, 2009.
190. Pundziute G, Schuijf JD, Jukema JW, et al: Head-to-head comparison of coronary plaque evaluation between multislice computed tomography and intravascular ultrasound radiofrequency data analysis. *JACC Cardiovasc Interv* 1:176–182, 2008.

191. Hoffmann U, Ferencik M, Cury RC, Pena AJ: Coronary CT angiography. *J Nucl Med* 47:797–806, 2006.
192. Kashiwagi M, Tanaka A, Kitabata H, et al: Feasibility of noninvasive assessment of thin-cap fibroatheroma by multidetector computed tomography. *JACC Cardiovasc Imaging* 2:1412–1419, 2009.
193. Rivera JJ, Nasir K, Cox PR, et al: Association of traditional cardiovascular risk factors with coronary plaque sub-types assessed by 64-slice computed tomography angiography in a large cohort of asymptomatic subjects. *Atherosclerosis* 206:451–457, 2009.
194. Kristensen TS, Kofoed KF, Kuhl JT, et al: Prognostic implications of nonobstructive coronary plaques in patients with non-ST-segment elevation myocardial infarction: a multidetector computed tomography study. *J Am Coll Cardiol* 58:502–509, 2011.
195. Papadopoulou SL, Neefjes LA, Garcia-Garcia HM, et al: Natural history of coronary atherosclerosis by multislice computed tomography. *JACC Cardiovasc Imaging* 5(Suppl):S28–S37, 2012.
196. Achenbach S: Can CT detect the vulnerable coronary plaque? *Int J Cardiovasc Imaging* 24:311–312, 2008.
197. Narula J, Achenbach S: Napkin-ring necrotic cores: defining circumferential extent of necrotic cores in unstable plaques. *JACC Cardiovasc Imaging* 2:1436–1438, 2009.
198. van der Giessen AG, Toepker MH, Donelly PM, et al: Reproducibility, accuracy, and predictors of accuracy for the detection of coronary atherosclerotic plaque composition by computed tomography: an ex vivo comparison to intravascular ultrasound. *Invest Radiol* 45:693–701, 2010.
199. Klass O, Kleinhans S, Walker MJ, et al: Coronary plaque imaging with 256-slice multidetector computed tomography: interobserver variability of volumetric lesion parameters with semiautomatic plaque analysis software. *Int J Cardiovasc Imaging* 26:711–720, 2010.
200. Brodoefel H, Burgstahler C, Sabir A, et al: Coronary plaque quantification by voxel analysis: dual-source MDCT angiography versus intravascular sonography. *AJR Am J Roentgenol* 192:W84–W89, 2009.
201. Schepis T, Marwan M, Pflederer T, et al: Quantification of noncalcified coronary atherosclerotic plaques with dual-source computed tomography: comparison with intravascular ultrasound. *Heart* 96:610–615, 2010.
202. Boogers MJ, Broersen A, van Velzen JE, et al: Automated quantification of coronary plaque with computed tomography: comparison with intravascular ultrasound using a dedicated registration algorithm for fusion-based quantification. *Eur Heart J* 33:1007–1016, 2012.
203. Ito T, Terashima M, Kaneda H, et al: Comparison of in vivo assessment of vulnerable plaque by 64-slice multislice computed tomography versus optical coherence tomography. *Am J Cardiol* 107:1270–1277, 2011.
204. Marwan M, Taher MA, El Meniawy K, et al: In vivo CT detection of lipid-rich coronary artery atherosclerotic plaques using quantitative histogram analysis: a head to head comparison with IVUS. *Atherosclerosis* 215:110–115, 2011.
205. Schlett CL, Maurovich-Horvat P, Ferencik M, et al: Histogram analysis of lipid-core plaques in coronary computed tomographic angiography: ex vivo validation against histology. *Invest Radiol* 48:646–653, 2013.
206. Maurovich-Horvat P, Ferencik M, Voros S, et al: Comprehensive plaque assessment by coronary CT angiography. *Nat Rev Cardiol* 11:390–402, 2014.
207. Maurovich-Horvat P, Schlett CL, Alkadhi H, et al: The napkin-ring sign indicates advanced atherosclerotic lesions in coronary CT angiography. *JACC Cardiovasc Imaging* 5:1243–1252, 2012.
208. Kodama T, Kondo T, Oida A, et al: Computed tomographic angiography-verified plaque characteristics and slow-flow phenomenon during percutaneous coronary intervention. *JACC Cardiovasc Interv* 5:636–643, 2012.
209. Otsuka K, Fukuda S, Tanaka A, et al: Napkin-ring sign on coronary CT angiography for the prediction of acute coronary syndrome. *JACC Cardiovasc Imaging* 6:448–457, 2013.
210. Gauss S, Achenbach S, Pflederer T, et al: Assessment of coronary artery remodelling by dual-source CT: a head-to-head comparison with intravascular ultrasound. *Heart* 97:991–997, 2011.
211. Maldonado N, Kelly-Arnold A, Vengrenyuk Y, et al: A mechanistic analysis of the role of microcalcifications in atherosclerotic plaque stability: potential implications for plaque rupture. *Am J Physiol Heart Circ Physiol* 303:H619–H628, 2012.
212. Rambhia SH, Liang X, Xenos M, et al: Microcalcifications increase coronary vulnerable plaque rupture potential: a patient-based micro-CT fluid-structure interaction study. *Ann Biomed Eng* 40:1443–1454, 2012.
213. Madder RD, Chinnaiyan KM, Marandici AM, Goldstein JA: Features of disrupted plaques by coronary computed tomographic angiography: correlates with invasively proven complex lesions. *Circ Cardiovasc Imaging* 4:105–113, 2011.
214. Inoue K, Motoyama S, Sarai M, et al: Serial coronary CT angiography-verified changes in plaque characteristics as an end point: evaluation of effect of statin intervention. *JACC Cardiovasc Imaging* 3:691–698, 2010.
215. Motoyama S, Kondo T, Sarai M, et al: Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol* 50:319–326, 2007.
216. Taylor CA, Fonte TA, Min JK: Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. *J Am Coll Cardiol* 61:2233–2241, 2013.
217. Gijsen FJ, Schuurbiers JC, van de Giessen AG, et al: 3D reconstruction techniques of human coronary bifurcations for shear stress computations. *J Biomech* 47:39–43, 2014.
218. Oberoi S, Meinel FG, Schoepf UJ, et al: Reproducibility of noncalcified coronary artery plaque burden quantification from coronary CT angiography across different image analysis platforms. *AJR Am J Roentgenol* 202:W43–W49, 2014.
219. Maurovich-Horvat P, Ferencik M, et al: Comprehensive plaque assessment by coronary CT angiography. *Nat Rev Cardiol* 11:390–402, 2014.
220. Hyafil F, Cornily JC, Feig JE, et al: Noninvasive detection of macrophages using a nanoparticulate contrast agent for computed tomography. *Nat Med* 13:636–641, 2007.
221. Cormode DP, Roessl E, Thran A, et al: Atherosclerotic plaque composition: analysis with multicolor CT and targeted gold nanoparticles. *Radiology* 256:774–782, 2010.
222. Langer HF, Haubner R, Pichler BJ, Gawaz M: Radionuclide imaging: a molecular key to the atherosclerotic plaque. *J Am Coll Cardiol* 52:1–12, 2008.
223. Teras M, Kokki T, Durand-Schaefer N, et al: Dual-gated cardiac PET-clinical feasibility study. *Eur J Nucl Med Mol Imaging* 37:505–516, 2010.
224. Wykrzykowska J, Lehman S, Williams G, et al: Imaging of inflamed and vulnerable plaque in coronary arteries with 18F-FDG PET/CT in patients with suppression of myocardial uptake using a low-carbohydrate, high-fat preparation. *J Nucl Med* 50:563–568, 2009.
225. Chen W, Dilsizian V: (18)F-fluorodeoxyglucose PET imaging of coronary atherosclerosis and plaque inflammation. *Curr Cardiol Rep* 12:179–184, 2010.
226. Joshi NV, Vesey AT, Williams MC, et al: 18F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. *Lancet* 383:705–713, 2014.
227. Chen W, Dilsizian V: Targeted PET/CT imaging of vulnerable atherosclerotic plaques: microcalcification with sodium fluoride and inflammation with fluorodeoxyglucose. *Curr Cardiol Rep* 15:364, 2013.
228. Schafers M, Schober O, Hermann S: Matrix-metalloproteinases as imaging targets for inflammatory activity in atherosclerotic plaques. *J Nucl Med* 51:663–666, 2010.
229. Ishino S, Mukai T, Kuge Y, et al: Targeting of lectinlike oxidized low-density lipoprotein receptor 1 (LOX-1) with 99mTc-labeled anti-LOX-1 antibody: potential agent for imaging of vulnerable plaque. *J Nucl Med* 49:1677–1685, 2008.
230. Laitinen I, Saraste A, Weidl E, et al: Evaluation of alphavbeta3 integrin-targeted positron emission tomography tracer 18F-galacto-RGD for imaging of vascular inflammation in atherosclerotic mice. *Circ Cardiovasc Imaging* 2:331–338, 2009.
231. Laufer EM, Winkens MH, Narula J, Hofstra L: Molecular imaging of macrophage cell death for the assessment of plaque vulnerability. *Arterioscler Thromb Vasc Biol* 29:1031–1038, 2009.
232. Skajaa T, Cormode DP, Falk E, et al: High-density lipoprotein-based contrast agents for multimodal imaging of atherosclerosis. *Arterioscler Thromb Vasc Biol* 30:169–176, 2010.
233. Muntendam P, McCall C, Sanz J, et al: The BioImage study: novel approaches to risk assessment in the primary prevention of atherosclerotic cardiovascular disease—study design and objectives. *Am Heart J* 160:49e1–57e1, 2010.
234. Fuster V, Fayad ZA, Moreno PR, et al: Atherothrombosis and high-risk plaque: Part II: approaches by noninvasive computed tomographic/magnetic resonance imaging. *J Am Coll Cardiol* 46:1209–1218, 2005.
235. Fuster V, Corti R, Fayad ZA, et al: Integration of vascular biology and magnetic resonance imaging in the understanding of atherothrombosis and acute coronary syndromes. *J Thromb Haemost* 1:1410–1421, 2003.
236. Sirol M, Fuster V, Fayad ZA: Plaque imaging and characterization using magnetic resonance imaging: towards molecular assessment. *Curr Mol Med* 6:541–548, 2006.
237. Zhao XQ, Dong L, Hatsukami T, et al: MR imaging of carotid plaque composition during lipid-lowering therapy a prospective assessment of effect and time course. *JACC Cardiovasc Imaging* 4:977–986, 2011.
238. Wilensky RL, Song HK, Ferrari VA: Role of magnetic resonance and intravascular magnetic resonance in the detection of vulnerable plaques. *J Am Coll Cardiol* 47:C48–C56, 2006.
239. Gerretsen SC, Kooi ME, Kessels AG, et al: Visualization of coronary wall atherosclerosis in asymptomatic subjects and patients with coronary artery disease using magnetic resonance imaging. *PLoS ONE* 5:e12998, 2010.
240. Jansen CH, Perera D, Makowski MR, et al: Detection of intracoronary thrombus by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation* 124:416–424, 2011.
241. Macedo R, Chen S, Lai S, et al: MRI detects increased coronary wall thickness in asymptomatic individuals: the multi-ethnic study of atherosclerosis (MESA). *J Magn Reson Imaging* 28:1108–1115, 2008.
242. Kelle S, Hays AG, Hirsch GA, et al: Coronary artery distensibility assessed by 3.0 Tesla coronary magnetic resonance imaging in subjects with and without coronary artery disease. *Am J Cardiol* 108:491–497, 2011.
243. Miao C, Chen S, Macedo R, et al: Positive remodeling of the coronary arteries detected by magnetic resonance imaging in an asymptomatic population: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 53:1708–1715, 2009.
244. Kim WY, Christiansen EH, Thrysoe SA, et al: First in vivo demonstration of coronary edema in culprit lesion of patient with acute coronary syndrome by cardiovascular magnetic resonance. *Circ Cardiovasc Imaging* 4:344–346, 2011.
245. Makowski MR, Henningsson M, Spuentrup E, et al: Characterization of coronary atherosclerosis by magnetic resonance imaging. *Circulation* 128:1244–1255, 2013.
246. Pedersen SF, Thrysoe SA, Paaske WP, et al: CMR assessment of endothelial damage and angiogenesis in porcine coronary arteries using gadofosveset. *J Cardiovasc Magn Reson* 13:10, 2011.
247. Pan D, Pramanik M, Senpan A, et al: Molecular photoacoustic imaging of angiogenesis with integrin-targeted gold nanobeacons. *FASEB J* 25:875–882, 2011.
248. Ambrose JA, D'Agate DJ: Classification of systemic therapies for potential stabilization of the vulnerable plaque to prevent acute myocardial infarction. *Am J Cardiol* 95:379–382, 2005.
249. Cannon CP, Steinberg BA, Murphy SA, et al: Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol* 48:438–445, 2006.
250. Scirica BM, Morrow DA, Cannon CP, et al: Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the PROVE IT-TIMI 22 study. *J Am Coll Cardiol* 47:2326–2331, 2006.
251. Hulten E, Jackson JL, Douglas K, et al: The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. *Arch Intern Med* 166:1814–1821, 2006.
252. Semenova AE, Sergienko IV, Masenko VP, et al: Effect of rosuvastatin therapy and myocardial revascularization on angiogenesis in coronary artery disease patients. *Kardiologiia* 47:4–8, 2007.
253. Goldenberg I, Goldbourt U, Boyko V, et al: Relation between on-treatment increments in serum high-density lipoprotein cholesterol levels and cardiac mortality in patients with coronary heart disease (from the Bezafibrate Infarction Prevention trial). *Am J Cardiol* 97:466–471, 2006.
254. Corti R, Osende J, Hutter R, et al: Fenofibrate induces plaque regression in hypercholesterolemic atherosclerotic rabbits: in vivo demonstration by high-resolution MRI. *Atherosclerosis* 190:106–113, 2006.
255. Tso C, Martinic G, Fan WH, et al: High-density lipoproteins enhance progenitor-mediated endothelium repair in mice. *Arterioscler Thromb Vasc Biol* 26:1144–1149, 2006.
256. Takarada S, Imanishi T, Kubo T, et al: Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome: assessment by optical coherence tomography study. *Atherosclerosis* 202:491–497, 2009.
257. Deschaseaux F, Selmani Z, Falcoz PE, et al: Two types of circulating endothelial progenitor cells in patients receiving long term therapy by HMG-CoA reductase inhibitors. *Eur J Pharmacol* 562:111–118, 2007.
258. Werner C, Kamani CH, Gensch C, et al: The peroxisome proliferator-activated receptor-gamma agonist pioglitazone increases number and function of endothelial progenitor cells in patients with coronary artery disease and normal glucose tolerance. *Diabetes* 56:2609–2615, 2007.
259. Massaro M, Scoditti E, Carluccio MA, et al: Omega-3 fatty acids, inflammation and angiogenesis: basic mechanisms behind the cardioprotective effects of fish and fish oils. *Cell Mol Biol (Noisy-Le-Grand)* 56:59–82, 2010.
260. Nishio R, Shinke T, Otake H, et al: Stabilizing effect of combined eicosapentaenoic acid and statin therapy on coronary thin-cap fibroatheroma. *Atherosclerosis* 234:114–119, 2014.
261. Petoumenos V, Nickenig G, Werner N: High-density lipoprotein exerts vasculoprotection via endothelial progenitor cells. *J Cell Mol Med* 13:4623–4635, 2009.
262. Hauer AD, Habets KL, van Wanrooij EJ, et al: Vaccination against TIE2 reduces atherosclerosis. *Atherosclerosis* 204:365–371, 2009.
263. Chauffe RJ, Wilensky RL, Mohler ER, 3rd: Recent developments with lipoprotein-associated phospholipase A2 inhibitors. *Curr Atheroscler Rep* 12:43–47, 2010.
264. Cannon CP, Braunwald E, McCabe CH, et al: Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 350:1495–1504, 2004.
265. Nicholls SJ, Ballantyne CM, Barter PJ, et al: Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med* 365:2078–2087, 2011.
266. Puri R, Libby P, Nissen SE, et al: Long-term effects of maximally intensive statin therapy on changes in coronary atheroma composition: insights from SATURN. *Eur Heart J Cardiovasc Imaging* 15:380–388, 2014.
267. Dong M, Zhong L, Chen WQ, et al: Doxycycline stabilizes vulnerable plaque via inhibiting matrix metalloproteinases and attenuating inflammation in rabbits. *PLoS ONE* 7:e39695, 2012.
268. Liang C, Xiaonan L, Xiaojun C, et al: Effect of metoprolol on vulnerable plaque in rabbits by changing shear stress around plaque and reducing inflammation. *Eur J Pharmacol* 613:79–85, 2009.
269. Waksman R, Leitch IM, Roessler J, et al: Intracoronary photodynamic therapy reduces neointimal growth without suppressing re-endothelialisation in a porcine model. *Heart* 92:1138–1144, 2006.
270. Dorval JF, Geoffroy P, Sirois MG, Tanguay JF: Endovascular cryotherapy accentuates the accumulation of the fibrillar

collagen types I and III after percutaneous transluminal angioplasty in pigs. *J Endovasc Ther* 13:104–110, 2006.
271. Magaraggia M, Marigo L, Pagnan A, et al: Porphyrin-photosensitized processes: their applications in the prevention of arterial restenosis. *Cardiovasc Hematol Agents Med Chem* 5:278–288, 2007.
272. Triesscheijn M, Baas P, Schellens JH, Stewart FA: Photodynamic therapy in oncology. *Oncologist* 11:1034–1044, 2006.
273. Waksman R, Leborgne L, Seaborn R, et al: Novel photopoint photodynamic therapy for the treatment of atherosclerotic plaques (abstract). *J Am Coll Cardiol* 41:259A, 2003.
274. Serruys PW: Fourth annual American College of Cardiology international lecture: a journey in the interventional field. *J Am Coll Cardiol* 47:1754–1768, 2006.
275. Davies MJ: Detecting vulnerable coronary plaques. *Lancet* 347:1422–1423, 1996.
276. Echeverri D, Purushothaman KR, Kilpatrick D, et al: Plaque stabilization by bare metal and drug-eluting stents in a rabbit model of thin-cap fibroatheroma. *Brazilian J Interv Cardiol* 16:160–177, 2008.
277. Kaluza GL, Alviar C, Tellez A, et al: First in-vivo experience with a novel low-pressure self-expanding intra-arterial shield: a one-month study comparing to balloon expandable stents in porcine coronary arteries. *Am J Cardiol* 100(Suppl):231L, 2007.
278. Ramcharitar S, Gonzalo N, van Geuns RJ, et al: First case of stenting of a vulnerable plaque in the SECRITT I trial-the dawn of a new era? *Nat Rev Cardiol* 6:374–378, 2009.
279. Granada JF, Milewski K, Uribe MP, et al: First clinical evaluation of a luminal self-expanding shield in patients with intermediate coronary lesions. *EuroIntervention* 7:780–788, 2011.
280. Wykrzykowska JJ, Diletti R, Gutierrez-Chico JL, et al: Plaque sealing and passivation with a mechanical self-expanding low outward force nitinol vShield device for the treatment of IVUS and OCT-derived thin cap fibroatheromas (TCFAs) in native coronary arteries: report of the pilot study vShield Evaluated at Cardiac Hospital in Rotterdam for Investigation and Treatment of TCFA (SECRITT). *EuroIntervention* 8:945–954, 2012.
281. Jain RK, Finn AV, Kolodgie FD, et al: Antiangiogenic therapy for normalization of atherosclerotic plaque vasculature: a potential strategy for plaque stabilization. *Nat Clin Pract Cardiovasc Med* 4:491–502, 2007.
282. Stefanadis C, Toutouzas K, Stefanadi E, et al: First experimental application of bevacizumab-eluting PC coated stent for inhibition of vasa vasorum of atherosclerotic plaque: angiographic results in a rabbit atheromatic model. *Hellenic J Cardiol* 47:7–10, 2006.
283. Stefanadis C, Toutouzas K, Stefanadi E, et al: Inhibition of plaque neovascularization and intimal hyperplasia by specific targeting vascular endothelial growth factor with bevacizumab-eluting stent: an experimental study. *Atherosclerosis* 195:269–276, 2007.
284. Kolodgie FD, Narula J, Yuan C, et al: Elimination of neoangiogenesis for plaque stabilization: is there a role for local drug therapy? *J Am Coll Cardiol* 49:2093–2101, 2007.
285. Roncal C, Buysschaert I, Gerdes N, et al: Short-term delivery of anti-PlGF antibody delays progression of atherosclerotic plaques to vulnerable lesions. *Cardiovasc Res* 86:29–36, 2010.
286. Prati F, Uemura S, Souteyrand G, et al: OCT-based diagnosis and management of STEMI associated with intact fibrous cap. *JACC Cardiovasc Imaging* 6:283–287, 2013.
287. Liu XL, Zhang PF, Ding SF, et al: Local gene silencing of monocyte chemoattractant protein-1 prevents vulnerable plaque disruption in apolipoprotein E-knockout mice. *PLoS ONE* 7:e33497, 2012.
288. Serruys PW, Kukreja N: Late stent thrombosis in drug-eluting stents: return of the "VB syndrome". *Nat Clin Pract Cardiovasc Med* 3:637, 2006.
289. Waksman R: Biodegradable stents: they do their job and disappear. *J Invasive Cardiol* 18:70–74, 2006.
290. Moreno P: First report of a vulnerable plaque specific stent capable of focal passivation without fibrous cap rupture. Presented at Transcatheter Cardiovascular Therapeutics meeting, Washington, DC, October 22–27, 2006.
291. Costopoulos C, Latib A, Naganuma T, et al: Comparison of early clinical outcomes between ABSORB bioresorbable vascular scaffold and everolimus-eluting stent implantation in a real-world population. *Catheter Cardiovasc Interv* 85:E10–E15, 2014.
292. Berry JD, Liu K, Folsom AR, et al: Prevalence and progression of subclinical atherosclerosis in younger adults with low short-term but high lifetime estimated risk for cardiovascular disease: the coronary artery risk development in young adults study and multi-ethnic study of atherosclerosis. *Circulation* 119:382–389, 2009.
293. Bild DE, Bluemke DA, Burke GL, et al: Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol* 156:871–881, 2002.
294. Fernandez-Ortiz A, Jimenez-Borreguero LJ, Penalvo JL, et al: The Progression and Early detection of Subclinical Atherosclerosis (PESA) study: rationale and design. *Am Heart J* 166:990–998, 2013.
295. Mancini GB, Hartigan PM, Shaw LJ, et al: Predicting outcome in the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation): coronary anatomy versus ischemia. *JACC Cardiovasc Interv* 7:195–201, 2014.
296. Windecker S, Bax JJ, Myat A, et al: Future treatment strategies in ST-segment elevation myocardial infarction. *Lancet* 382:644–657, 2013.
297. Pflederer T, Marwan M, Schepis T, et al: Characterization of culprit lesions in acute coronary syndromes using coronary dual-source CT angiography. *Atherosclerosis* 211:437–444, 2010.
298. Versteylen MO, Kietselaer BL, Dagnelie PC, et al: Additive value of semiautomated quantification of coronary artery disease using cardiac computed tomographic angiography to predict future acute coronary syndrome. *J Am Coll Cardiol* 61:2296–2305, 2013.
299. Ferencik M, Nieman K, Achenbach S: Noncalcified and calcified coronary plaque detection by contrast-enhanced multi-detector computed tomography: a study of interobserver agreement. *J Am Coll Cardiol* 47:207–209, 2006.
300. Yamamoto H, Kitagawa T, Ohashi N, et al: Noncalcified atherosclerotic lesions with vulnerable characteristics detected by coronary CT angiography and future coronary events. *J Cardiovasc Comput Tomogr* 7:192–199, 2013.
301. Tanaka A, Shimada K, Yoshida K: Non-invasive assessment of plaque rupture by 64-slice multidetector computed tomography—comparison with intravascular ultrasound. *Circ J* 72:1276–1281, 2008.
302. Hoffmann U, Moselewski F, Nieman K, et al: Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. *J Am Coll Cardiol* 47:1655–1662, 2006.
303. Kim SY, Kim KS, Seung MJ: The culprit lesion score on multidetector computed tomography can detect vulnerable coronary artery plaque. *Int J Cardiovasc Imaging* 26(Suppl 2):245–252, 2010.

62 Optical Coherence Tomography

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KEY POINTS

- Optical coherence tomography (OCT) is an innovative catheter-based imaging technology that uses light and fiberoptic technology to obtain unique details of the vessels on a microscopic scale. OCT provides real-time, full tomographic views of the coronary arteries with accurate measurements.
- OCT is used to quickly map the extension and type of coronary artery disease, guiding precise percutaneous coronary interventions (PCI) in complex patient and lesion cohorts immediately and over time, increasing safety and vascular acceptance of novel devices, including bioresorbable scaffolds. Because of its unique properties and high axial imaging resolution, OCT is able to overcome many of the limitations of coronary angiography and intravascular ultrasound (IVUS) for evaluating calcium, plaque at risk of rupture, and stent strut coverage. Additionally, OCT provides quantitative indices that can be used to assess the effectiveness of new device and drug interventions.
- OCT can reliably assess and quantify atherosclerotic plaque characteristics (thin fibrous cap, thrombus, neovessels, lipid pool, foamy macrophages), differentiating early from advanced coronary lesions, with close correlation with pathology. OCT can easily detect and penetrate calcium, revealing spiky superficial calcification that can block stent progression into the vessel and measuring thickness and circumferential distribution. Based on accurate vessel mapping, a procedural plan, including stent length, size, and landing zone, can be generated. In complex interventional settings in which risk of PCI failure is increased (e.g., complex bifurcation, late stent thrombosis, in-stent restenosis, neoatherosclerosis), OCT may add critical information and orient more precise treatment. Frequency-domain OCT (FD-OCT) systems produce a clear vision of very long segments of coronary arteries in only a few seconds, with a more complete picture of the vessel involvement and easier image interpretation compared with standard methods. Three-dimensional (3-D) reconstruction of OCT images automatically detects, quantifies, and displays features of interest, such as the shape of the lumen and the longitudinal position of the minimal luminal area (MLA).
- For OCT to be accepted by the medical community in the future, ease of use and interpretation, even by the least experienced operators, will be required. A direct link between OCT and angiography will soon be available with angio-OCT coregistration. Coregistration enables synchronization of imaging during the procedure, leading to better integration of OCT into PCI workflow. Direct tableside control of acquisition and analysis by the operator will make easier the use of OCT in daily practice, and automatic detection of site and amount of stent strut malapposition and thrombus volume will be possible. Finally, the combination of FD-OCT with spectroscopic techniques will improve discrimination among tissue constituents in complex atherosclerotic lesions and allow detailed analysis of the cellular and biochemical composition for vulnerable plaque detection. Concurrent data collection from combined modalities will dramatically expand the structural and functional information available to the cardiologist and guide development and clinical use of novel cardiovascular therapies.

Optical coherence tomography (OCT) is an innovative real-time, tomographic imaging modality that is able to assess and display tissue microstructure, providing close correlation with pathology. OCT delivers near-infrared light to the wall of the coronary artery through small-diameter optical fibers. The light that illuminates the vessel is absorbed and reflected (backscattered) by the structures in the tissue to different degrees, with an axial resolution of 2 to 15 µm. This resolution is ideal for measurement of tissue-level properties. Different tissue types have different optical characteristics. This feature makes OCT especially useful for following plaque progression and regression and the vascular response to coronary stent implantation.

Although its resolution is not sufficient to distinguish individual cells (including regenerating endothelium), OCT is able to measure the density of cellular aggregates and to provide information about their composition. For example, the OCT imaging signal characteristics observed in ex vivo coronary arteries in the presence of a pool of foamy macrophages (high signal intensity with sharp attenuation) have been demonstrated to correlate with cell density,[1] and in a preclinical model, fibrin deposition on stent struts, as detected by light microscopy and scanning electron microscopy (SEM), has specific attenuation properties by OCT.[2] Data also indicate that OCT imaging can be used to monitor the progress and transformation of cells in culture.[3]

The new generation of FD-OCT systems has significantly improved signal-to-noise ratio, with superior near-field image quality and faster acquisition. OCT provides excellent differentiation between the lumen and the arterial wall, with accurate measurements of lumen areas and volumes and bright stent strut identification. The lumen profile display automatically detects lumen contour on every frame and provides immediate identification of the minimal luminal area (MLA) for PCI procedures. Quantitative measurements of lumen, stent, and neointimal areas obtained by OCT are highly reproducible.[4] OCT acquires 3-D images of the entire coronary artery in less than 5 seconds, enabling the use of a nonocclusive, contrast-flushing method without risk of major arrhythmias. Based on these properties, OCT may be used at different times as part of diagnostic and interventional procedures, before and after stent implantation (Fig. 62-1).

By taking advantage of progress in miniaturization, OCT can potentially be combined with additional techniques, including Doppler ultrasound, IVUS,[5] or sensors, to further improve its diagnostic capabilities. Fully integrated FD-OCT system with near-infrared molecular imaging has been developed for the study of lipid-rich plaques with inflammation in preclinical models.[6]

PHYSICAL PRINCIPLES OF OCT IMAGING

The ability of OCT to create tomographic cross-sectional images of a vessel is based on optical interference of near-infrared light.[7] Light is emitted and collected back from the tip of a small-diameter optical fiber that rotates rapidly inside a transparent sheath of the catheter. For longitudinal scanning of the vessel, a drive motor unit on the table pulls back the fiber as it rotates within the sheath. The collected light carries information about the depth-resolved backscattering reflectivity of the tissue structures at the illuminated spot. Unlike ultrasound, in which the depth information can be resolved by measuring the time-of-flight of acoustic reflections, light is too fast to resolve depth information by direct measurement of photon time-of-flight. To overcome this property, the collected light is combined with a reference light beam to

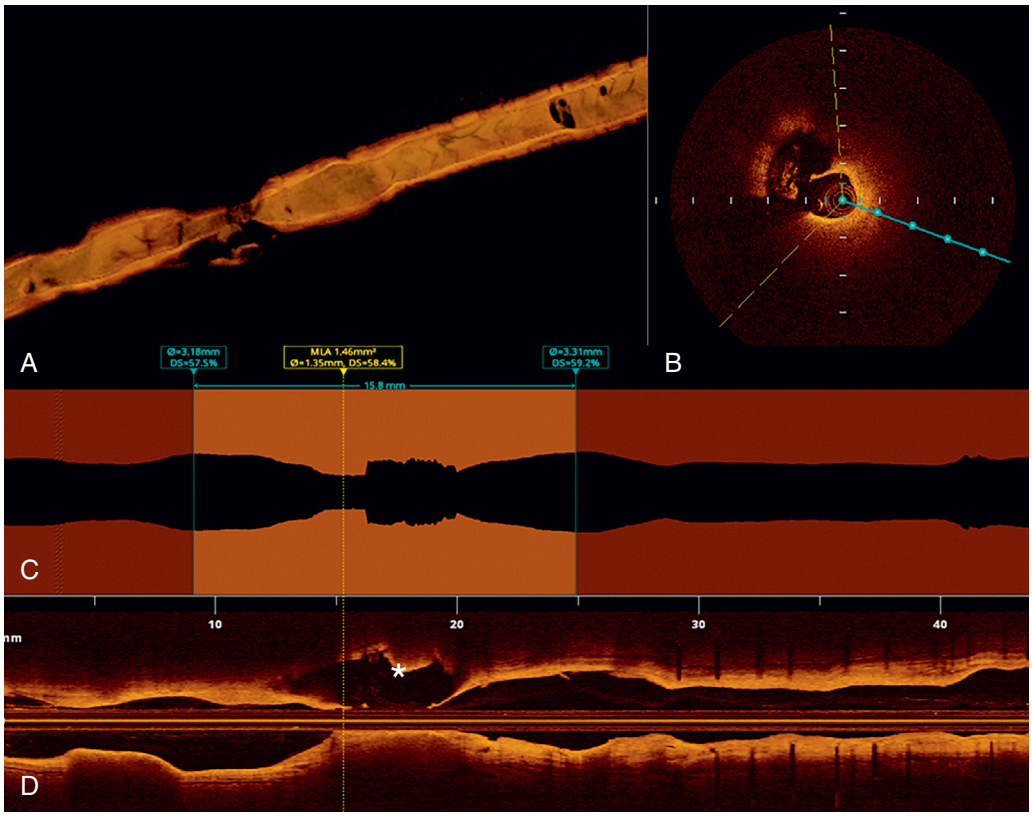

FIGURE 62-1 Culprit lesion in acute myocardial infarction during primary percutaneous coronary intervention. **A,** Real-time, high-resolution, three-dimensional reconstruction of the culprit vessel. **B,** Cross-sectional analysis supplying information on the morphology and severity of the lesion. **C,** Automatically traced contour detection using an algorithm to provide lumen profile changes across the entire vessel and to immediately assess the severity and extension of coronary lesions. **D,** Longitudinal reconstruction displays the extension of the ruptured plaque *(asterisk)*.

generate lower-frequency optical interference signals. These modulated interference signals can be measured with electronic components and digitally decoded to generate an optical backscattering profile of the tissue at the illuminated spot (A-scan). Multiple backscattering profiles are collected as the catheter core rapidly rotates within the vessel. These profiles are then represented in a 2-D grayscale image, the OCT B-scan frame displayed to the user (Fig. 62-2).

In FD-OCT, interference signals generated by an interferometer at various wavelengths are mathematically processed by Fourier transformation to determine the amplitudes of reflections returning from different depths. As in magnetic resonance imaging, the frequency of the recorded signal encodes position in the image. Although this makes FD-OCT more computationally intensive, A-scan repetition rates are 10 to 100 times greater than in time-domain OCT (TD-OCT), allowing dramatically faster B-scan frame rates (hundreds of Hertz). FD-OCT provides a far more comprehensive visualization of the intravascular region during the transient blood displacement period.

FD-OCT can be further subcategorized into two approaches: swept-source OCT (SS-OCT), also known as optical frequency domain imaging (OFDI), and spectral-domain OCT (SD-OCT). SS-OCT uses a narrowband light source; the wavelength is tuned or "swept" through a broad spectral range as a function of time. The mechanical actuation necessary to sweep the source wavelength and create interference fringe modulation is on the nanometer scale and therefore can be accomplished rapidly and in compact microelectromechanical systems (MEMS)–based packaging. Conversely, SD-OCT uses a broadband light source, similar to TD-OCT, but avoids the need for mechanical actuation by dispersing the broadband spectral components in a spectrometer and capturing modulated fringes using a parallel array of detectors, such as a charge-coupled device (CCD) camera. Commercial and research intravascular OCT imaging systems are usually SS-OCT, primarily because of instrumentation cost and complexity advantages of SS-OCT in the 1250- to 1360-nm wavelength regions that are appropriate for intravascular imaging.

The C7XR OCT system, manufactured by St. Jude Medical (St. Paul, MN), formerly LightLab Imaging (Westford, MA), was introduced as the first commercially available FD-OCT system for coronary imaging in the European Union in 2009 and in the United States in 2010. Employing a 2.7-Fr intravascular catheter with a rapid-exchange monorail tip, the C7XR system has a spatial resolution of 15 µm and acquires 500 axial lines per frame at a rate of 100 frames/sec. At the tip of the catheter is a 125-µm-diameter optical fiber assembly that consists of an integral side-looking lens. The optical assembly is encapsulated in a hollow torque wire that translates motion from a drive motor located outside the patient's body. The C7XR system can volumetrically image a 5-cm vessel segment in approximately 3 seconds. High-speed data acquisition is a key feature of the C7XR system, because it enables pullback image acquisition during a low-volume injection of contrast medium or saline through the guide catheter.[8] The current instructions for use of the C7XR system recommend injection of a maximum 14-mL bolus of contrast material at a maximum rate of 4 mL/sec.

The latest generation of St. Jude Medical's OCT system, the ILUMIEN OPTIS PCI optimization system, has a higher image acquisition rate (180 frames/sec) and can acquire a 75-mm pullback image in only 2.1 seconds. This system combines OCT and wireless fractional flow reserve (FFR) measurement on the same console and has instant 3-D reconstruction capability of the lumen and vessel wall for optimizing stent planning.

Two additional FD-OCT systems are commercialized or in an advanced phase of development and testing. The Massachusetts General Hospital (MGH, Boston, MA) OFDI system, developed by the

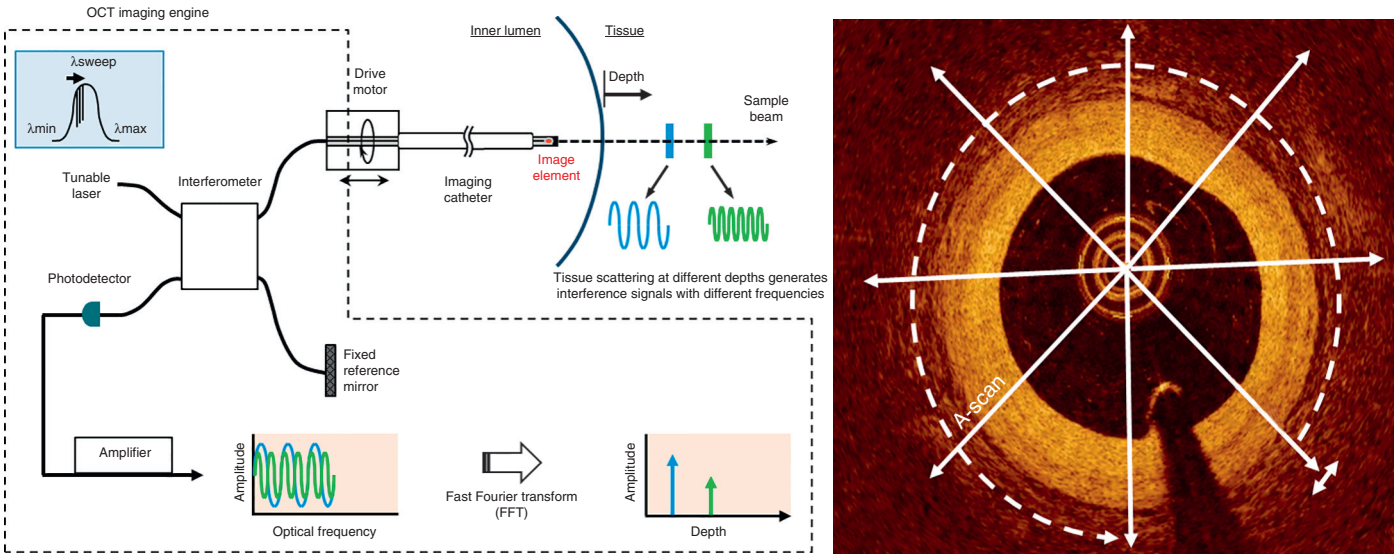

FIGURE 62-2 **A,** Schematic representation of the principles of frequency-domain optical coherence tomography (FD-OCT). Interference signals generated by an interferometer at various wavelengths are processed mathematically by Fourier transformation to determine the amplitudes of reflections returning from different depths. The frequency of the recorded signal encodes position in the image. **B,** Cross-sectional tomogram of the coronary artery. The reflectivity profile of the tissue, obtained from the light beam, called *A-scan,* contains information about the spatial dimensions and location of structures within the item of interest. A cross-sectional tomograph may be achieved by laterally combining a series of these axial depth scans *(circumferential dotted line).* A-scan repetition rates are typically 10 to 100 times greater than in previous systems, allowing dramatically faster frame rates.

academic research group led by Drs. Brett E. Bouma and Gary Tearney at the MGH Wellman Center for Photomedicine, is the first second-generation intracoronary OCT system to be used in vivo.[9] The light source of the MGH OFDI system is a high-speed wavelength swept laser that uses a polygon-mirror/grating filter to tune over a broad (120-nm-wide) bandwidth centered at 1320 nm. The high speed of this laser enables cross-sectional imaging at 100 frames/sec with 512 A-lines per image. The axial resolution of the MGH OFDI system is 7 μm, and the ranging depth is 4.6 mm in tissue (refractive index n = 1.4). MGH also fabricates their own OFDI catheters; an asymmetric ball lens at the tip is custom designed to correct for aberrations in the catheter sheath. The MGH OFDI system and catheter produce images of very high resolution; the demonstration of 2-D and 3-D images obtained from this system paved the way for the development of current commercial FD-OCT systems that are now largely adopted in interventional cardiology.

The same MGH academic group constructed an OCT system that uses a very broad bandwidth light source and common-path SD-OCT technology, termed microoptical coherence tomography (μOCT), whose resolution is improved by an order of magnitude of 10 (axial resolution ≤1 μm and a lateral resolution ≤2 μm in tissue), compared with the FD-OCT systems. μOCT images of cadaver coronary arteries provide clear pictures of cellular and subcellular features associated with atherogenesis, thrombosis, and responses to coronary stents.[10]

The Terumo (Tokyo, Japan) OFDI system uses a 1.3-μm scanning laser as a light source. The imaging range is 5 mm with an axial resolution of less than 20 μm in the water. The OFDI catheter (2.4-Fr crossing profile) is a short monorail design for a 0.014-inch guidewire and contains the imaging core rotating within a close sheath. No catheter priming is required for use, and no blood comes into the sheath during the pullback. The imaging core rotates at a speed of 9600 rpm, allowing imaging at 158 frames/sec. A pullback length of up to 150 mm is supported at the maximum pullback speed of 40 mm/sec (among eight available speeds).

Image Acquisition

The second-generation FD-OCT devices improved image quality and significantly increased the speed of image acquisition by a factor of 10. FD-OCT uses a contrast flush (3 to 4 mL/sec for 2 to 3 sec) to clear the blood column and allow a clear path for the light beams to be emitted, reflected, and detected.[11] Imaging catheters are designed for rapid exchange over a 0.014-inch guidewire delivery, have a crossing profile of 2.4 to 2.8 Fr, and are compatible with 6-Fr or larger guiding catheters. Because of the very high speed of the pullback, FD-OCT has the ability to scan longer segments of artery in few seconds, without need to occlude the vessel, resulting in minimal ischemic electrocardiographic changes and no major arrhythmias during imaging acquisition.[12]

Barlis and associates[13] reported data on 468 patients from six European medical centers with occlusive and nonocclusive flushing technique. Major complications during OCT imaging included ventricular fibrillation (1.1%) due to balloon occlusion or deep guide catheter insertion or both, air embolism (0.6%), and vessel dissection (0.2%). There was no major adverse cardiac events within the 24 hours after OCT examination. Lehtinen and colleagues[14] evaluated the safety of FD-OCT in 230 OCT evaluations in 210 patients. PCI was performed in 44.3% of the examinations. OCT was successful in 87.8% of examinations. Periprocedural complications were rare; chest pain, the most commonly seen complication, occurred in 10.9% of OCT examinations.

Artifacts

Artifacts can be detected in all types of imaging, including OCT. Some artifacts are common to OCT and IVUS, whereas others are unique to the OCT imaging systems. Nonuniform rotational distortion (NURD) is caused by increased friction on the rotating components of the catheter during image acquisition and results in circumferential imaging loss or shape distortion. Data on bench tests have shown fewer NURD

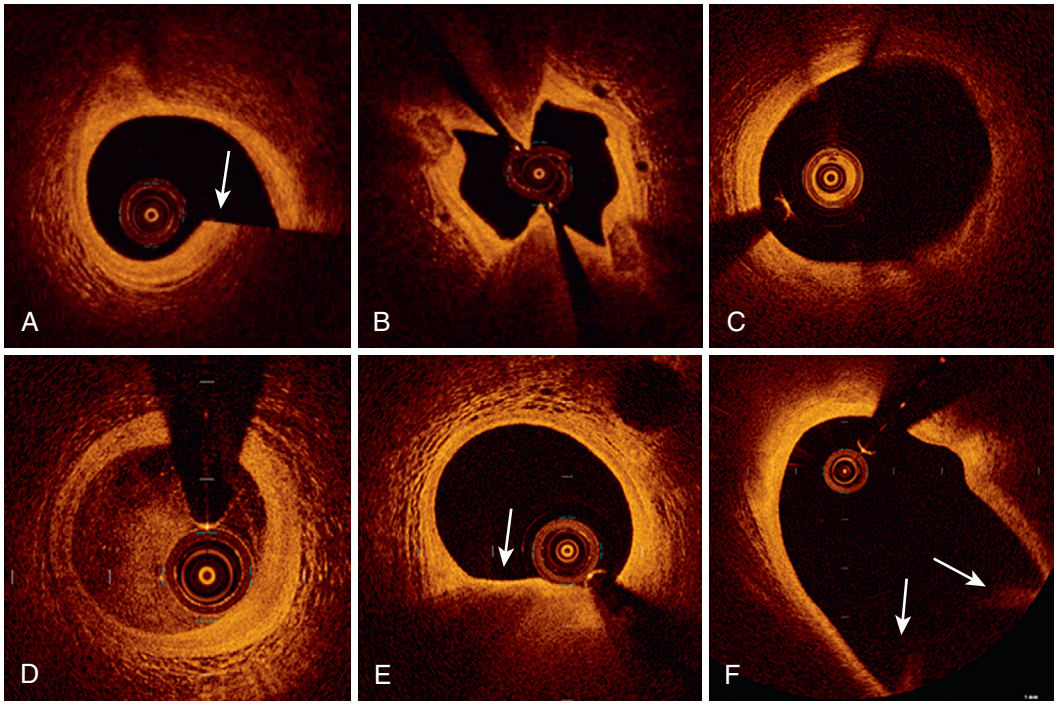

FIGURE 62-3 Increased friction and deformation on the rotating components of the optical convergence tomography catheter can result in multiple artifacts. **A,** Seam line artifact *(arrow)* is caused by rapid artery or imaging wire movement during single-frame imaging formation, leading to misalignment of the luminal border. Nonuniform rotational distortion can lead to shape distortion and mirror artifacts (**B**). **C,** Image attenuation due to suboptimal purge of the imaging catheter. **D,** Image attenuation due to subobtimal flushing of the coronary artery. **E,** Tangential signal dropout *(arrow)*. **F,** Fold-over artifacts *(arrows)*.

artifacts with OCT compared with IVUS.[15] The sew-up artifact results from rapid artery or imaging wire movement during single-frame imaging formation, leading to single-point misalignment of the luminal border. Increased friction and deformation on the rotating components of the catheter, mainly caused by tortuous segments of coronary arteries or narrow calcified lesions, may result in coexisting multiple artifacts (Fig. 62-3). The fold-over artifact is more specifically related to the new generation of FD-OCT devices. It is the consequence of "phase wrapping" or "aliasing" along the Fourier transformation when structure signals are reflected from outside the system's field of view.

Eccentric catheter position may affect OCT images differently before and after stent implantation. Tangential signal dropout due to eccentric catheter position adjacent to the luminal wall can lead to misinterpretation of lesions, generating a false impression of thin-cap fibroatheroma (TCFA) (Fig. 62-3, E). In stented coronary arteries, eccentric catheter position may distort the strut image at the far site as a result of the longer distance between each A-line and reduced lateral resolution.[7]

All cross-sectional images (frames) obtained with a pullback need to be initially screened for quality assessment and should be excluded from analysis if any portion of the image is out of the screen or if a side branch occupied more than 45 degrees of the cross section, or if the image had poor quality caused by residual blood, artifacts, or reverberation.

Image Interpretation

The high resolution of OCT allows superb definition in the near field with precise bordering of the intima and media within the coronary arterial wall. In the OCT image, the intima appears as a signal-rich layer nearest to the lumen, whereas the media is visualized as a signal-poor middle layer that in normal segments encircles the vessel. The ability to evaluate subtle intimal thickening in vivo allows detection of the early phase of coronary atherosclerosis and monitoring of the progression over time. The OCT measurements of the intimal thickness are well correlated with findings on histologic examination.[16] Pathologic evaluations have demonstrated that OCT is highly sensitive and specific for plaque characterization.

Yabushita and coworkers[17] developed objective OCT imaging criteria for differentiating distinct components of atherosclerotic tissues. In their histology-controlled OCT study of 357 autopsy segments from 90 cadavers, fibrous plaques were characterized by homogeneous signal-rich regions, fibrocalcific plaques by signal-poor regions with sharp borders, and lipid-rich plaques by signal-poor regions with diffuse borders. Validation tests revealed good intraobserver and interobserver reliability ($\kappa = 0.83$ to 0.84), as well as excellent sensitivity and specificity: 71% to 79% and 97% to 98%, respectively, for fibrous plaques, 95% to 96% and 97% for fibrocalcific plaques, and 90% to 94% and 90% to 92% for lipid-rich plaques. These definitions formed the basis for the in vivo assessment of plaque components. Using these definitions, Kawasaki and colleagues[18] reported that OCT provides better separation of coronary plaque constituents than integrated backscatter or conventional IVUS. For fibrotic plaques, the sensitivities were 98%, 94%, and 93%, respectively, and the specificities were 94%, 84%, and 61%. For calcified plaques, the sensitivities were 100%, 100%, and 100%, and the specificities were 100%, 99%, and 99%. For lipidic plaques, the sensitivities were 95%, 84%, and 67%, and the specificities were 98%, 97%, and 95%, respectively (Fig. 62-4).

Coronary thrombus can easily be detected in vivo by OCT in various clinical settings, including acute coronary syndromes and stent thrombosis.[19] A close correlation with pathology was demonstrated in 108 coronary arterial segments at postmortem examination.[20] White thrombus is imaged as an homogeneous, signal-rich, irregular mass with low-backscattering attenuation, whereas red thrombi are irregularly shaped, mural or luminal masses protruding into the lumen, characterized by high-backscattering attenuation and signal-free

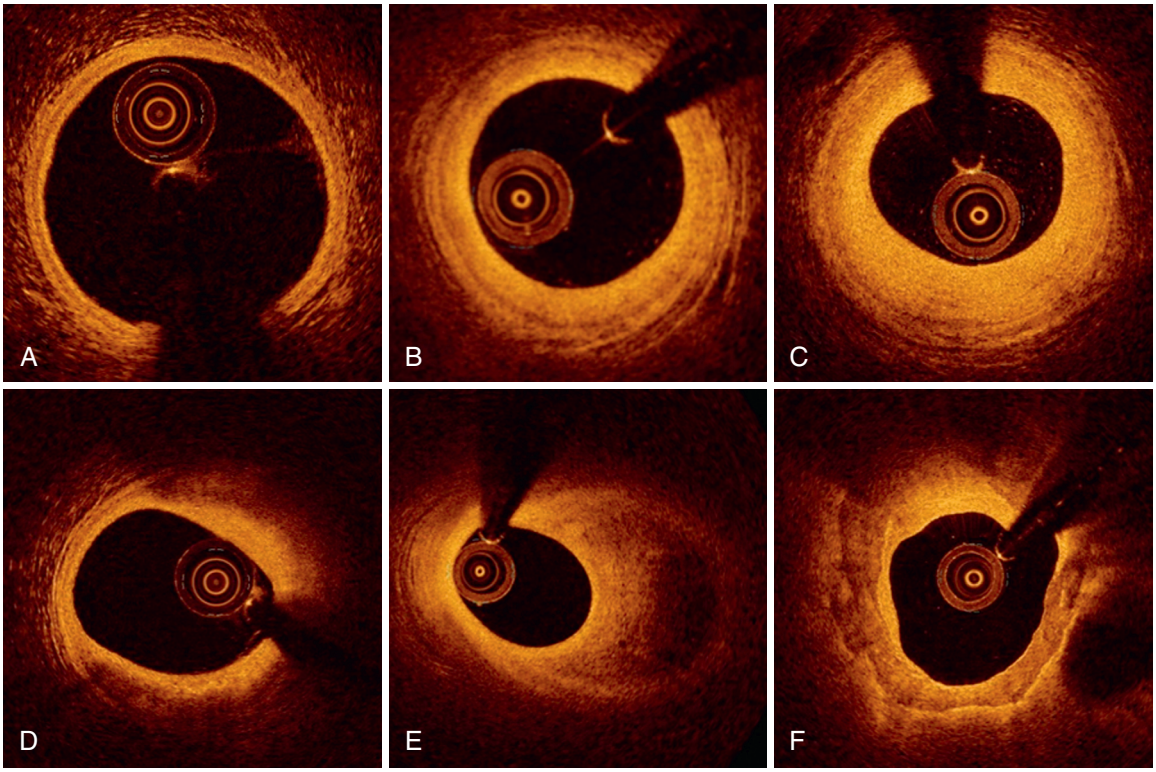

FIGURE 62-4 Imaging of normal and diseased coronary arteries. **A,** Normal healthy vessel wall. There is a uniform, three-layered structure composed of intima, media, and adventitia. Intima is identified as a bright area nearest to the lumen, whereas the media layer can be seen as a low-intensity area encircling the normal vessel. **B,** Intimal thickening. Concentric intimal thickening appears as a homogeneous signal-rich lesion; the external elastic membrane is visible. **C,** Fibrous plaque with concentric intimal thickening and a homogeneous, signal-rich appearance. Sometimes the internal or external elastic membrane can be identified. **D,** Fibroatheroma lesion with lipid pool and an overlying thick fibrous cap (cap thickness = 500 μm). The lipid core is characterized as a signal-poor region within an atherosclerotic plaque, with poorly delineated borders and fast signal drop-off (from 12 to 2 o'clock). **E,** Thin-cap fibroatheroma. The lipid-rich plaque has a cap thickness of less than 65 μm (from 4 to 8 o'clock, the cap thickness = 60 μm). **F,** Fibrocalcific plaque with 360 degrees of calcified arc seen as a signal-poor, heterogeneous region with sharply delineated borders.

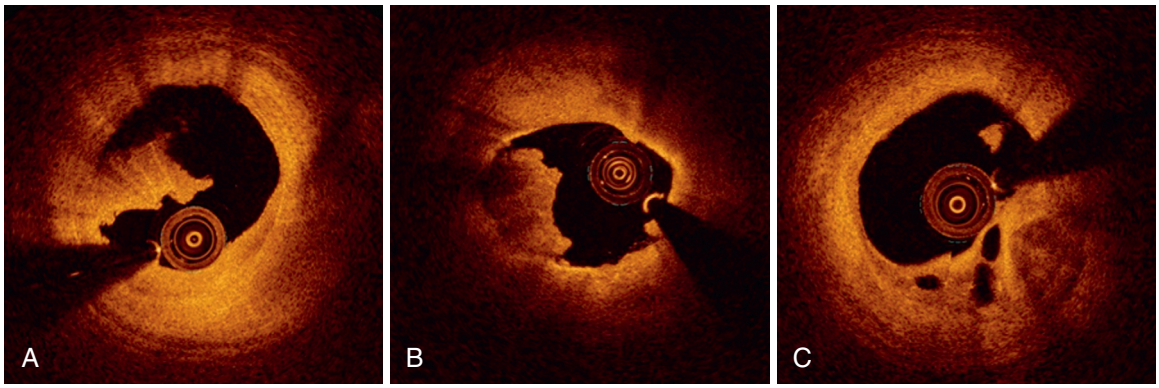

FIGURE 62-5 Thrombus evaluation by optical coherence tomography. **A,** White thrombus (8 to 9 o'clock) is visualized as intraluminal, protruding tissue with low attenuation and low backscattering of the optical signal. **B,** Red thrombus (7 to 10 o'clock) is identified as a high-backscattering mass that protrudes into the lumen with signal-free shadowing due to high attenuation. **C,** Recanalized thrombus is characterized by signal-rich, high-backscattering septa dividing the vessel lumen into multiple small cavities that communicate with each other ("Swiss cheese" morphology at pathology assessment).

shadowing. Using a measurement of OCT signal attenuation within the thrombus, Kume and colleagues[19] demonstrated that a cutoff value of 250 μm in the half-width of signal attenuation can differentiate white from red thrombi with a high sensitivity (90%) and specificity (88%) (Fig. 62-5).

Among the various plaque components with clinical impact, macrophage accumulation plays a major role to trigger progression and instability of atherosclerotic coronary lesions. Autopsy series have shown that the thin caps of ruptured plaques are heavily infiltrated by macrophages. Given the close proximity to the lumen and its unique

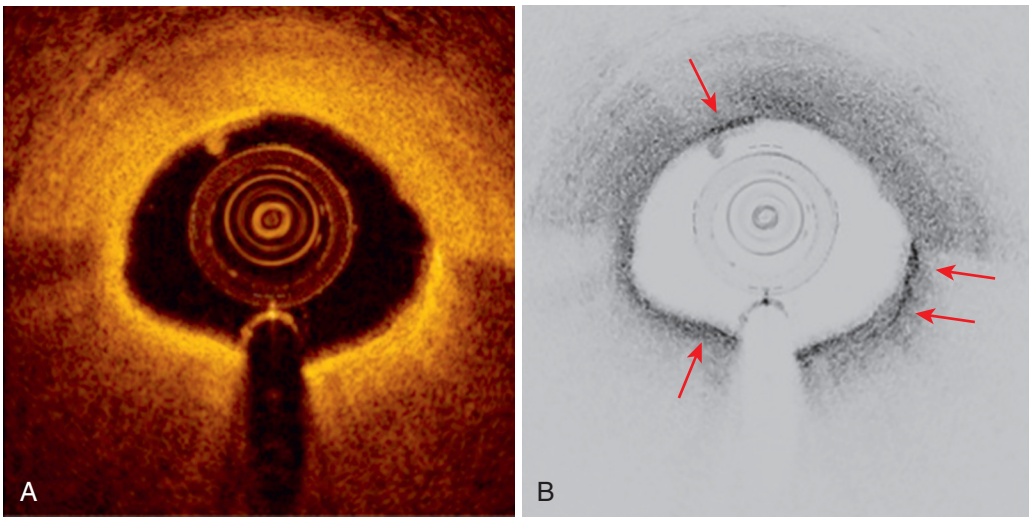

FIGURE 62-6 Macrophage evaluation by optical coherence tomography (OCT). **A,** Accumulations of foamy macrophages appear as confluent or punctuate, high-backscattering regions within the artery wall (3 to 9 o'clock and 11 o'clock). The close proximity to the luminal surface provides more reliable detection of the pool of macrophages in thin-cap fibroatheroma, compared with similar signals located in deeper vessel layers. **B,** Signals of macrophages may be more clearly visualized by OCT imaging with the use of an inverse gray scale *(red arrows)*. Macrophage accumulations cause shadowing of the underlying tissues.

axial resolution, OCT enables detection of the pool of foamy macrophages confined to the luminal surface of the plaque.[21] Macrophages are identified in OCT by the presence of high-intensity, signal-rich, linear or confluent punctuate regions (bright spots) accompanied by high attenuation and confirmed in adjacent consecutive frames. Tearney and associates[21] tested ex vivo the ability of OCT to assess macrophage distribution within the fibrous cap. A high degree of positive correlation was reported between OCT signals and histologic measurements of fibrous cap macrophage density ($r < .84$, $P < .0001$). A range of OCT signal standard deviation thresholds (6.15% to 6.35%) yielded 100% sensitivity and specificity for identification of caps containing greater than 10% CD68 staining (Fig. 62-6). Concerns have been raised about the specificity of bright-spot signals with intense attenuation in identifying macrophages. OCT may fail to discriminate macrophages from calcified tissue, especially if deeply embedded into the vessel wall.[21a]

Thanks to the technology ameliorations in optics and to efforts to standardize the methodology of imaging acquisition and interpretation, the adoption of OCT by cardiovascular centers is continuously increasing. A consensus document on standardization, validation, and reporting for OCT was published in 2012 by the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation.[22] This document, which is currently undergoing a revision process, provides a common platform for collecting and interpreting imaging data with a high standard of quality and reliability. The following main topics are included in the document:

- Equipment for OCT imaging
- Image display techniques
- Image acquisition protocols
- Qualitative assessment, including definition
- Quantitative manual and automatic measurements
- Validation
- Reporting standards

Quantitative Measurements

When OCT and IVUS measurements were evaluated in postmortem, perfusion-fixed samples, both techniques were found to significantly overestimate the lumen and stent dimensions compared with pathology findings.[23] However, postfixation and frozen measurements in excision tissues are not easily comparable to in vivo assessment because of possible changes in arterial optical properties caused by technical preparation and tissue shrinkage.[24] The processes of dehydration, paraffin embedding, sectioning, and staining result in a reduction of the circumference by approximately 19% ± 5% and a reduction in wall thickness of 18% ± 2%. Furthermore, backscattering of OCT signals due to fixation of cross-linked collagen may significantly enhance the delineation between lumen and vessel wall, compared with in vivo lumen measures, resulting in an artificial increase of reflectivity. The wide gap in lumen dimensions observed between OCT and histology findings in nonstented coronary segments was less clear when the arteries were treated with metallic stent implantation, with approximately 6% greater stent area and 10% greater luminal area by OCT across all stent types.[25]

In measurements of lumen diameter and luminal area, there is a good correlation between OCT and IVUS.[26,27] However, compared with IVUS, the earlier generation of image wire TD-OCT systematically underestimated the lumen dimensions.[28] Several factors may explain this difference, including inadequate spatial resolution of IVUS, stretch of small arteries by the IVUS catheter (Dotter effect), and reduction of intracoronary perfusion pressure during occlusive OCT image acquisition. Nevertheless, current FD-OCT no longer uses occlusive acquisition and is much accurate in lumen profile measures compared with the old TD-OCT.

To clarify differences in measures among current imaging techniques, a prospective, multicenter study comparing quantitative coronary angiography, IVUS, and FD-OCT was performed by Kubo and colleagues[29] in 100 patients and in a phantom model. OCT accurately measured the MLA compared with the actual phantom, whereas IVUS significantly overestimated the MLA in 10% of the patients and was less reproducible than OCT ($P < .001$ vs. OCT). In the clinical study Optical Coherence Tomography Compared with IVUS in a Coronary Lesion Assessment Study (OPUS-CLASS), the minimal lumen diameter (MLD) measured by quantitative coronary angiography was significantly smaller than that measured by FD-OCT or IVUS ($P < .001$), and the MLA measured by IVUS was significantly greater than that measured by OCT, demonstrating that more accurate measurements of the coronary lumen may be achieved by using FD-OCT compared with IVUS or angiography.

Reproducibility of OCT lumen and length measurements was evaluated by Fedele and associates.[26] In their study, OCT measurements were taken twice at intervals of 5 minutes in 25 patients undergoing coronary angiography. The per-segment and per-frame analyses proved to have excellent reproducibility with high correlation for intraobserver and interobserver measurements and intra-pullback assessments of both lumen area and segment length ($R \geq .95$ and $P < .001$ for all). Similarly, Jamil and colleagues reported good interstudy correlation for FD-OCT in evaluating both stented and native coronary arteries undergoing PCI ($R^2 = .99$ and $P < .001$ for mean luminal area and MLA in repeated evaluations of the same coronary lesion).[27]

A dedicated, semiautomated contour-detection system is used for measurements. A significant advantage of FD-OCT imaging systems is in delineating three-dimensional (3-D) contours of long segments of coronary arteries in only few seconds. A contour-detection algorithm that automatically traces lumen boundaries of the longitudinal (L)-mode view has been implemented in the OPTIS coronary system. The software automatically shows the cross-sectional areas calculated at all frames of a pullback as a graph superimposed on the longitudinal image. This lumen contour function enables quick and precise comparison of the automatically detected MLA with the reference areas over the entire length of the vessel scanned. A good correlation ($r = .99$) between manual and quantitative, fully automated 3-D lumen contour detection methods has been demonstrated.[28]

CURRENT CLINICAL APPLICATIONS

Assessment of Coronary Atherosclerosis

Rupture of vulnerable plaque is responsible for most thrombotic coronary events. Morphologic features of vulnerable plaque include a large lipid core, a TCFA (fibrous cap thickness <65 μm), and an accumulation of macrophages localized at the subsurface of the fibrous cap. Because OCT has a near–histologic grade resolution, many in vitro and in vivo studies have been done to validate the capability of OCT to visualize these advanced and risky plaque features[30-32] (Fig. 62-7).

Kubo and colleagues[31] used OCT, IVUS, and angioscopy in 30 consecutive patients with acute myocardial infarction (AMI) to assess the ability of each imaging method to detect the specific characteristics of vulnerable plaque. OCT was superior in detecting plaque rupture (73% compared with 40% for IVUS and 43% for angioscopy; $P = .021$), erosion (23%, 0%, and 3%, respectively; $P = .003$), and thrombus (100%, 33%, and 100%; $P < .001$). Intraobserver and interobserver variability of OCT yielded acceptable concordance for these characteristics ($\kappa = .61$ to $.83$).

Because fibrous cap thickness in most ruptured plaques is less than 65 μm, the resolution required for imaging of risky plaques should be at the level of 50 μm or better. OCT is the only available imaging technique with enough resolution to detect TCFAs.[33,34] Kume and coworkers[34] examined the reliability of OCT in measuring fibrous cap

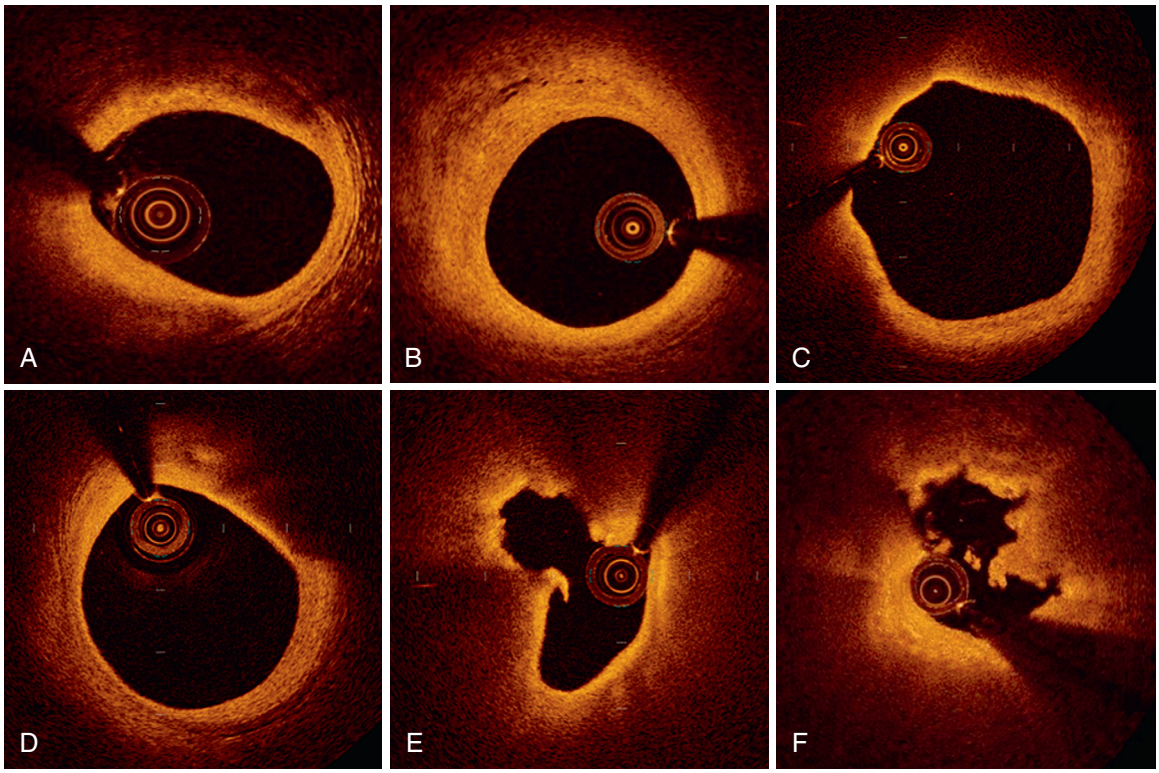

FIGURE 62-7 Unstable plaque features. **A,** Lipid-rich lesion with overlying thick fibrous cap (6 to 2 o'clock, 500 μm) distinguished by a signal-poor region with poorly delineated borders and fast signal drop-off. **B,** Microvessels in the far field (10 o'clock) are identified as low-signal cavities with a diameter of 50 to 150 μm and a trajectory parallel to the lumen. Inflammatory cells and red blood cells may flow into a stable plaque through these structures, resulting in conversion into an unstable lipid plaque. Longitudinal optical coherence tomography follow-up of these plaques might better clarify their role in the pathogenesis of advanced lipid plaque. **C,** Thin-cap fibroatheroma (TCFA) with lipid-rich plaque and a cap thickness of less than 65 μm (7 to 2 o'clock). **D,** Macrophages are seen as a signal-rich, confluent or punctuate region that exceeds the intensity of background speckle noise (1 to 2 o'clock). **E,** Plaque rupture is distinguished by the presence of fibrous-cap discontinuity and a cavity formation (11 o'clock) in continuity with the lumen. Ruptured plaques usually have an extensive lipid core and a thin fibrous cap. The fibrous cap is typically thinnest at the site of rupture, and the plaque cavity indicates loss of lipid core due to the rupture. **F,** Plaque rupture (from 10 to 1 o'clock) and protruding luminal thrombus (from 1 to 3 o'clock).

thickness. In 35 lipid-rich plaques from 38 human cadavers, a good correlation was observed between OCT cap thickness and histologic measures ($r = .90$; $P < .001$). Sawada and colleagues[35] compared the feasibility of combined use of OCT and virtual histology (VH-IVUS) for detection of in vivo TCFA. VH-IVUS significantly overestimated the presence of TCFA compared with OCT. Jang and associates[36] analyzed OCT images in 57 patients with stable angina pectoris (SAP), acute coronary syndrome (ACS), or AMI. The AMI group more often had a thinner cap, more lipid, and a higher percentage of TCFA (72%, compared with 50% for the ACS group and 20% for the SAP group; $P = .012$).

Using OCT, Tanaka and colleagues[30] investigated the relationship between culprit lesion morphology and the patient's activity at the onset of ACS. TCFA was a lesion predisposed to rupture in both rest-onset and exertion-triggered ACS, whereas plaque rupture in those with fibrous caps thicker than 65 μm was strictly related to exertion level. Fujii and associates[37] performed a prospective OCT analysis of all three major coronary arteries to evaluate the incidence and predictors of TCFA in patients with AMI and SAP. Multiple TCFAs were observed more frequently in AMI patients than in SAP patients (69% vs. 10%; $P < .001$). In the entire cohort, multivariate analysis revealed that the only independent predictor of TCFA was AMI (odds ratio [OR] = 4.12; 95% confidence interval [CI] = 2.35 to 9.87; $P = .02$). In addition to its reliability as a tool to accurately measure fibrous cap thickness in vivo, an OCT study conducted by Takarada and coworkers[38] demonstrated that statin therapy in patients with hyperlipidemia significantly increased the thickness of the fibrous cap (from 151 ± 110 to 280 ± 120 μm; $P < .01$) at 9 months' follow-up. Therapies to prevent or cause regression of atherosclerosis are under intense research, and OCT may become a unique invasive tool for monitoring the impact of pharmacotherapy on advanced coronary plaques (Fig. 62-8).

Increasing attention has been paid to plaque erosion, involving a culprit plaque underneath an occlusive thrombus with no communication between the plaque and the lumen.[39] It remains a challenge to distinguish erosion-prone plaques from stable plaques by imaging. However, OCT has demonstrated the ability to identify nonruptured plaque underlying coronary thrombosis.[40,41] A prospective, multicenter, age-matched study conducted with OCT in 140 patients with ST-segment elevation myocardial infarction (STEMI) treated with primary PCI established the real incidence of plaque erosion in living patients and demonstrated similar incidences in men and women, independently by age.[42]

In patients with acute coronary syndrome and large thrombus burden, the morphology of the culprit plaque has been used to decide invasive strategies.[43] A recent nonrandomized study tested the use of a nonstent strategy in selected cases, based on OCT-derived morphology of the culprit plaque after thrombus removal. The initial strategy involved thrombus aspiration and treatment with medical therapy (aspirin, a loading dose of clopidogrel or prasugrel, and a bolus of abciximab). Stenting was performed only if one or more of the components of "optimal reperfusion"—Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow, angina relief, and greater than 50% reduction in ST elevation on the postintervention electrocardiogram—were absent. If optimal reperfusion was achieved, stenting could be either immediate or postponed, to allow more time for the antithrombotic regimen to work, as determined by results of a second angiogram and OCT. The trigger for stenting was residual stenosis in the culprit lesion of greater than 70% or evidence of plaque prolapse. Only 62% of the patients received stent implantation. During a minimum follow-up period of 12 months, only one nonfatal myocardial infarction occurred, and only one additional stent implantation was performed for angina. The authors concluded[43] that medical management without stents is safe and feasible in OCT-selected patients with ACS and large thrombus burden, possibly reducing the risk of no reflow phenomena in this setting. In this study, OCT revealed culprit lesion characteristics that were not disclosed by angiography and facilitated the treatment decisions (Fig. 62-9). Considering the possible impact on clinical, logistical, and legal aspects, similar studies should be considered only as hypothesis-generating and need eventually to be proved in prospective randomized clinical trials.

The natural history of the atherosclerotic plaque is not well understood. Prospective studies that use OCT are important to define which features of the plaque are associated with negative clinical outcome. Uemura and colleagues prospectively studied the ability of OCT to predict the natural history of coronary plaques.[44] They enrolled 53 patients, with 69 nonobstructing coronary plaques, who underwent both PCI and OCT. A second coronary angiogram was performed at a mean follow-up time of 7 months to assess progression of the original

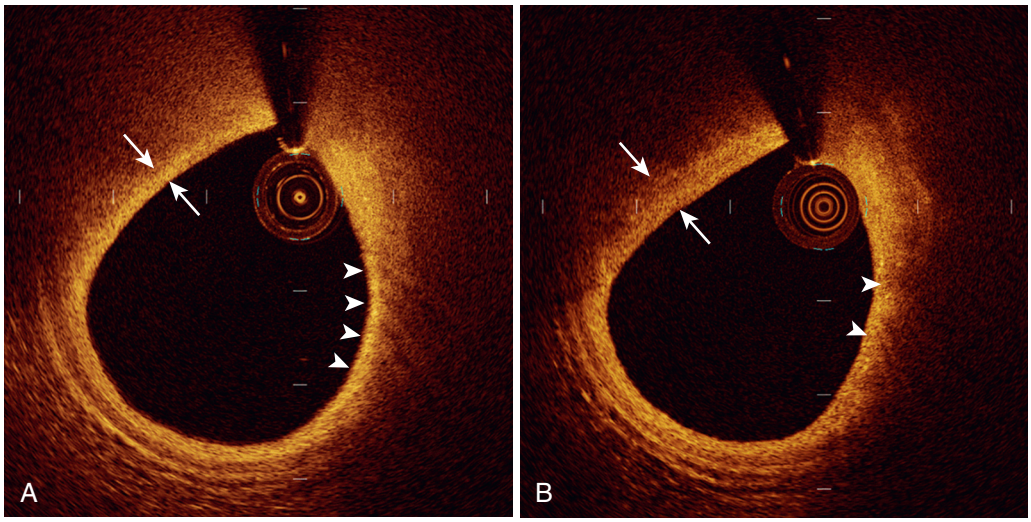

FIGURE 62-8 Change in cap thickness after treatment with high-dose 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors. **A,** A lipid-rich plaque with a cap thickness of 120 μm *(arrows)* and dense macrophage signal accumulation *(arrowheads)* at a nonculprit site of the left anterior descending coronary artery. **B,** After 9 months of medical treatment with a high-dose statin (atorvastatin, 80 mg once daily), optical coherence tomography revealed an increased thickening of the cap (320 μm, *arrows*), paralleled by a decrease in signals of macrophages *(arrowheads)*. Serum levels of cholesterol and C-reactive protein showed significant changes between these time points: low-density lipoprotein cholesterol from 162 to 68 mg/dL, high-density lipoprotein cholesterol from 35 to 61 mg/dL, and C-reactive protein from 2.16 to 0.68 mg/L.

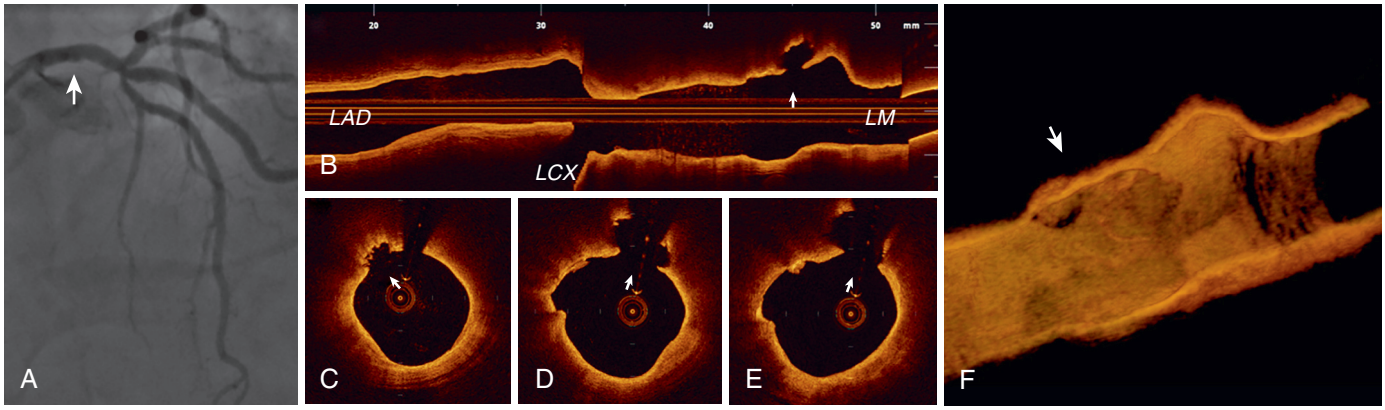

FIGURE 62-9 Angiographically silent ruptured TCFA. **A,** Coronary angiogram displays minimal perivascular contrast at the body of the left main coronary (LM, *arrow*) and a significant narrowing at the ostium of the left anterior descending (LAD) coronary artery. **B,** Optical coherence tomography pullback technique demonstrates a large lumen at the left main site with thin-cap fiberatheroma (minimum cap thickness = 40 μm) and multiple plaque ruptures (**C, D,** and **E**) involving the proximal body *(arrows)*. The more severe lesion at the LAD ostium had stable characteristics. **F,** Three-dimensional navigation views display the locations of plaque disruptions *(arrow)*. *LCX,* Left circumflex coronary artery.

plaques. Thirteen (18.8%) of 69 lesions showed progression on angiography at follow-up. Several plaque characteristics detected by OCT were predictive of progression: intimal laceration (61.5% in those plaques with progression vs. 8.9% in those without progression; $P < .01$), presence of microchannels (76.9% vs. 14.3%; $P < .01$), lipid pools (100% vs. 60.7%; $P = .02$), TCFA (76.9% vs. 14.3%; $P < .01$), macrophage images (61.5% vs. 14.3%; $P < .01$), and intraluminal thrombi (30.8% vs. 1.8%; $P < .01$). Regression analysis revealed TCFA and microchannel images to be strong predictors of disease progression, each with an odds ratio of approximately 20. The luminal diameter of the stenosis was not predictive of plaque progression.

Cross-sectional studies of risk stratification by OCT have also been published. Yonetsu and associates[45] reported a study of 266 coronary plaques identified on angiography. A reliable measure of cap thickness was obtained in 188 (70.7%). The thickness of the fibrous cap was an independent predictor of plaque rupture, and the cutoff thickness for plaque rupture prediction was estimated to be less than 67 μm, in line with the data described by pathology.

Finally, Guo and associates performed a cross-sectional study to evaluate the characteristics of coronary plaques associated with coronary thrombosis.[46] They included 42 patients with coronary plaque rupture detected by OCT in 216 native coronary artery lesions. Plaques were divided into those with thrombus (64% of coronary plaques) and those without thrombus. Ruptured plaques with thrombus had significantly thinner fibrous caps than those without thrombus (57 μm vs. 96 μm; $P = .008$).

Putting all this information together, OCT can be used to evaluate morphologic features of atherosclerotic plaques and attempt risk-stratification of rupture or progression according to specific morphologic characteristics. However, it remains unknown which patients undergoing diagnostic or interventional procedures should be screened for early detection of high-risk plaque and which changes in therapeutic management might occur after such accurate evaluation. The possibility of online synchronization of coronary angiography with OCT through coregistration might have a significant impact on patients and lesions, answering some of these questions.

Stent Assessment

Given the large number of stents implanted each year, the exceptional technical evolution, and the major remaining issues of stent failure and thrombosis, OCT plays a very significant role for immediate and long-term stent assessment. OCT may contribute at various stages of stent placement: mapping the vessel pathology before implantation, optimizing the stent deployment, quantifying the degree of stent coverage, and evaluating the mechanisms of delayed healing and thrombus formation.[47]

OCT can be used as an adjunct to PCI:

1. Preprocedure (assessment of the intracoronary environment before stent implantation to select stent strategy and devices)
   a. To establish the real extent and severity of the atherosclerotic disease and choose the appropriate stent size and length (Fig. 62-10)
   b. To carefully assess the landing zone to avoid lipid-rich plaque or TCFA sitting at the stent edges (Fig. 62-11)
   c. To establish the presence, type, and distribution of coronary calcium; speckled calcification, spotty calcified nodules, circumferential distribution, and thickness of calcium can be used to guide lesion preparation for metallic stents or bioresorbable scaffolds (Figs. 62-12 and 62-13)
   d. To establish the 3-D anatomy and identify plaque distribution in complex lesion settings (e.g., bifurcation: plaque distribution involving the flow divider region or limited to the opposite vessel wall; carina characteristics: spared or involved by pathology, "eyebrow" carina, eventually prone to displacement and occlusion of the side branch) (Fig. 62-14)
2. Immediately after stent implantation
   a. To detect stent apposition and full expansion
   b. To establish the full coverage of the diseased segment
   c. To unmask stent distortions, edge dissections, tissue protrusion, and remaining thrombus
   d. To determine the access to major side branches (Fig. 62-15)
3. Stent observed at follow-up
   a. To disclose and measure the degree of stent strut coverage by tissues (quantitative analyses)
   b. To assess strut coverage tissue characteristics (e.g., backscatter intensity) and differentiate restenosis from neoatherosclerosis (Fig. 62-16)
   c. To discover late stent apposition, peristrut cavities, and local signs of toxicity in the case of a drug-eluting stent (DES) (Fig. 62-17)
   d. To eventually detect causative mechanisms of stent failure and possibly individualize the treatment

PRINCIPLES OF STENT IMAGING

Metallic stent struts are strong reflectors of light and appear as bright points along the circumference of the vessel. Because light cannot penetrate the metallic strut, a shadow is generated behind. Therefore

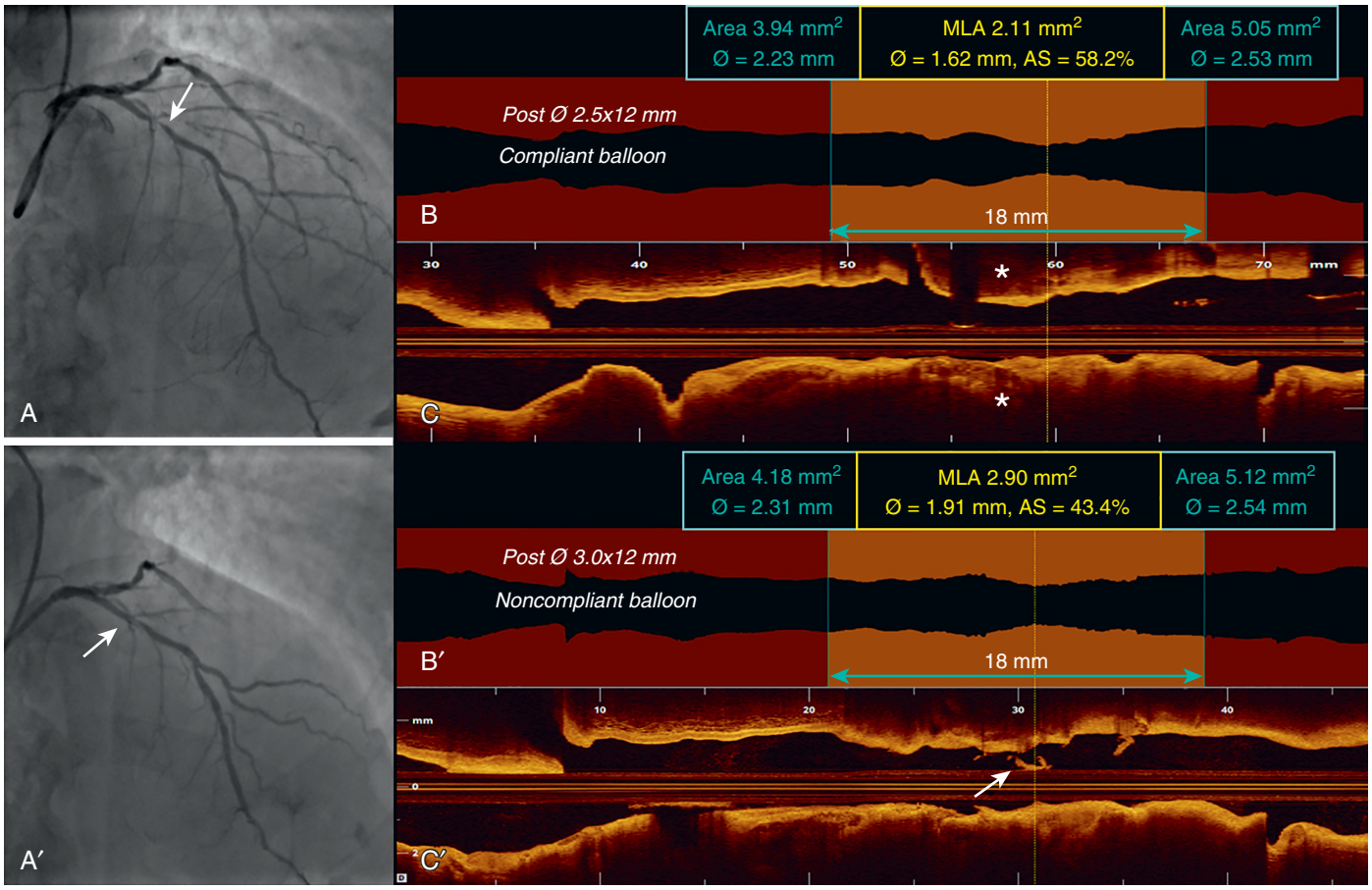

FIGURE 62-10 Optical coherence tomography (OCT) for lesion preparation. OCT performed before stent implantation allows one to map the extension and type of coronary plaque and to immediately plan the most appropriate stent selection (i.e., size, length). Given the escalating role of the fully bioresorbable scaffold, OCT has an increasing value in monitoring the effect of lesion preparation for scaffold implants. **A,** Coronary angiography shows a proximal lesion on the left anterior descending (LAD) coronary artery after dilation with a compliant balloon *(arrow)*. **B,** Corresponding lumen profile display produces a visual overview of the treated segment with automatic detection of minimal luminal area (MLA) and lesion length. An inadequate result of balloon dilation, with insufficient plaque modification, is displayed. **C,** Longitudinal view shows the presence of calcification at the MLA site *(asterisks)*. **A′,** Coronary angiography of the LAD after additional high-pressure dilation with a noncompliant balloon *(arrow)*. **B′,** Lumen profile display demonstrates sufficient plaque modification with adequate gain at MLA site. **C′,** Longitudinal reconstruction confirms the presence of cracks at calcified plaque without major dissection *(arrow)*; the vessel is ready for stent implantation. *AS,* Area stenosis; *Φ,* diameter.

light reflection from the luminal surface of the metal does not provide a direct measurement of strut thickness. The luminal surface of the strut is expected to be found in the middle of the blooming, so half of the blooming value should be used as standard for calculation. When strut-level analysis is performed, the center of the luminal surface of the strut blooming is determined for each strut, and its distance to the lumen contour of the vessel wall is automatically calculated.

The monochromatic peak wavelength of the FD-OCT is differently reflected, refracted, and absorbed by biodegradable polymeric scaffolds compared with the metallic struts. Because a larger amount of the OCT light energy is transmitted through the polymeric struts, only part of it is reflected at the endoluminal and abluminal sides of the struts, generating a visible optical frame border. As a consequence, the vessel wall can be imaged through the struts without any major signs of attenuation, and its luminal area can be readily measured behind the polymeric struts. At follow-up, most of the struts are fully covered and embedded in the vessel wall, and the luminal area can be drawn with an automated detection algorithm.[47] Because polymeric struts are accurately imaged at baseline, the device area can be obtained manually by joining the middle point of each consecutive strut around the circumference[48] (Fig. 62-18).

Strut Apposition

For accurate evaluation of stent apposition, the stent surface must be measured from the center of the stent reflection.[49] Two forms of strut apposition exist: protruding, in which the strut boundary is located above the level of the luminal surface, and embedded, in which the strut boundary is below the level of the luminal surface.[50] Incomplete stent apposition (ISA), synonymous with malapposition, is defined as separation of the strut from the lumen border by a distance greater than the width of the stent strut according to each stent specification.[51] ISA can be addressed at a cross-sectional level, expressed as number and length of consecutive cross sections with ISA together with area and volume measurements, or at a strut level, expressed as maximum distance of ISA at each strut. Acute malapposition can be readily displayed by OCT immediately after stent deployment, whereas the

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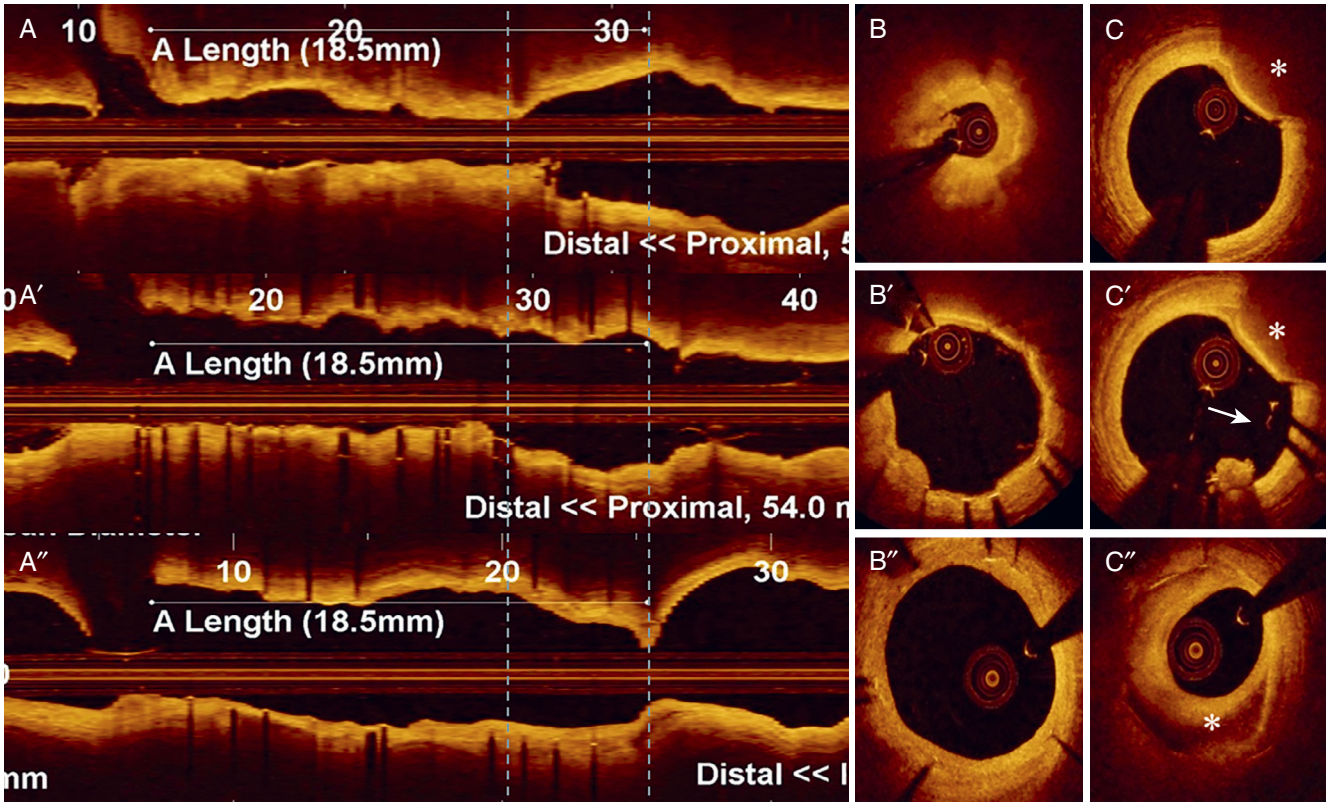

FIGURE 62-11 Role of the landing zone in coronary stenting. Baseline optical coherence tomography of the culprit vessel in a patient with ST-segment elevation myocardial infarction (STEMI) was performed immediately after manual thrombus aspiration. The extent of the culprit lesion is shown in the longitudinal reconstruction **(A)**, whereas the severity is better appreciated in the cross-sectional view **(B)**. Proximally to the culprit plaque, a mild, lipid-rich thin-cap fibroatheroma (TCFA, *asterisk*) is observed (**A** and **C**), with foamy macrophages bordering the subsurface (high-density signal with sharp attenuation). After implantation of an everolimus-eluting stent (EES) **(A′)**, a wide lumen was obtained at the culprit site **(B′)**. However, the proximal edge of the EES *(arrow)* landed exactly at the TFCA (**C′,** *asterisk*), disrupting the surface. At 9-month elective follow-up **(A″)**, the EES shows a perfect result at the culprit site, with full strut coverage and minimal neointima **(B″)**. However, a high-degree focal restenosis is visible at the proximal edge, with large lipid infiltration masking the struts underneath (**C″,** *asterisk*). The trauma induced by stent implantation on a mild TCFA at the landing zone **(C′)** might have been responsible for the accelerated neoatherosclerosis, leading to significant in-stent edge restenosis **(C″)**.

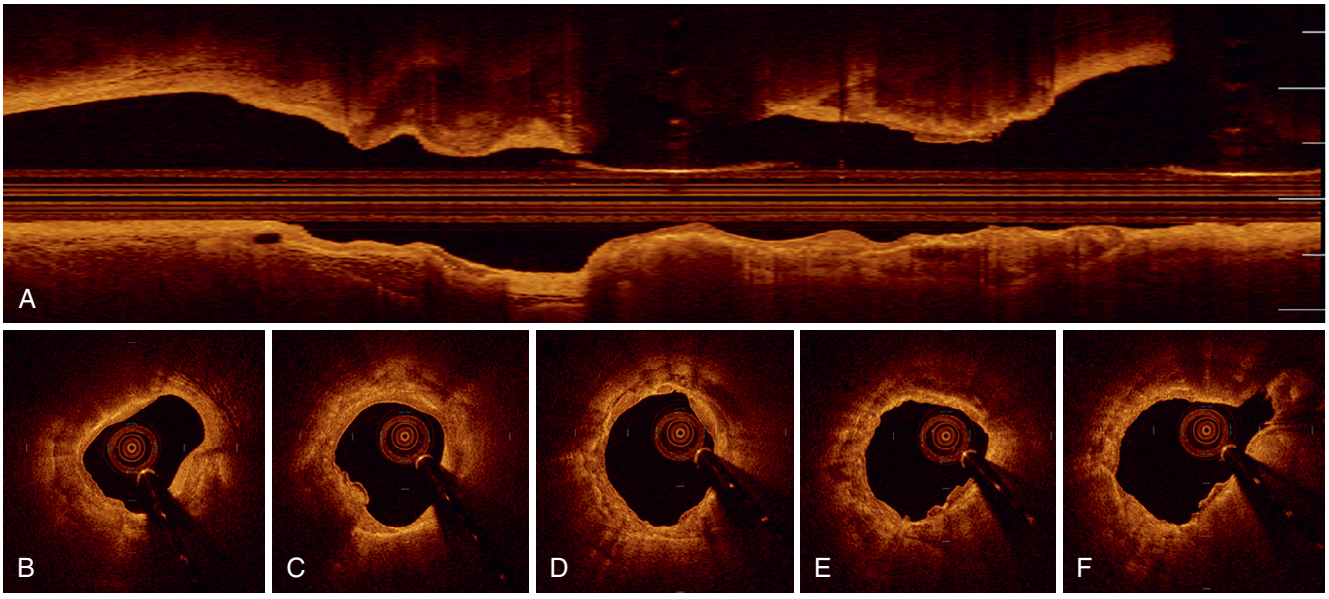

FIGURE 62-12 Calcium detection and quantification by optical coherence tomography (OCT). Near-infrared light easily penetrates calcium, without any shadowing (different from intravascular ultrasound). Therefore OCT can be applied as a superior imaging tool for calcium detection and quantification, providing information on circumferential extension, thickness, and distance from the luminal surface. Calcified lesions in OCT result in signal-poor regions with sharp, well-delineated borders visible in longitudinal and cross-sectional views. **A,** OCT longitudinal reconstruction of multiple heavily calcified lesions. **B** through **F,** Cross-sections provide information on calcium location, circumferential distribution, and depth. Superficial spikes of calcium may protrude into the lumen, blocking the stent and making difficult to progress inside the coronary arteries.

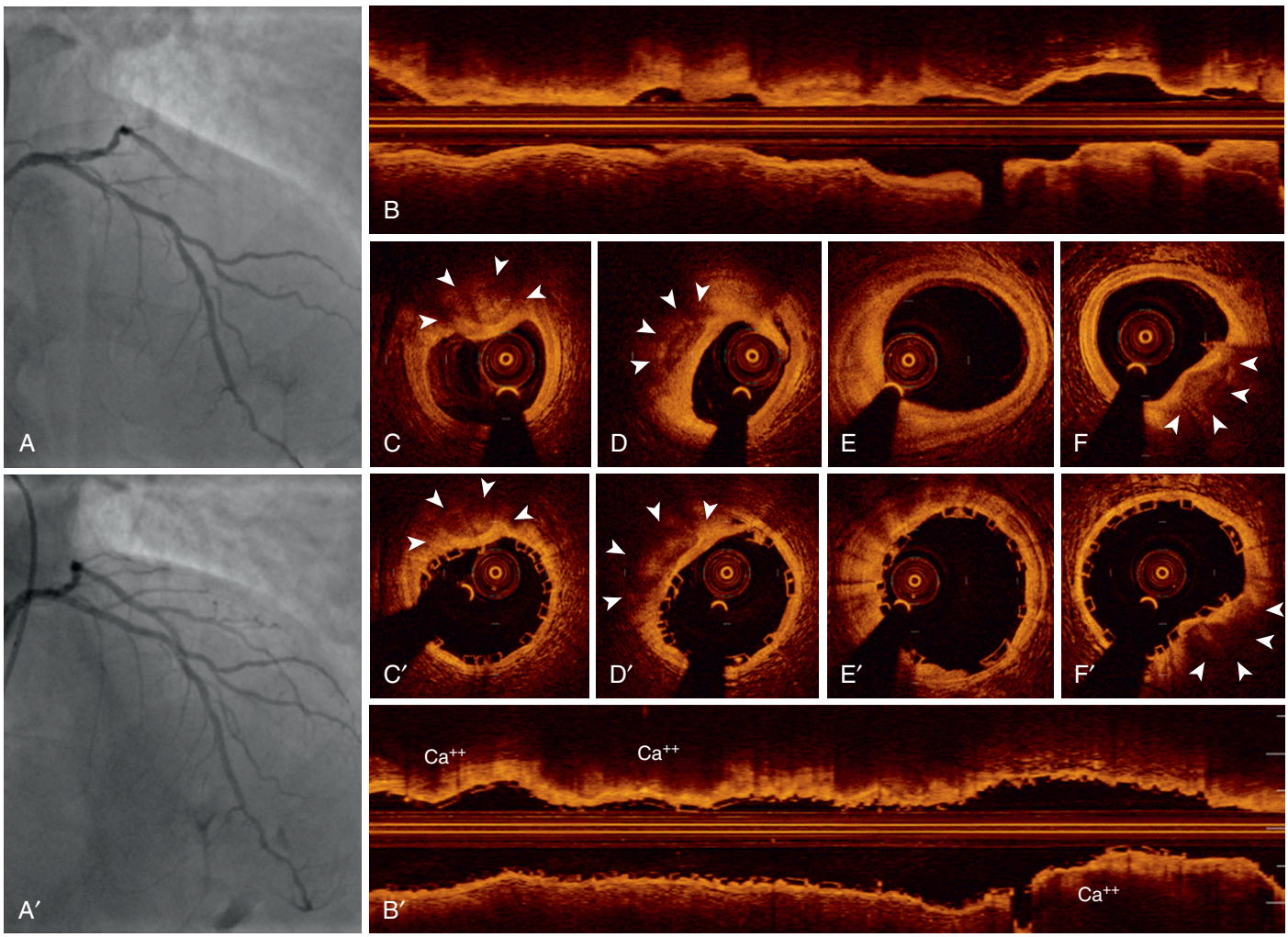

FIGURE 62-13 Optical coherence tomography (OCT) is used to guide implantation of a bioresorbable vascular scaffold (BVS). Plaque type and constituents and lesion preparation may significantly impact scaffold expansion and nonuniform distribution of polymeric struts. Adequate lesion preparation and BVS sizing are crucial, because large malapposition is uncorrectable and excessive overexpansion results in acute stent disruption. Given the ability of OCT to visualize coronary plaques, side branches, stent apposition, expansion, and mechanical integrity, combined with a superb lumen accuracy in measurements, this imaging technique has become the choice for guiding BVS implantation in complex lesions. **A,** Coronary angiography shows the target lesion on the middle left anterior descending (LAD) coronary artery, without any evidence of calcification. OCT longitudinal **(B)** and cross-sectional (**C** to **F**) views of the target lesion after balloon preparation based on morphologic criteria show calcified nodules and plaques with calcium extending for no more than one arc of quadrants (**C, D,** and **F**, *arrowheads*). **A′,** Coronary angiography after BVS implantation on the LAD shows a good luminal result. The results at various cross section levels corresponding to the longitudinal view **(B′)** display full strut apposition, even in the presence of calcified components (**C′** to **F′**), with nonuniform strut distribution.

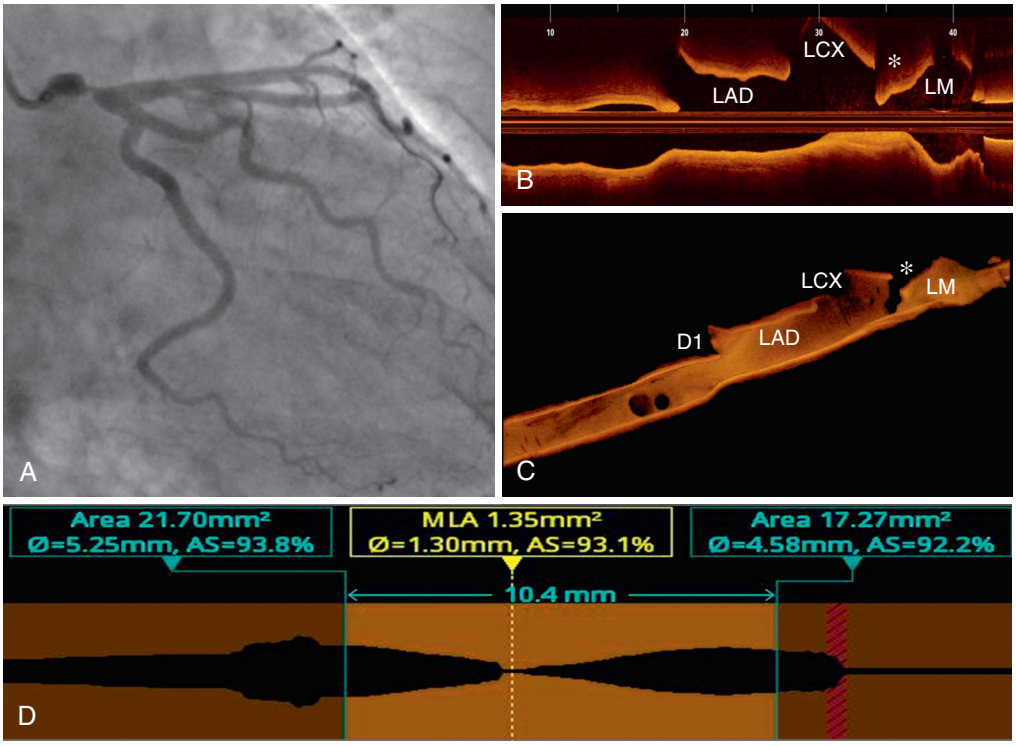

FIGURE 62-14 Optical coherence tomography (OCT) multimodality views in complex lesion settings. **A,** Coronary angiography reveals a severe stenosis involving the left main coronary artery (LM). Longitudinal view **(B)** and three-dimensional reconstruction **(C)** show the lesion characteristics (e.g., large lipid content, *asterisk*) and extent. The LM bifurcation and the ostia of the left anterior descending (LAD) and left circumflex (LCX) arteries were not involved by pathology. No difference in size between LM and the landing zone for stenting at the proximal LAD was observed, limiting the risk of mismatch and vessel dissection. A second lesion was disclosed by OCT at the bifurcation with D1. **D,** Automatic lumen profile display makes accurate measurement of lesion severity, extension, and reference segments immediately available. *AS,* Area stenosis; *MLA,* minimal luminal area; *Φ,* diameter.

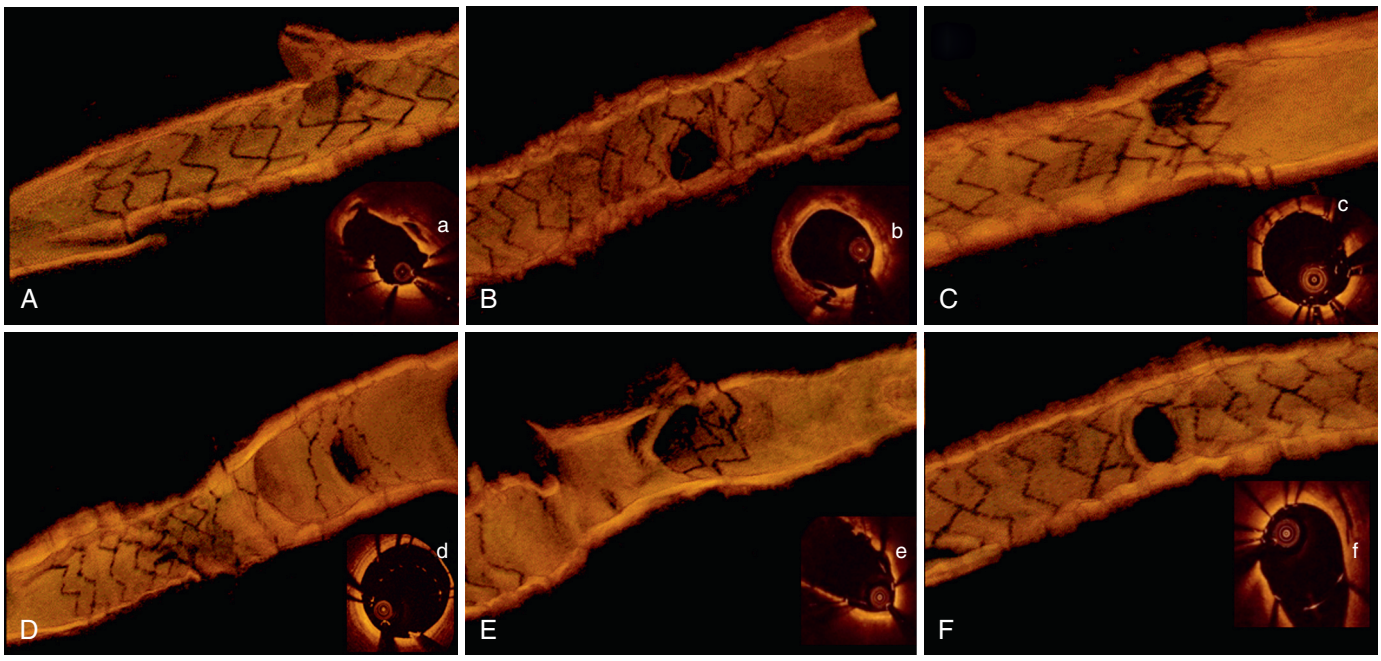

FIGURE 62-15 Optical coherence tomography (OCT) findings immediately after stent implantation. **A,** Distal edge dissection induced by the stent at the transition between calcified and lipid plaque components. The cross section (inset *a*) shows an additional dissection of a lipid-rich plaque at the origin of a side branch. **B,** Proximal edge dissection extending for 4 mm in length. The cross section (*b*) shows a tear deeply penetrating into the media. **C,** Stent malapposition caused by proximal edge distortion ("concertina effect"). The cross section (*c*) shows multiple strut layers in a single stent resulting from deformation and strut fold-over. **D,** Stent underexpansion and overexpansion caused by tapering of the underlying vessel, with nonuniform stent cell expansion. Despite dilation with a high-pressure larger balloon, some cells remained unexpanded and others were deformed and excessively opened at the proximal stent site (*d*). **E,** OCT pullback in the main vessel documents stent protrusion after treatment of a side branch (*e*). **F,** Perfect result of a stent implantation shows full stent expansion and apposition and wide access to the side branch (*f*).

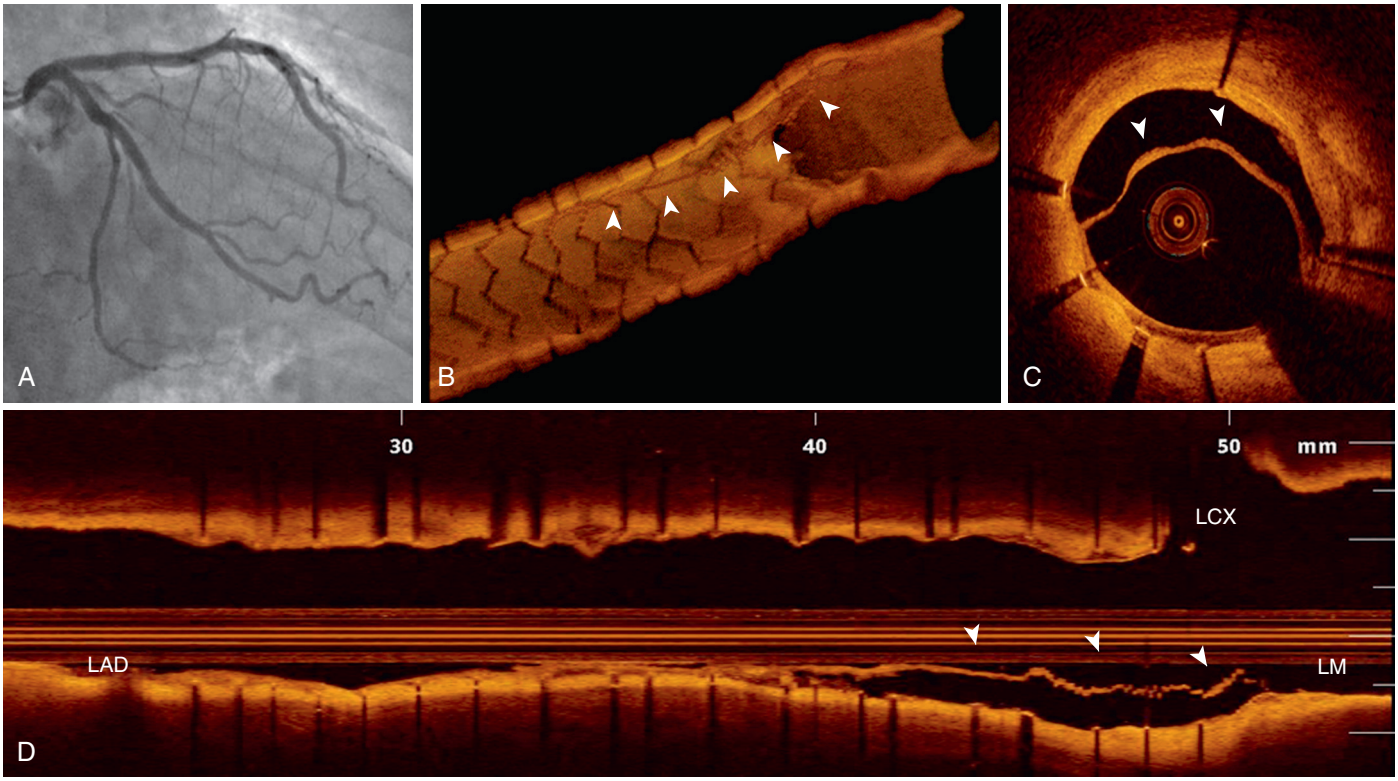

FIGURE 62-16 Angiographically silent detachment of immature neointima in drug-eluting stent (DES). A 62-year-old man was admitted for stage revascularization of the right coronary artery 2 months after percutaneous coronary intervention and DES implantation on the proximal left anterior descending (LAD) coronary artery. **A,** Coronary angiography displays a perfect result of the LAD procedure. No stenosis and a TIMI 3 flow grade were observed. Multimodality OCT reveals a long intimal flap detached from the stent strut surface. **B,** Three-dimensional reconstruction shows tissue detachment *(arrowheads)*. **C,** The intimal flap is more evident in the cross-sectional view from 9 o'clock to 3 o'clock (*arrowheads*) and discloses optical tissue properties of immature intima formation with signal attenuation (3 o'clock to 7 o'clock). **D,** The detachment is also seen in the longitudinal reconstruction. *LCX,* Left circumflex coronary artery; *LM,* left main coronary artery.

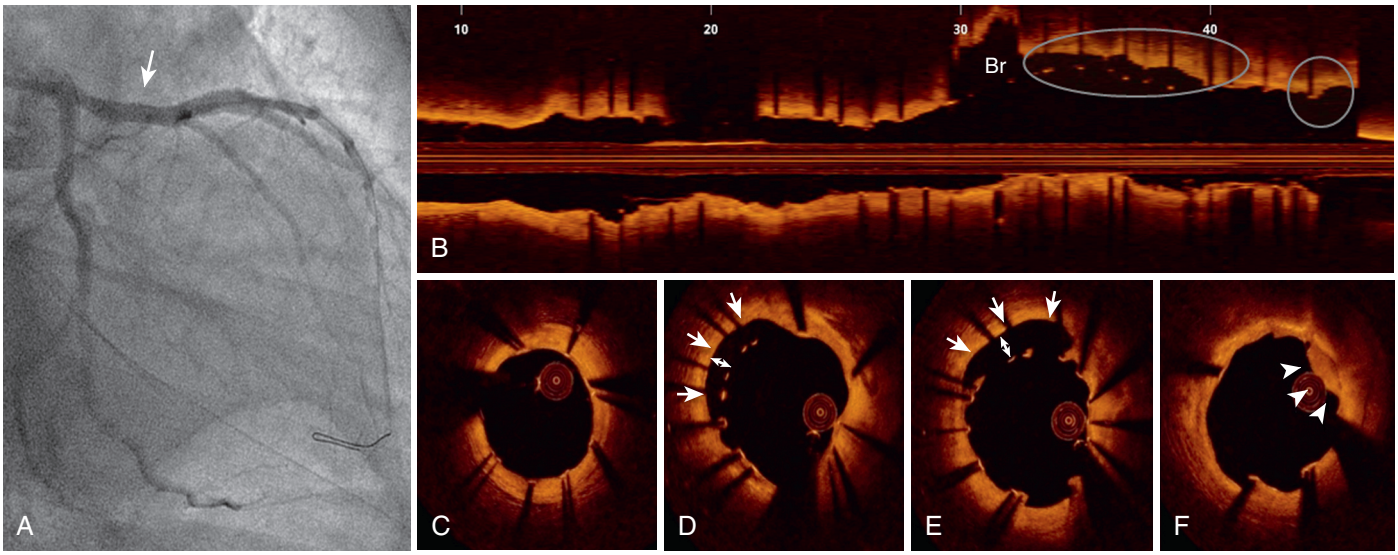

FIGURE 62-17 Optical coherence tomography (OCT) detection of asymptomatic large stent malapposition at follow-up. Long segment of incomplete stent apposition (ISA) was discovered by OCT at the time of elective follow-up after implantation of a drug-eluting stent in a patient with ST-segment elevation myocardial infarction (STEMI). This finding might have been caused by the underlying characteristics of the culprit plaque (reabsorption of the original plaque or remaining thrombus), or it might have been acquired at a late stage (inflammatory response to drug or polymer). **A,** Coronary angiography shows a perfect result on the left anterior descending coronary artery at midterm follow-up *(arrow)*. **B,** Longitudinal view shows a long segment (10 mm) of malapposed struts *(oval),* immediately before the bifurcation (Br). **C,** Cross section of the middistal stent shows perfect strut apposition and coverage. **D** and **E,** Cross sections of the segment with large area of ISA *(double-headed arrows)* show cluster of malapposed struts, partially uncovered *(arrows)*. **F,** Cross section of the proximal stent shows the presence of subclinical white thrombus attached to the stent struts (*arrowheads* on **F**, *circle* on the longitudinal reconstruction, **B**).

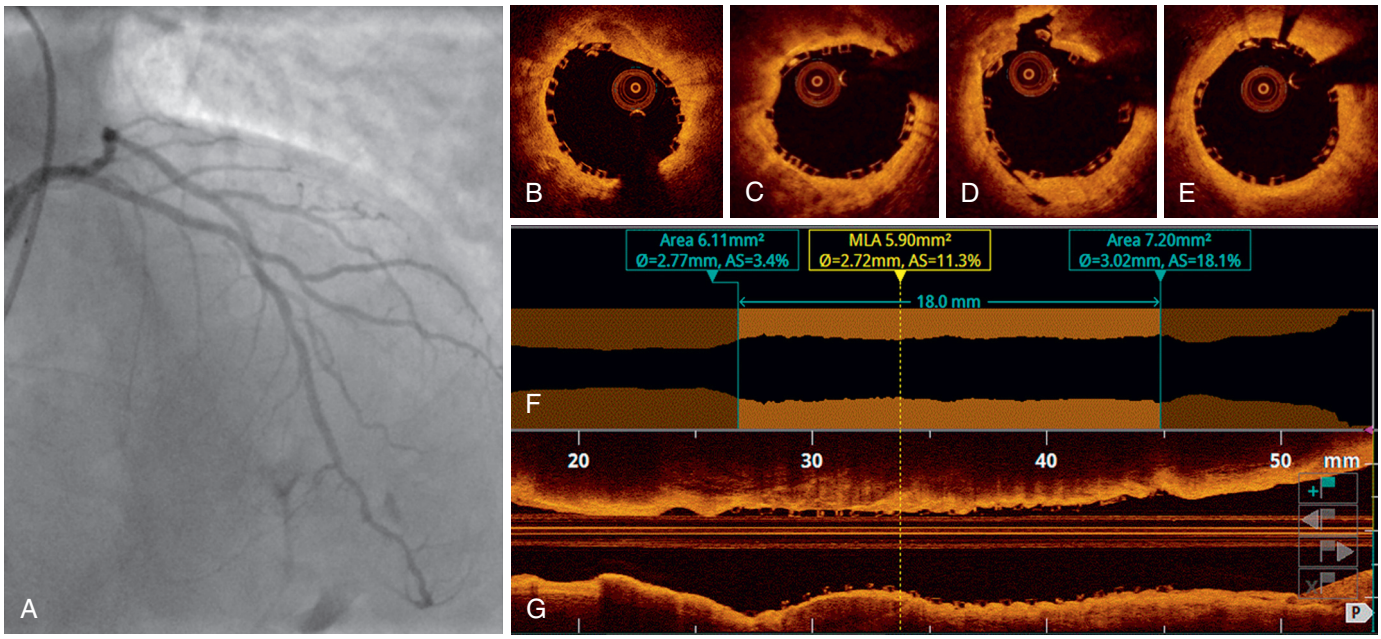

FIGURE 62-18 Optical coherence tomography assessment enables full visualization of the box structure of the bioresorbable polymeric strut, permitting accurate assessment of stent expansion and malapposition without shadowing of the underlying pathology. Because a significant amount of the light energy is transmitted through the polymeric struts, a visible optical frame border can be generated. As the light is penetrating the plastic boxes, the vessel wall can be imaged through the struts without any major signs of attenuation, and its luminal area can be readily measured behind the polymeric struts. **A,** Coronary angiography shows good result after implantation of a bioresorbable vascular scaffold on the proximal left anterior descending coronary artery, with maintained side-branch patency. **B** to **E,** Cross sections show good scaffold expansion after lesion preparation (plaque cracks in **D**) and no edge dissection. **F,** Automatic lumen profile display demonstrates a perfect result, with a minimal luminal area (MLA) of 5.9 mm^2 and limited residual area stenosis (AS) of 11%. **G,** Longitudinal reconstruction confirms the absence of residual pathology at reference segments. *Φ,* Diameter.

detection of persistent or late malapposition requires comparison of images obtained immediately after stent implantation with corresponding (sister) images at follow-up.

By using serial OCT, Ozaki and colleagues[52] demonstrated that ISA observed at follow-up after implantation of a sirolimus-eluting stent was more frequently derived from acute malapposition without neointimal growth, rather than acquired late due to positive vascular remodeling. Similar findings were reported by Inoue and associates[53] with the use of current-generation DES. Acute malapposition with a strut vessel distance of 380 µm or greater remained persistent more frequently over lipid or calcified plaque than over fibrous plaques (lipid, 13.4%; calcified, 18.2%; fibrous, 4.2%; lipid vs. fibrous, $P = .001$; calcified vs. fibrous, $P = .02$) and was associated with the presence of thrombi at follow-up (Fig. 62-19). Therefore the outcome was influenced by both the amount of malapposition at stent implantation and the underlying nature of the treated plaque.

Kubo and colleagues[54] showed that ISA (47% vs. 18%), dissection (40% vs. 16%), and tissue protrusion (58% vs. 20%) immediately after stent implantation are more often detected by OCT than by IVUS. With the systematic use of OCT in daily practice, suboptimal results including stent malapposition, remaining thrombus, plaque prolapse, and edge dissection are observed more frequently than expected. Gonzalo and coworkers[55] evaluated the reproducibility of these findings with OCT. The reproducibility of edge dissection, tissue prolapse, in-stent dissection, and strut malapposition detected by OCT was 100% ($\kappa = 1.0$). However, minor abnormalities detected by OCT might not always require additional treatment. Kawamori and associates[56] studied such abnormalities immediately after stent implantation and at follow-up. In most cases, limited stent malapposition, plaque prolapse, or minor edge dissections substantially improved or resolved at follow-up.

A comprehensive analysis of OCT edge dissections was recently reported by Chamié and colleagues.[57] Qualitative and morphometric assessments at the stent edges revealed that the dissections were frequently associated with remaining plaques (TCFA and lipid-rich lesions) at the landing zone and with the technique of implantation, suggesting some geographic mismatch as the main causative factor. They concluded that dissections with longitudinal length less than 1.75 mm, fewer than two concomitant flaps, a flap depth of less than 0.52 mm, and a flap opening of less than 0.33 mm and not extending into the media have favorable outcomes and can be left untreated. Similar findings were reported by Radu and coworkers[58] using serial OCT after DES implantation to assess the morphology, healing response, and clinical outcomes of angiographically silent OCT edge dissections. Angiographically silent dissections were not associated with acute stent thrombosis or restenosis during follow-up of up to 1 year, and in almost all cases resulted in a complete sealing (Fig. 62-20).

On the other hand, Prati and colleagues[59] reported a clinical benefit of OCT guidance in correcting stent abnormalities by optimizing decisions during PCI (the Centro per la Lotta contro o'Infarto-Optimisation of Percutaneous Coronary Intervention [CLI-OPCI] study). The addition of adjunctive information obtained by OCT resulted in significantly lower 1-year cardiac mortality (1.2% vs. 4.5%; $P = .010$), combination of cardiac death and MI (6.6% vs. 13.0%; $P = .006$), and combination of all composite major adverse cardiac events (9.6% vs. 14.8%; $P = .044$).[59]

Strut Coverage

Histopathology obtained from autopsy cases highlights delayed healing and incomplete endothelial coverage as predictors of late stent thrombosis after DES implantation. Unlike BMS, which develop circumferential coverage with an average thickness of 500 µm or more, easily measured by IVUS and angiography, the smaller amount of neointimal growth after DES implantation is largely under the limit of resolution

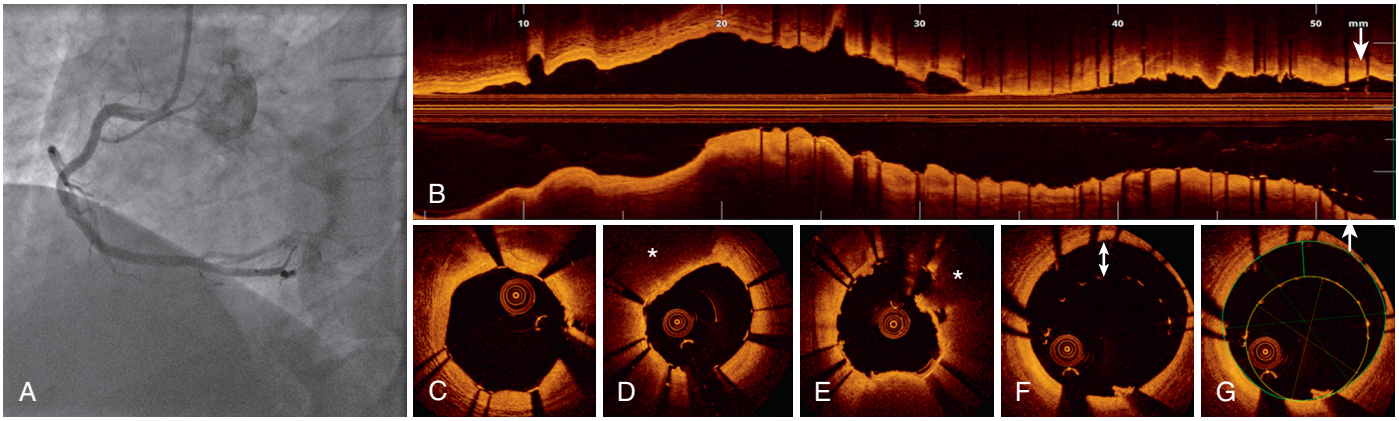

FIGURE 62-19 Stent implantation during primary percutaneous coronary intervention: detection of acute malapposition. **A,** Coronary angiography after stent implantation in a patient with ST-elevation myocardial infarction (STEMI). A perfect angiographic result is seen at the culprit site in the proximal right coronary artery, with restored coronary patency. **B,** Optical coherence tomography (OCT) longitudinal reconstruction confirms a wide lumen but reveals a large malapposition at the proximal stent edge, extending for 5 mm *(white arrows)*. **C** to **G,** OCT cross-sectional views demonstrate full coverage of a thin-cap fibroatheroma (**D,** *asterisk*), some plaque protrusion at the culprit site (**E,** *asterisk*), and a large proximal edge malapposition undetected by angiography (**F** and **G**). The malapposition extends for almost the entire stent circumference, with an area of malapposition greater than 3 mm^2 (**F,** *double arrowhead*).

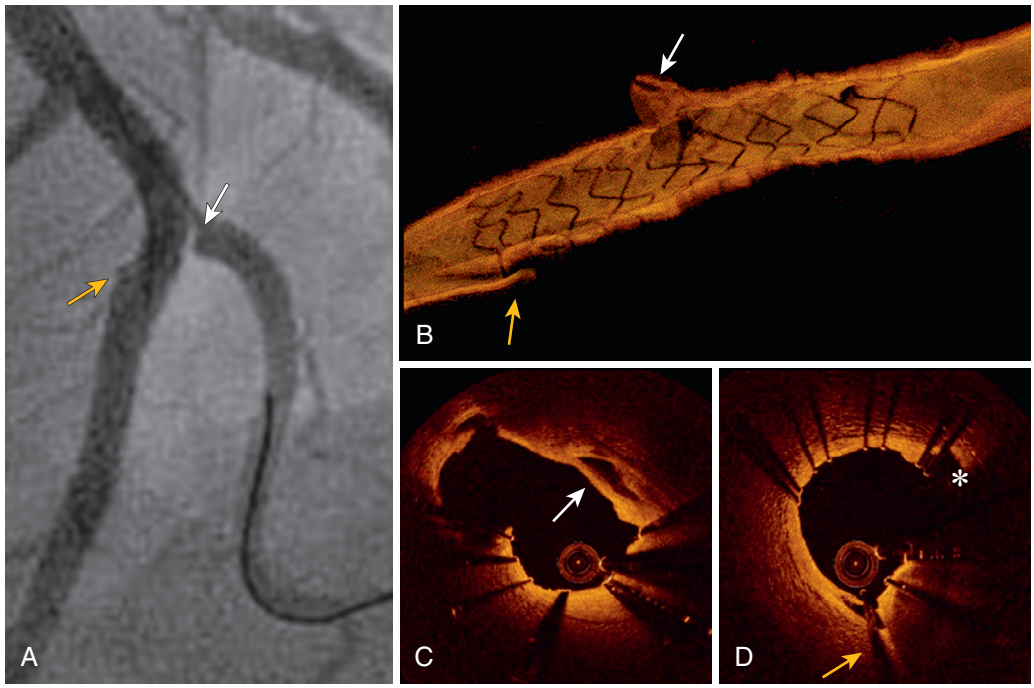

FIGURE 62-20 Optical coherence tomography (OCT) use in bifurcation lesions. Corresponding coronary angiography and OCT findings after implantation of a provisional stent on the left anterior descending coronary artery across the D1 bifurcation. **A,** Angiography. A linear defect was encroaching the ostium of the first diagonal artery *(white arrow)*, and a hazy area was observed at the distal stent edge *(yellow arrow)*. **B,** Three-dimensional OCT reconstruction provides additional insights in the presence of ambiguous angiographic imaging. In this case, a linear dissection involved the ostium of the side branch *(white arrow)*, without obstructing the lumen, whereas the haziness at the distal stent edge was caused by a longer dissection extending for more than 4 mm longitudinally *(yellow arrow)*. An adjunctive stent was implanted to correct this edge dissection. No additional treatment was done at the bifurcation. **C,** Superficial dissection flap *(white arrow)* at the ostium of D1. **D,** Distal stent edge dissection deeply penetrates into the media *(yellow arrow)* due to incomplete coverage of a fibrocalcific plaque at the landing zone (Ca^{++}) with additional stent malapposition *(asterisk)*.

of these imaging techniques.[60] Preclinical studies have demonstrated a close degree of correlation between OCT, light microscopy, and SEM in detecting coverage in DES.[2] In particular, all struts completely covered by FD-OCT were also fully covered by SEM.

The time course of tissue coverage after stent implantation is different according to stent type. In BMS, normal neointima was observed in all cross sections 6 months after stent implantation. In contrast, at a later phase during an extended period of 5 years or longer, neointima undergoes various OCT signal changes with increase neovascularization, late lipid infiltration up to plaque disruption, and eventually, thrombus formation.[60] In DES, OCT performed at different time points demonstrated a higher rate of uncovered stent struts compared with BMS, ranging from 15% at 3 months to 5% at 2 years, and a higher degree of heterogeneity in coverage.[61,62] However, different DES devices have different rates of coverage and uneven neointima response, possibly related to the polymer characteristics and specific drug kinetics.[63] Paclitaxel-eluting stents (PES) implanted in patients with STEMI resulted in a significantly higher rate of uncovered and malapposed struts compared with BMS,[64] but in the same setting, a similar vascular response to BMS was observed with first-generation zotarolimus-eluting stents (ZES).[51] Despite the fact that neointimal coverage in DES may progress overtime, previous midterm OCT studies have shown that uncovered stent struts in first-generation DES decreased but did not disappear in 6 to 12 months.[62] More recent OCT data on current-generation DES (biolimus- and everolimus-eluting) has shown less heterogeneity, a higher degree of coverage, and a low rate of malapposition compared with first-generation DES across all indications, including STEMI, supporting the better-observed clinical outcome.[46,53,63,65]

The optimal time for assessing DES coverage remains to be defined. Early assessment of strut coverage can involve the more difficult separation between fibrin and neointima tissues. Optical density of stent strut coverage, measured with novel OFDI, revealed that fibrin-covered struts had lower signal density than mature neointima tissue. Densitometry analysis may be a promising method for characterization of early stent tissue coverage. Conversely, longer time intervals (6 to 13 months) might be more useful for measuring the advanced rate of strut coverage and the accelerated progression of the lesions.[66] The extent of strut coverage has been used as a surrogate variable of outcome in numerous OCT trials. However, the clinical relevance of measuring the completeness of stent coverage has not been fully demonstrated. Although this parameter may provide prognostic information, it is not clear how patient management might be changed or outcomes improved by this analysis. In any case, strut coverage must be interpreted with caution because OCT cannot detect endothelial cells or their functionality. Further, the composition of the material covering stent struts (whether cellular or noncellular in nature) remains incompletely addressed by current-generation OCT.

ANALYSIS OF STENT FAILURE

In-Stent Restenosis

OCT provides an in vivo characterization of the tissue involved in in-stent restenosis (ISR). Gonzalo and colleagues[67] evaluated the morphologic characteristics of ISR by OCT in 24 patients (DES, 84%; BMS, 16%). The ISR tissue was classified based on optical pattern characteristics (homogeneous, heterogeneous, or layered), signal backscatter (high vs. low), presence and type of microvessels (peristruts vs. intraintimal), lumen shape (regular vs. irregular), and presence of abnormal intraluminal material. Tissue structure was layered in 52%, homogeneous in 28%, and heterogeneous in 20%. The predominant optical pattern was backscattering, found in 72% of cases. This classification has been adopted in studies addressing OCT findings and treatment of ISR.

The OCT studies assessing ISR were able to detect a new pathologic entity of late stent failure, neoatherosclerosis. The current concept and knowledge of in-stent neoatherosclerosis evolved quite recently, based on accurate pathologic and OCT tissue assessment.[68,69] Neoatherosclerosis is recognized by pathology as clusters of lipid-laden foamy macrophages within the neointima, with or without necrotic core formation, neovessels, and microcalcifications. Pathology and OCT studies have demonstrated that neoatherosclerosis is more common and occurs earlier in DES compared with BMS, with significantly more TCFA.[69-71] Despite the outstanding details provided by FD-OCT, current systems may be limited as to proper evaluation of the entire spectrum of qualitative characteristics of the neointima. Consequently, the definitions of lipid-laden neointima used in OCT publications may differ, from a signal-poor region with invisible struts to neointima with a diffuse border and high-attenuation signals.[72] Intraintima neovascularization or calcification or both were frequently observed by OCT in presence of neoatherosclerosis.[73,74] Sometimes, neointima with echolucent layers[75] mimics or partially overlaps advanced OCT patterns of neoatherosclerosis (Fig. 62-21).

Characterization of neoatherosclerosis by OCT also provides some prognostic data and is useful to guide the most appropriate therapeutic strategy for patients with stent failure. Indeed, neoatherosclerosis, characterized by a large amount of lipid and TCFAs, frequently manifests with an acute coronary syndrome and is associated with more periprocedural myocardial infarction.[71] Therefore the soft composition of neoatherosclerotic tissue detected by OCT may suggest a different treatment strategy compared with the fibrotic tissue of conventional ISR.[76]

Stent Thrombosis

One of the most useful clinical applications of OCT is in the evaluation and treatment of stent thrombosis, which remains a potential life-threatening complication after stent implantation. Through better mechanistic understanding of the processes involved, OCT allows tailored and more effective treatments of stent thrombosis. OCT may differentiate the presence of stent under expansion, malapposition, aggressive ISR, neoatherosclerosis, and the degree of stent coverage, identifying the main causative factors and bystanders. In a small-scale OCT study comparing patients with subacute stent thrombosis with those with an uneventful course (controls), a smaller MLA was observed in patients with stent thrombosis, with the MSA preferentially located at the thrombus site.[77] Guagliumi and associates[78] assessed with OCT 18 consecutive cases of late and very late stent thrombosis. Stent malapposition was observed in 78% of all cases, with a maximal area of malapposition significantly greater than in the uneventful matched controls. Patients with stent thrombosis also showed a significantly higher percentage of uncovered struts and a higher number of sections with greater than 30% uncovered struts. The length of the segment with consecutive uncovered struts was the only OCT predictive factor for stent thrombosis at multivariate analysis. Kang and colleagues[79] demonstrated in a series of 33 patients with very late stent thrombosis that neoatherosclerosis was the primary mechanism in 70% (median time from initial stent implantation to stent thrombosis, 62 months), whereas malapposition was observed in only 25%.

Very large cohorts of patients with stent thrombosis have been prospectively recruited since 2011 at the European level with a multimodalities approach that includes OCT, blood platelet function, and genetic information collected at the time of stent thrombosis. OCT was used during the acute phase of stent thrombosis, immediately after thrombus aspiration, to differentiate the main mechanism implicated and possibly provide the most appropriate treatment (Fig. 62-22). The Prevention of Stent Thrombosis by an Interdisciplinary Global European Effort (PRESTIGE) project, supported by a grant of the European Union Community (FP7-Seventh Health Program, Health 201o.2.4.2-1, Reducing in-stent thrombosis) has been completed, and the final results will be available in late 2015.

BIORESORBABLE VASCULAR SCAFFOLDS

The bioresorbable vascular scaffold (BVS) represents a breakthrough innovation in the treatment of coronary artery disease. Because the

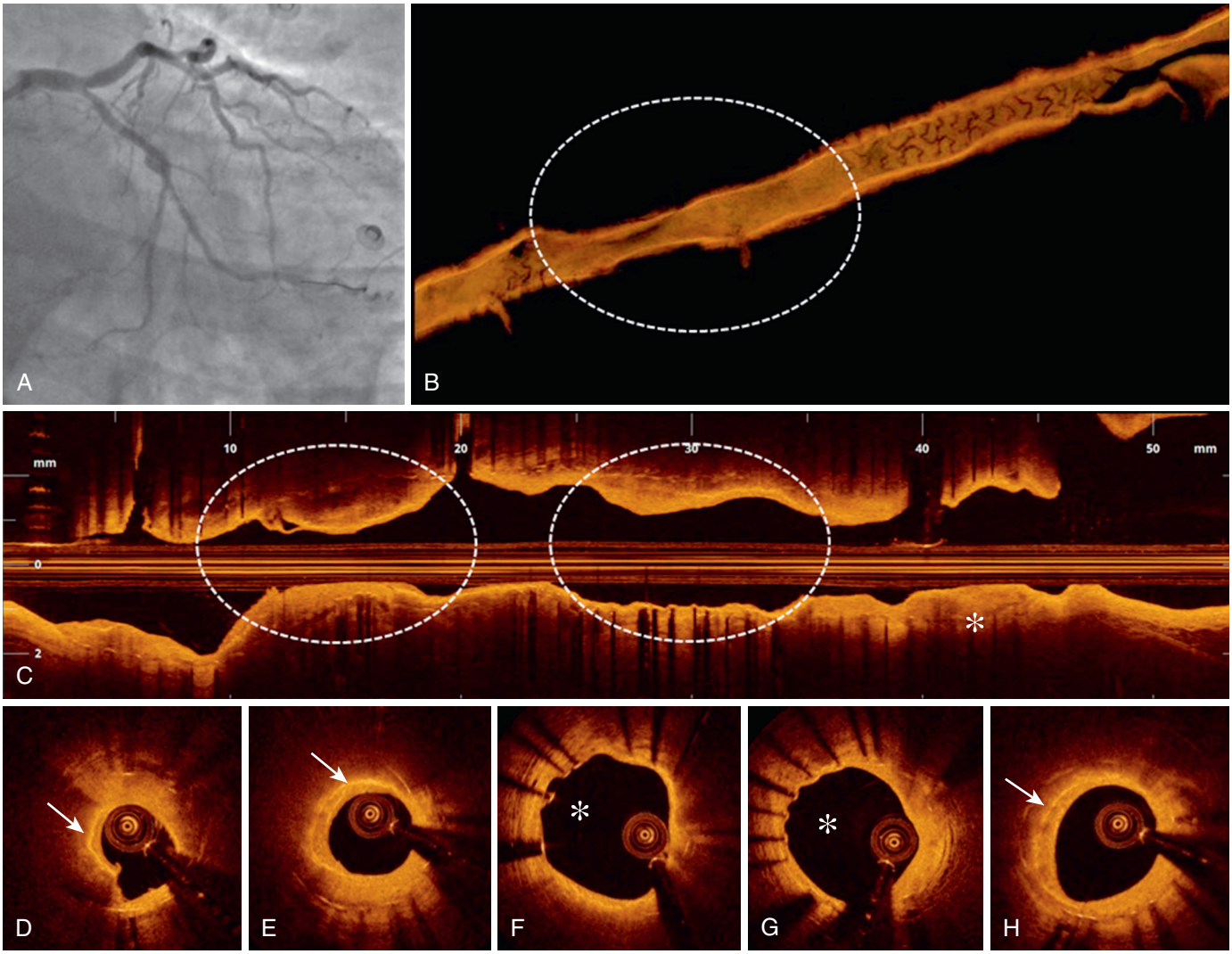

FIGURE 62-21 Late stent thrombosis due to advanced neoatherosclerosis. A 63-year-old man previously treated with two paclitaxel-eluting stents on left circumflex obtuse marginal (LCx-OM) coronary arteries was admitted 3 years later for a non–ST-elevation myocardial infarction (NSTEMI). **A,** Coronary angiography after thrombus aspiration. Three-dimensional **(B)** and longitudinal **(C)** optical coherence tomography views display multiple in-stent segments infiltrated by lipid-laden neointima (i.e., neoatherosclerosis) *(ovals)*. Cross sections substantiate the heterogeneity of the vascular response, showing coexisting sections of lipid-rich plaques (**D, E,** and **H**), signals of foamy macrophage accumulation (**D, E,** and **H,** *arrows*), and uncovered stent struts (**F** and **G**, *asterisks*).

strut is completely absorbed, fully biodegradable stents can provide short-term vessel scaffolding of the coronary lesions without permanent implantation, restoring vessel anatomy and vasomotion tone in a reasonable time.[80] OCT has a major role in assisting BVS technology development and in vivo proof of concept. Serial OCT assessment of the vascular response to BVS implantation demonstrates complete strut reabsorption at 3 to 5 years, with an increase of scaffold area compensating for the increase of the neointima. As a consequence, an unchanged lumen area has been reported between 1 and 3 years. The amount of coverage seems to be related to the local shear stress after implantation, highlighting the critical role of optimal stent expansion to avoid persistent malapposition and speed the healing of thicker struts (Fig. 62-23).

Current BVS have a large crossing profile (1.4 to 1.5 mm), thicker struts (approximately 160 μm), less radial force, and less radiopacity compared with last-generation DES. Therefore BVS implantation, particularly in the setting of a complex lesion, can provide advantages through the use of high-resolution imaging techniques. Plaque type and constituents, plaque burden, and lesion preparation may have significant effects on scaffold expansion, including nonuniform strut distribution (see Fig. 62-23). In addition, the reduced device expandability with first generation BVS (dilation after implantation is limited to a 0.5-mm larger balloon) requires an accurate matching between scaffold size and the reference vessel, because large malapposition is uncorrectable and overexpansion can cause acute scaffold disruption. In dealing with long and diffuse disease, implantation of multiple BVS may be required. Because of the thickness of the current scaffolds, overlap implantation should be avoided. In this setting, OCT provides unique details of the actual position of the two platinum markers, the only visible part of the scaffold (Fig. 62-24).

Despite the reassuring safety data of BVS reported in trials, some concern has recently been addressed by registries regarding the real-world rate of stent thrombosis. A large European multicenter registry, the Gauging coronary Healing with biOresorbable Scaffolding plaTforms in EUrope (GHOST-EU) registry,[81] including 1189 patients treated with BVS, reported a cumulative incidence of definite or

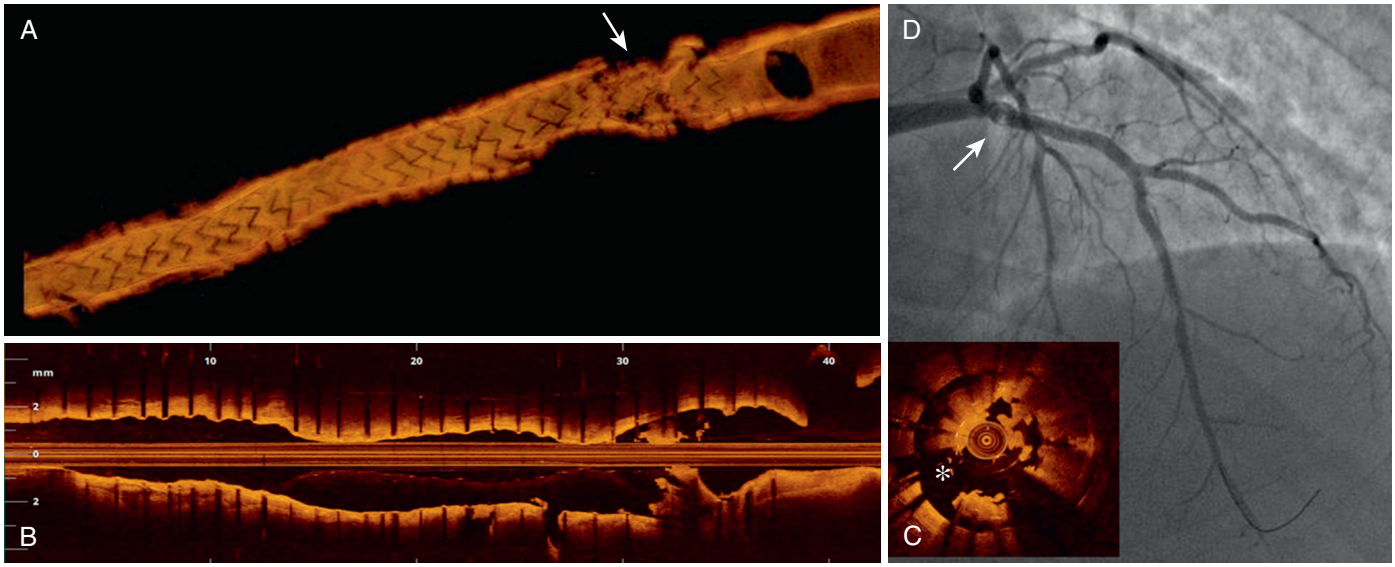

FIGURE 62-22 Very late stent thrombosis due to stent malapposition. Multiple second-generation drug-eluting stents (DES) were implanted in partial overlap to treat an occluded left descending coronary artery during an anterior ST-elevated myocardial infarction (STEMI). The patient remained asymptomatic for 4 years and continued to take aspirin. He was urgently rehospitalized due to a recurrent anterior STEMI. **A,** Three-dimensional optical coherence tomography (OCT) pullback image obtained after manual thrombus aspiration identified an in-stent thrombotic lesion at the proximal stent segment *(arrow)*. **B,** Long view reconstruction shows an overall uniform and good stent expansion, no significant neointimal tissue, and good coverage with the exception of a short proximal segment where thrombus was deposited. **C,** OCT cross-sectional view at that level reveals a cluster of grossly malapposed and uncovered struts *(asterisk)* with large remaining thrombus. **D,** Coronary angiography after manual thrombus aspiration shows a small filling defect corresponding to the site of occlusion *(arrow)*. Large malapposition associated with lack of coverage was identified as the causative mechanism in this case of late DES thrombosis. OCT proved that large malapposed and uncovered struts may remain asymptomatic for years, then suddenly precipitate stent thrombosis in the presence of a trigger thrombogenic factor despite aspirin prophylaxis.

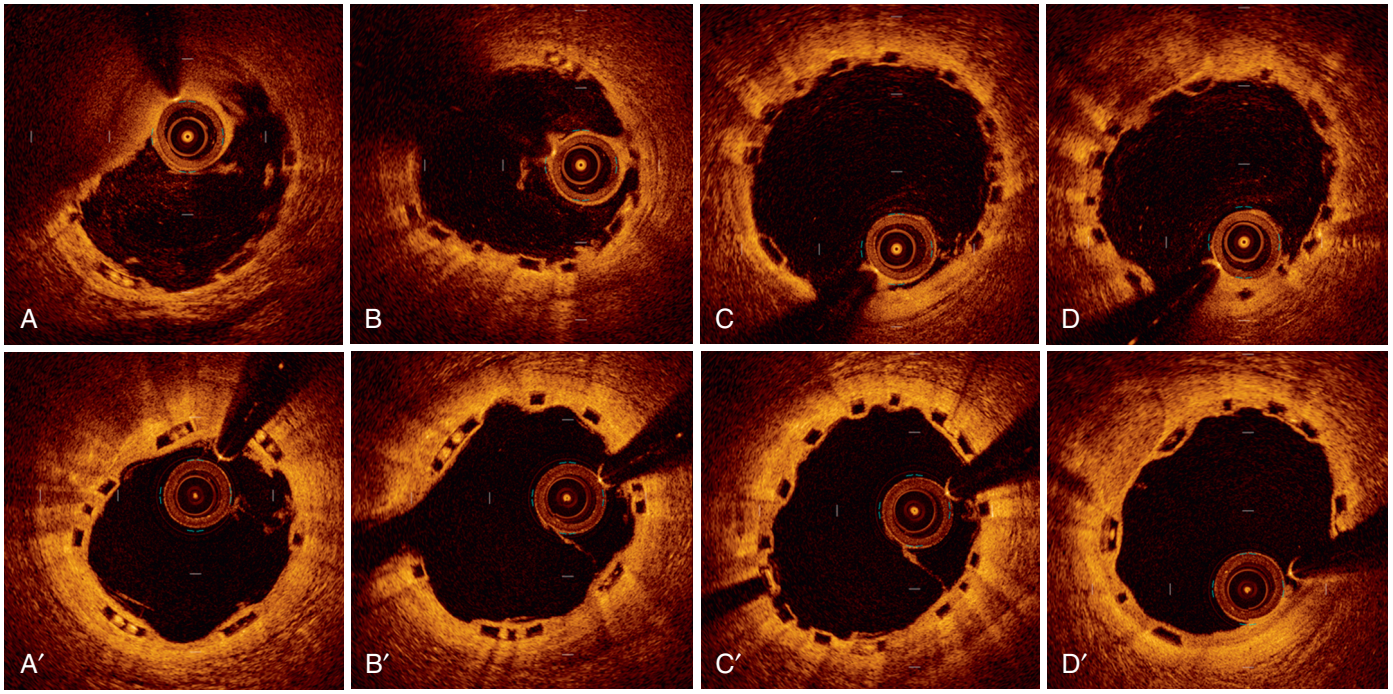

FIGURE 62-23 Acute and follow-up evaluation of bioresorbable vascular scaffolds (BVS). Current BVS have a large crossing profile, thicker struts (approximately 160 μm), and less tensile strength compared with last-generation drug-eluting stents (DES). This device is not recommended for lesions that cannot be adequately prepared because of the presence of calcification. Less symmetry of strut distribution can be acutely observed in the presence of calcium **(A)**. Optical coherence tomography (OCT) identifies different plaque components and, through optimal lesion preparation, may prevent nonuniform strut distribution (**B** to **D**). Given the thicker struts, BVS coverage is more sensitive to local shear stress after implantation. Complete apposition at implantation allows substantial polymer strut coverage even at 3 months' follow-up **(A′, B′, C′, D′)**.

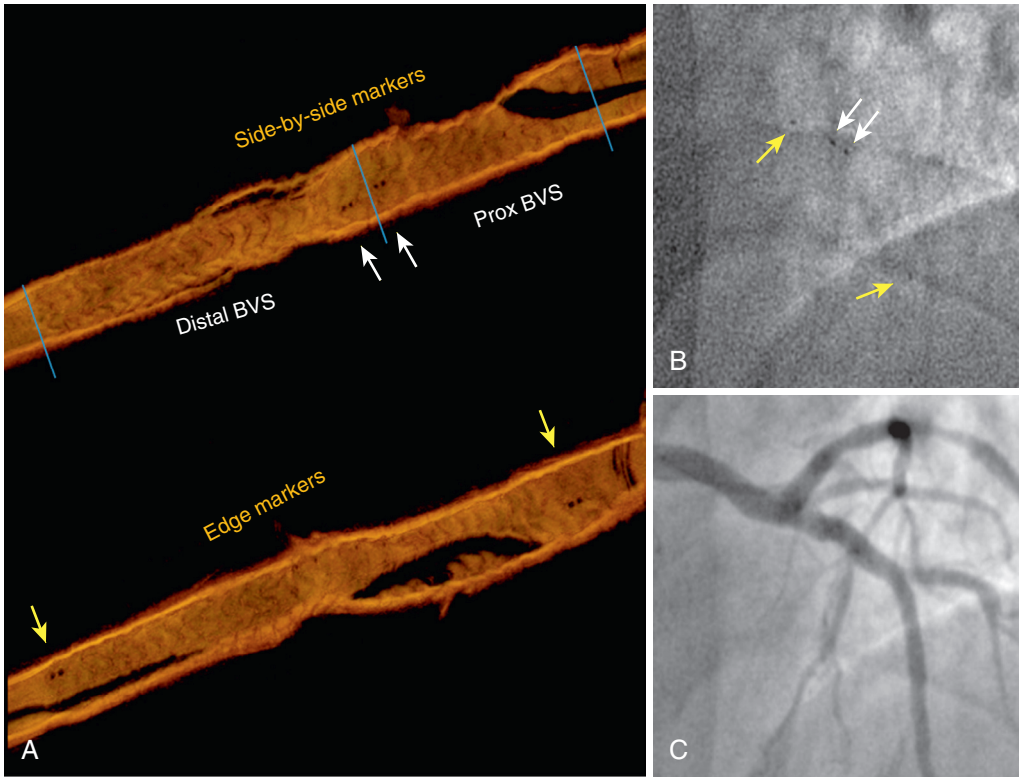

FIGURE 62-24 Optical coherence tomography (OCT) allows precise side-by-side positioning of the BRS. **A,** Three-dimensional OCT reconstruction after BRS implantation. The *blue dotted line* represents the side-by-side position of the two stents. The *white arrows* indicate the distal markers of the proximal stent and the proximal markers of the distal stent. The *yellow arrows* indicate the proximal markers of the proximal stent and distal markers of the distal stent. **B,** Angiogram depicts the stented segment during implantation. The *white arrows* indicate the distal markers of the proximal stent and the proximal markers of the distal stent. The *yellow arrows* indicate the proximal markers of the proximal stent and distal markers of the distal stent. **C,** Coronary angiography showing the BRS and final result.

probable scaffold thrombosis of 1.5% at 30 days and 2.1% at 6 months, with 16 of 23 cases occurring within the first 30 days. These data highlight the adjunctive role of high-resolution imaging techniques to get a more in-depth understanding of BVS procedures when used in lesions of increased complexity.

PROMISING CLINICAL APPLICATIONS IN STENTED CORONARY LESIONS

The use of OCT in PCI and in patients with stents has been demonstrated to be safe and effective for providing additional information. However, the benefit of OCT guidance in complex coronary interventions is not fully understood or yet documented. Nevertheless, at least three major clinical settings that hold the highest risk of PCI failure and negative outcome might reap large benefits from the immediate use of OCT: late and very late stent thrombosis, recurrences of ISR, and complex bifurcation requiring advanced operative techniques.[82]

In late stent thrombosis, OCT may detect and measure the rate and distribution of uncovered and malapposed struts, the heterogeneity of the in-stent vascular response, and eventually the formation of de novo atherosclerotic lesions within the stented segment. In addition in this setting, OCT permits quantification of the completeness of thrombus removal after manual or mechanical thrombus aspiration and may eventually suggest additional antithrombotic treatments. Because of the small size of the tip of hydrophilic coating catheters, OCT may easily reach and cross difficult lesions, including severe ISR. Various patterns of ISR have been demonstrated, suggesting possible different tissue components to guide tailored therapy. In this context, OCT can be useful in assessing the immediate results of different mechanical and pharmacologic interventions.

Bifurcation lesions and related stent procedures are actively investigated with OCT because of the limited accuracy of angiography in detecting complex anatomy at the branching points. OCT performed before the procedure can provide unique data on carina type, plaque distribution, and accumulation at flow divider. In bifurcation, OCT was able to identify the proximal rim at the ostium of the side branch as a region more likely to contain TCFA.[83,84] After stent placement, OCT may reveal incomplete strut apposition, guiding distal cell recrossing in bifurcation stenting to reduce malapposition and stent deformity.[85] The new generation of dedicated stents for bifurcation lesions and the fully resorbable polymeric stent implanted across a branch may present additional reasons for investigation by OCT (Fig. 62-25).

USE OF OCT IN NONCORONARY ARTERIES

The ability of OCT to characterize the nature of atherosclerotic plaque can be expanded to the assessment of the carotid and peripheral vasculature. OCT was tested for possible use in the detection of carotid stenosis and to distinguish between stable and advanced atherosclerotic plaques.[86] Meissner and colleagues[87] studied the role of OCT in ex vivo peripheral vascular diseases, showing morphometric findings comparable with those reported in coronary arteries.[87] Although the evidence for OCT application in carotids and peripheral arteries is still missing, FD-OCT with suitable imaging elements offers greater tissue penetration at distance and may represent a promising technology for future vascular medicine.

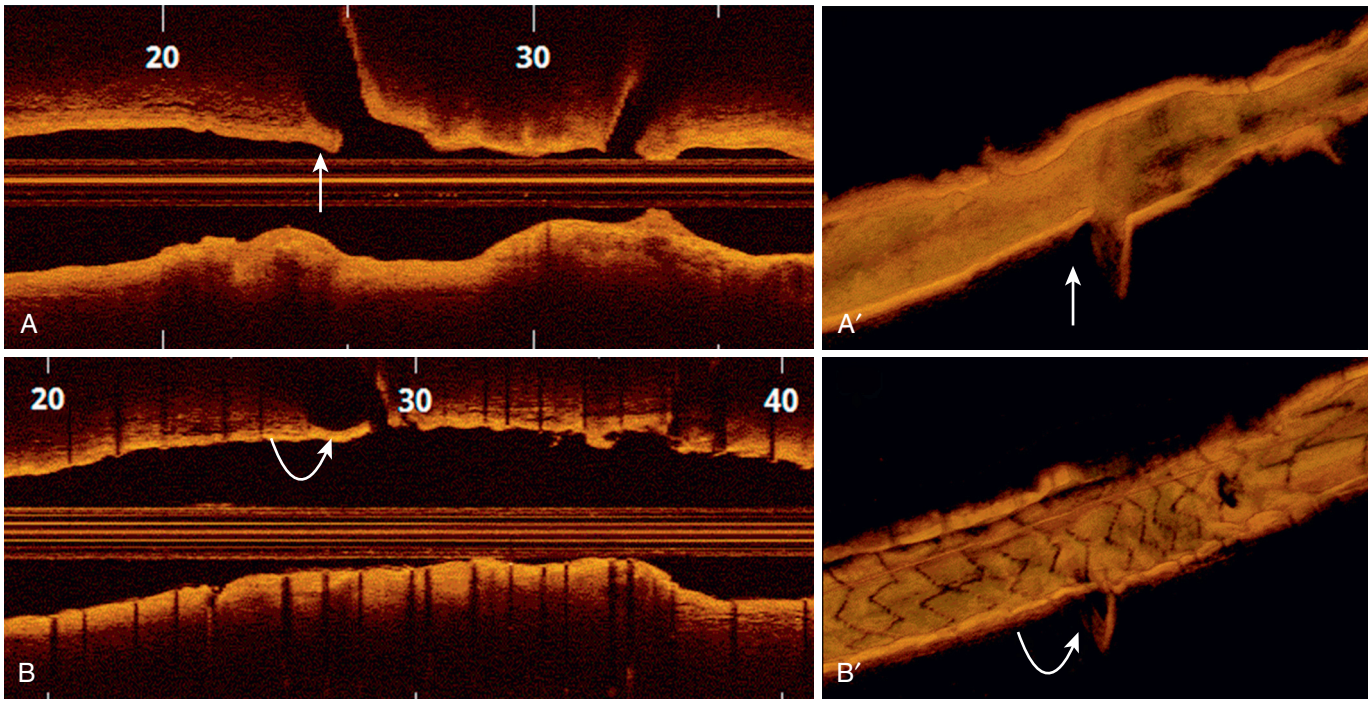

FIGURE 62-25 Optical coherence tomography use in bifurcation lesions. Treatment of coronary bifurcation lesions is challenging because of the risk of jailing or occluding major side branches. Plaque distribution and distinctive characteristics of the carina (i.e., spared or involved, morphology) play a major role in complications. The eyebrow carina, even spared from pathology, may shift toward the side branch during provisional stenting, obstructing the ostium. Guidewire protection of the side branch is mandatory in the case of an elongated carina. Longitudinal **(A)** and three-dimensional **(A′)** reconstructions before stent implantation show the eyebrow carina at the bifurcation level *(straight arrows)*. **B** and **B′,** The same vessel after stent implantation demonstrates the shifting of the carina to obstruct the side branch *(curved arrows)*.

UPCOMING TECHNOLOGIES

Despite advantages in intracoronary imaging technology, angiography is the only tool available at the very time point of stent placement. Translating a desired implantation location, obtained from OCT data, to the angiogram could result in better immediate and long-term outcomes. To avoid the difficulties in matching the geographic position of the cross-sectional OCT images on angiography, an angiography with OCT coregistration system has been proposed. The basic principle of this system consists of tracking the radiopaque lens marker of the OCT catheter on cine, acquired during the OCT pullback. It offers the possibility to directly display a matched side-by-side view of OCT and angiography in the catheterization laboratory. Instant precise automatic measurements provide the data necessary to guide stent selection and positioning. Stent implantation based on accurate device sizing and its positioning, which in turn is based on vessel wall morphology, could result in potential benefit for clinical outcome.[88]

FD-OCT allows the acquisition of spectroscopic data and polarization, Doppler, and other imaging modes for plaque characterization.[89] Interpretation of current images is limited to the evaluation of gray-scale signals and identification of individual plaque components that requires individual experience. The application of a postprocessing color-coding software-based algorithm on analysis of either spectral OCT backscattered data or other optical tissue properties should improve the characterization of atherosclerotic coronary plaques and provide a more objective assessment. Moreover, Tearney and colleagues reported on a new type of micro-OCT that enables imaging of the 3-D microstructure; this outstanding level of resolution may dramatically improve evaluation of lesion vulnerability and the TCFA approaching the rupture. Also, OCT identification of plaque cellular components, such as inflammatory cells, is likely to be improved by 3-D microstructure visualization.[90] When FD-OCT is fully exploited, it has the potential to significantly impact physicians' and researchers' understanding of coronary artery disease in order to better diagnose and treat substantial components.

FUTURE OF OCT

Some expected advances in intravascular OCT technology are improved imaging speed and usability, automated image classification and enhanced visualization, incorporation of alternative optical contrast sources, and OCT-combination devices.

Improvements in light-source sweep rates will enable faster rotational and pullback rates and provide physicians with the ability to capture a high-density scan of the entire coronary artery between consecutive heartbeats, minimizing motion artifacts and reducing further the volume of contrast injected to displace blood during image acquisition. Clinical usability of OCT systems will be improved by features such as robust catheter autocalibration, debris-insensitive connectors, self-synchronizing flush and acquisition, and integration with existing catheter laboratory systems and networks.

Advanced image processing algorithms will be developed to classify tissue types and automatically detect in 3-D display features of interest such as the shape of the vessel lumen, stent strut malappostion, and thrombi deposition. The longitudinal position between the reference and where the cross-sectional area is smallest (MLA) will be found automatically. The algorithm will recognize and avoid residual blood, guidewire reflections, and other structures that may appear to be part of the vessel wall. Interpolation across side branches will be accomplished by imposing continuity of the inner surface of the vessel across neighboring frames. Volume coregistration with IVUS, angiography, computed tomography, or previous OCT data sets will lead to better four-dimensional visualization of pathology and interventional guidance and feedback.

To provide functional information and a wider range of classifiable tissue types, future OCT systems will incorporate alternative optical approaches such as polarization sensitivity, Doppler/phase sensitivity, and spectral sensitivity to both endogenous and exogenous sources of contrast (spectrally tunable optical nanoparticles). Other intravascular diagnostic devices that provide complementary information, such as ultrasound, absorption spectroscopy, fluorescence spectroscopy, and Raman spectroscopy, may be engineered to reside alongside OCT in the same catheter probe. IVUS and OCT imaging with a single catheter may enable visualization of tissue microstructure in superficial layers of the artery wall at the same time as the deeper layers of the artery for evaluation of plaque burden and vessel remodeling. The combination of OCT with near-infrared, Raman, or other spectroscopic techniques may improve discrimination among tissue constituents in complex atherosclerotic lesions and allow for detailed analysis of the cellular and biochemical composition of TCFA lesions for vulnerable plaque detection.

Concurrent data collection from these modalities will dramatically expand the structural and functional information available to the cardiologist and should guide development and clinical use of novel cardiovascular therapies.

CONCLUSIONS

OCT enables real-time, full tomographic, in situ visualization of vessel microstructure with a unique high axial resolution. Previously unrevealed details on atherosclerotic plaque architecture and stent vascular response can be easily observed and quantified and would accelerate the understanding of coronary artery disease formation and treatment. Advances in the technology of FD-OCT have improved the ease of use and broadened the application of OCT from a research diagnostic tool toward an established technique for guiding coronary procedures.

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REFERENCES

1. Tanaka A, Tearney GJ, Bouma BE: Challenges on the frontier of intracoronary imaging: atherosclerotic plaque macrophage measurement by optical coherence tomography. *J Biomed Opt* 15: 011104, 2010.
2. Templin C, Meyer M, Müller MF, et al: Coronary optical frequency domain imaging (OFDI) for in vivo evaluation of stent healing: comparison with light and electron microscopy. *Eur Heart J* 31:1792–1801, 2010.
3. Kull S, Celi S, Bertì S, et al: Pre-implant evaluation of tissue engineered small diameter vascular grafts with optical coherence tomography: preliminary results on bench-test. In Bàrtolo P, editor: *Proceedings ECCOMAS, International Conference on Tissue Engineering (ICTE) 2009*, Portugal, 2009, Leiria, pp 301–308.
4. Gonzalo N, García-García HM, Serruys PW, et al: Reproducibility of quantitative optical coherence tomography for stent analysis. *EuroIntervention* 5:224–232, 2009.
5. Yin J, Yang HC, Li X, et al: Integrated intravascular optical coherence tomography ultrasound imaging system. *J Biomed Opt* 15: 0105121–0105123, 2010.
6. Lee S, Lee MW, Cho HS, et al: Fully integrated high-speed intravascular optical coherence tomography/near infrared fluorescence structural/molecular imaging in vivo using a clinically available near-infrared fluorescence-emitting indocyaninegreen to detect inflamed lipid-rich atheromata in coronary-sized vessels. *Circ Cardiovasc Interv* 7(4):560–569, 2014.
7. Bezerra HG, Costa MA, Guagliumi G, et al: Intracoronary optical coherence tomography: a comprehensive review clinical and research applications. *JACC Cardiovasc Interv* 2:1035–1046, 2009.
8. Tearney GJ, Waxman S, Shishkov M, et al: Three-dimensional coronary artery microscopy by intracoronary optical frequency domain imaging. *JACC Cardiovasc Imaging* 1:752–761, 2008.
9. Yun SH, Tearney GJ, Vakoc BJ, et al: Comprehensive volumetric optical microscopy in vivo. *Nat Med* 12:1429–1433, 2006.
10. Liu L, Gardecki JA, Nadkarni SK, et al: Imaging the subcellular structure of human coronary atherosclerosis using micro-optical coherence tomography. *Nat Med* 17(8):1010–1014, 2011.
11. Yamaguchi T, Terashima M, Akasaka T, et al: Safety and feasibility of an intravascular optical coherence tomography image wire system in the clinical setting. *Am J Cardiol* 101:562–567, 2008.
12. Prati F, Cera F, Ramazzotti V, et al: Safety and feasibility of a new non-occlusive technique for facilitated intracoronary optical coherence tomography (OCT) acquisition in various clinical and anatomical scenarios. *EuroIntervention* 3:365–370, 2007.
13. Barlis P, Gonzalo N, Di Mario C, et al: A multicentre evaluation of the safety of intracoronary optical coherence tomography. *EuroIntervention* 5:90–95, 2009.
14. Lehtinen T, Nammas W, Airaksinen JK, et al: Feasibility and safety of frequency-domain optical coherence tomography for coronary artery evaluation: a single-center study. *Int J Cardiovasc Imaging* 29(5):997–1005, 2013.
15. Kawase Y, Suzuki Y, Ikeno F, et al: Comparison of nonuniform rotational distortion between mechanical IVUS and OCT using a phantom model. *Ultrasound Med Biol* 33(1):67–73, 2007.
16. Kume T, Akasaka T, Kawamoto T, et al: Assessment of coronary intima-media thickness by optical coherence tomography: comparison with intravascular ultrasound. *Circ J* 69:903–907, 2005.
17. Yabushita H, Bouma BE, Houser SL, et al: Characterization of human atherosclerosis by optical coherence tomography. *Circulation* 106:1640–1645, 2002.
18. Kawasaki M, Bouma BE, Bressner J, et al: Diagnostic accuracy of optical coherence tomography and integrated backscatter intravascular ultrasound images for tissue characterization of human coronary plaques. *J Am Coll Cardiol* 48:81–88, 2006.
19. Kume T, Akasaka T, Kawamoto T, et al: Assessment of coronary arterial thrombus by optical coherence tomography. *Am J Cardiol* 97:1713–1717, 2006.
20. Gonzalo N, Serruys PW, García-García HM, et al: Quantitative ex vivo and in vivo comparison of lumen dimensions measured by optical coherence tomography and intravascular ultrasound in human coronary arteries. *Rev Esp Cardiol* 62:615–624, 2009.
21. Tearney GJ, Yabushita H, Houser SL, et al: Quantification of macrophage content in atherosclerotic plaques by optical coherence tomography. *Circulation* 107:113–119, 2003.
21a. Phipps JE, Vela D, Hoyt T, et al: Macrophages and intravascular OCT bright spots: a quantitative study. *JACC Cardiovasc Imaging* 8(1):63–72, 2015.
22. Tearney GJ, Regar E, Akasaka T, et al: Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol* 59(12): 1058–1072, 2012.
23. Nakano M, Vorpahl M, Otsuka F, et al: Ex vivo assessment of vascular response to coronary stents by optical frequency domain imaging. *JACC Cardiovasc Imaging* 5(1):71–82, 2012.
24. Siegel RJ, Swan K, Edwalds G, et al: Limitations of postmortem assessment of human coronary artery size and luminal narrowing: differential effects of tissue fixation and processing on vessels with different degrees of atherosclerosis. *J Am Coll Cardiol* 5:342–346, 1985.
25. Murata A, Wallace-Bradley D, Tellez A, et al: Accuracy of optical coherence tomography in the evaluation of neointimal coverage after stent implantation. *JACC Cardiovasc Imaging* 3:76–84, 2010.
26. Fedele S, Biondi-Zoccai G, Kwiatkowski P, et al: Reproducibility of coronary optical coherence tomography for lumen and length measurements in humans (The CLI-VAR [Centro per la Lotta contro l'Infarto-VARiability] study). *Am J Cardiol* 110(8):1106–1112, 2012.
27. Jamil Z, Tearney G, Bruining N, et al: Interstudy reproducibility of the second generation, Fourier domain optical coherence tomography in patients with coronary artery disease and comparison with intravascular ultrasound: a study applying automated contour detection. *Int J Cardiovasc Imaging* 29:39–51, 2013.
28. Sihan K, Botha C, Post F, et al: Fully automatic three-dimensional quantitative analysis of intracoronary optical coherence tomography: method and validation. *Catheter Cardiovasc Interv* 74:1058–1065, 2009.
29. Kubo T, Akasaka T, Shite J, et al: OCT compared with IVUS in a coronary lesion assessment: the OPUS-CLASS study. *J Am Coll Cardiol Imaging* 6:1095–1104, 2013.
30. Tanaka A, Imanishi T, Kitabata H, et al: Morphology of exertion-triggered plaque rupture in patients with acute coronary syndrome: an optical coherence tomography study. *Circulation* 118:2368–2373, 2008.
31. Kubo T, Imanishi T, Takarada S, et al: Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angioscopy. *J Am Coll Cardiol* 50:933–939, 2007.
32. Kubo T, Imanishi T, Takarada S, et al: Implication of plaque color classification for assessing plaque vulnerability: a coronary angioscopy and optical coherence tomography investigation. *JACC Cardiovasc Interv* 1:74–80, 2008.
33. Tanaka A, Imanishi T, Kitabata H, et al: Distribution and frequency of thin-capped fibroatheromas and ruptured plaques in the entire culprit coronary artery in patients with acute coronary syndrome as determined by optical coherence tomography. *Am J Cardiol* 102:975–979, 2008.
34. Kume T, Akasaka T, Kawamoto T, et al: Measurement of the thickness of the fibrous cap by optical coherence tomography. *Am Heart J* 152:e1–e4, 2006.
35. Sawada T, Shite J, García-García HM, et al: Feasibility of combined use of intravascular ultrasound radiofrequency data analysis and optical coherence tomography for detecting thin-cap fibroatheroma. *Eur Heart J* 29:1136–1146, 2008.
36. Jang IK, Tearney GJ, MacNeill B, et al: In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography. *Circulation* 111:1551–1555, 2005.
37. Fujii K, Masutani M, Okumura T, et al: Frequency and predictor of coronary thin-cap fibroatheroma in patients with acute myocardial infarction and stable angina pectoris: a 3-vessel optical coherence tomography study. *J Am Coll Cardiol* 52:787–788, 2008.
38. Takarada S, Imanishi T, Kubo T, et al: Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome: assessment by optical coherence tomography study. *Atherosclerosis* 202:491–497, 2009.
39. Burke A, Virmani R, Galis Z, et al: What is the pathologic basis for new atherosclerosis imaging techniques? *J Am Coll Cardiol* 41:1855–1917, 2003.
40. Prati F, Uemura S, Souteyrand G, et al: OCT-based diagnosis and management of STEMI associated with intact fibrous cap. *JACC Cardiovasc Imaging* 6:283–287, 2013.
41. Jia H, Abtahian F, Aguirre AD, et al: In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. *J Am Coll Cardiol* 62:1748–1758, 2013.
42. Guagliumi G, Capodanno D, Saia F: Mechanisms of atherothrombosis and vascular response to primary percutaneous coronary intervention in women versus men with acute myocardial infarction: results of the OCTAVIA (Optical Coherence Tomography Assessment of Gender Diversity in Primary Angioplasty) study. *JACC Cardiovasc Interv* 7:958–968, 2014.
43. Souteyrand G, Amabile N, Combaret N, et al: Invasive management without stents in selected acute coronary syndrome patients with a large thrombus burden: a prospective study of optical coherence tomography guided treatment decisions. *EuroIntervention* 2014 Jul 19. pii: 20130704-03. doi: 10.4244/EIJY14M07_18. [Epub ahead of print].
44. Uemura S, Ishigami K, Soeda T, et al: Thin-cap fibroatheroma and microchannel findings in optical coherence tomography correlate with subsequent progression of coronary atheromatous plaques. *Eur Heart J* 33:78–85, 2012.
45. Yonetsu T, Kakuta T, Lee T, et al: In vivo critical fibrous cap thickness for rupture-prone coronary plaques assessed by optical coherence tomography. *Eur Heart J* 32:1251–1259, 2011.
46. Guo J, Chen YD, Tian F, et al: Thrombosis and morphology of plaque rupture using optical coherence tomography. *Chin Med J (Engl)* 126:1092–1095, 2013.
47. Guagliumi G, Sirbu V: Optical coherence tomography: high resolution intravascular imaging to evaluate vascular healing after coronary stenting. *Catheter Cardiovasc Interv* 72:237–247, 2008.
48. Allahwala UK, Cockburn JA, Shaw E, et al: Clinical utility of optical coherence tomography (OCT) in the optimisation of Absorb bioresorbable vascular scaffold deployment during

percutaneous coronary intervention. *EuroIntervention* 10(11): 1154–1159, 2015.
49. Sawada T, Shite J, Negi N, et al: Factors that influence measurements and accurate evaluation of stent apposition by optical coherence tomography assessment using a phantom model. *Circ J* 73:1841–1847, 2009.
50. Guagliumi G, Musumeci G, Sirbu V, et al: Optical coherence tomography assessment of in vivo vascular response after implantation of overlapping bare-metal and drug-eluting stents. *JACC Cardiovasc Interv* 3:531–539, 2010.
51. Guagliumi G, Sirbu V, Bezerra H, et al: Strut coverage and vessel wall response to zotarolimus-eluting and bare-metal stents implanted in patients with ST-segment elevation myocardial infarction: the OCTAMI (Optical Coherence Tomography in Acute Myocardial Infarction) study. *JACC Cardiovasc Interv* 3:680–687, 2010.
52. Ozaki Y, Okumura M, Ismail TF, et al: The fate of incomplete stent apposition with drug-eluting stents: an optical coherence tomography-based natural history study. *Eur Heart J* 31:1470–1476, 2010.
53. Inoue T, Shinke T, Otake H, et al: Impact of strut-vessel distance and underlying plaque type on the resolution of acute strut malapposition: serial optimal coherence tomography analysis after everolimus-eluting stent implantation. *Int J Cardiovasc Imaging* 30:857–865, 2014.
54. Kubo T, Imanishi T, Kitabata H, et al: Comparison of vascular response after sirolimus-eluting stent implantation between patients with unstable and stable angina pectoris: a serial optical coherence tomography study. *JACC Cardiovasc Imaging* 1:475–484, 2008.
55. Gonzalo N, Serruys PW, Okamura T, et al: Optical coherence tomography assessment of the acute effects of stent implantation on the vessel wall: a systematic quantitative approach. *Heart* 95:1913–1919, 2009.
56. Kawamori H, Shite J, Shinke T, et al: The ability of optical coherence tomography to monitor percutaneous coronary intervention: detailed comparison with intravascular ultrasound. *J Invasive Cardiol* 22:541–545, 2010.
57. Chamié D, Bezerra HG, Attizzani GF, et al: Incidence, predictors, morphological characteristics, and clinical outcomes of stent edge dissections detected by optical coherence tomography. *JACC Cardiovasc Interv* 6(8):800–813, 2013.
58. Radu MD, Räber L, Heo J, et al: Natural history of optical coherence tomography-detected non-flow-limiting edge dissections following drug-eluting stent implantation. *EuroIntervention* 9: 1085–1094, 2014.
59. Prati F, Di Vito L, Biondi-Zoccai G, et al: Angiography alone versus angiography plus optical coherence tomography to guide decision-making during percutaneous coronary intervention: the Centro per la Lotta contro l'Infarto-Optimisation of Percutaneous Coronary Intervention (CLI-OPCI) study. *EuroIntervention* 8:823–829, 2012.
60. Takano M, Yamamoto M, Inami S, et al: Appearance of lipid-laden intima and neovascularization after implantation of bare-metal stents extended late-phase observation by intracoronary optical coherence tomography. *J Am Coll Cardiol* 55:26–32, 2010.
61. Matsumoto D, Shite J, Shinke T, et al: Neointimal coverage of sirolimus-eluting stents at 6-month follow-up: evaluated by optical coherence tomography. *Eur Heart J* 28:918–919, 2007.
62. Katoh H, Shite J, Shinke T, et al: Delayed neointimalization on sirolimus-eluting stents: 6-month and 12-month follow up by optical coherence tomography. *Circ J* 73:1033–1037, 2009.
63. Guagliumi G, Capodanno D, Ikejima H, et al: Impact of different stent alloys on human vascular response to everolimus-eluting stent: an optical coherence tomography study, the OCTEVEREST. *Catheter Cardiovasc Interv* 81:510–518, 2013.
64. Guagliumi G, Costa MA, Sirbu V, et al: Strut coverage and late malapposition with paclitaxel-eluting stents compared with bare metal stents in acute myocardial infarction: optical coherence tomography substudy of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. *Circulation* 123:274–281, 2011.
65. Barlis P, Regar E, Serruys PW, et al: An optical coherence tomography study of a biodegradable vs. durable polymer-coated limus-eluting stent: a LEADERS trial sub-study. *Eur Heart J* 31:165–176, 2010.
66. Nakazawa G, Vorpahl M, Finn AV, et al: One step forward and two steps back with drug-eluting-stents: from preventing restenosis to causing late thrombosis and nouveau atherosclerosis. *JACC Cardiovasc Imaging* 2:625–628, 2009.
67. Gonzalo N, Serruys PW, Okamura T, et al: Optical coherence tomography patterns of stent restenosis. *Am Heart J* 158(2):284–293, 2009.
68. Otsuka F, Vorpahl M, Nakano M, et al: Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. *Circulation* 129:211–223, 2014.
69. Nakazawa G, Otsuka F, Nakano M, et al: The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol* 57(11):1314–1322, 2011.
70. Yonetsu T, Kim JS, Kato K, et al: Comparison of incidence and time course of neoatherosclerosis between bare metal stents and drug-eluting stents using optical coherence tomography. *Am J Cardiol* 110(7):933–939, 2012.
71. Ali ZA, Roleder T, Narula J, et al: Increased thin-cap neoatheroma and periprocedural myocardial infarction in drug-eluting stent restenosis: multimodality intravascular imaging of drug-eluting and bare-metal stents. *Circ Cardiovasc Interv* 6(5):507–517, 2013.
72. Kozuki A, Shinke T, Otake H, et al: Temporal course of vessel healing and neoatherosclerosis after DES implantation. *JACC Cardiovasc Imaging* 6:1121–1123, 2013.
73. Kang SJ, Mintz GS, Akasaka T, et al: Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. *Circulation* 123(25):2954–2963, 2011.
74. Tian J, Ren X, Uemura S, et al: Spatial heterogeneity of neoatherosclerosis and its relationship with neovascularization and adjacent plaque characteristics: optical coherence tomography study. *Am Heart J* 167:884–892.e2, 2014.
75. Nagai H, Ishibashi-Ueda H, Fujii K: Histology of highly echolucent regions in optical coherence tomography images from two patients with sirolimus-eluting stent restenosis. *Catheter Cardiovasc Interv* 75:961–963, 2010.
76. Komukai K, Bernelli C, Sirbu V, et al: Stent failure due to simultaneous aggressive neoatherosclerosis of first and current generation drug eluting stents, EuroIntervention (in press).
77. Parodi G, La Manna A, Di Vito L, et al: Stent-related defects in patients presenting with stent thrombosis: differences at optical coherence tomography between subacute and late/very late thrombosis in the Mechanism Of Stent Thrombosis (MOST) study. *EuroIntervention* 9(8):936–944, 2013.
78. Guagliumi G, Sirbu V, Musumeci G, et al: Examination of the in vivo mechanisms of late drug-eluting stent thrombosis: findings from optical coherence tomography and intravascular ultrasound imaging. *JACC Cardiovasc Interv* 5(1):12–20, 2012.
79. Kang SJ, Lee CW, Song H, et al: OCT analysis in patients with very late stent thrombosis. *JACC Cardiovasc Imaging* 6(6):695–703, 2013.
80. Serruys PW, Ormiston JA, Onuma Y, et al: A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. *Lancet* 373:897–910, 2009.
81. Capodanno D, Gori T, Nef H, et al: Percutaneous coronary intervention with everolimus-eluting bioresorbable vascular scaffolds in routine clinical practice: early and midterm outcomes from the European multicentre GHOST-EU registry. *EuroIntervention* 10(11):1144–1153, 2015.
82. Ferrante G, Kaplan AV, Di Mario C: Assessment with optical coherence tomography of a new strategy for bifurcational lesion treatment: the Triton side-branch stent. *Catheter Cardiovasc Interv* 73:69–72, 2009.
83. Gonzalo N, García-García HM, Regar E, et al: In vivo assessment of high-risk coronary plaques at bifurcations with combined intravascular ultrasound and optical coherence tomography. *JACC Cardiovasc Imaging* 2:473–482, 2009.
84. Kyono H, Guagliumi G, Sirbu V, et al: Optical coherence tomography (OCT) strut-level analysis of drug-eluting stents (DES) in human coronary bifurcations. *EuroIntervention* 6:69–77, 2010.
85. Alegría-Barrero E, Foin N, Chan PH, et al: Optical coherence tomography for guidance of distal cell recrossing in bifurcation stenting: choosing the right cell matters. *EuroIntervention* 8(2): 205–213, 2012.
86. Prabhudesai V, Phelan C, Yang Y, et al: The potential role of optical coherence tomography in the evaluation of vulnerable carotid atheromatous plaques: a pilot study. *Cardiovasc Intervent Radiol* 29:1039–1045, 2006.
87. Meissner OA, Rieber J, Babaryka G, et al: Intravascular optical coherence tomography: comparison with histopathology in atherosclerotic peripheral artery specimens. *J Vasc Interv Radiol* 17:343–349, 2006.
88. Karanasos A, van der Sijde JN, Ligthart J, et al: Utility of optical coherence tomography imaging with angiographic co-registration for the guidance of percutaneous coronary intervention. 2015. Available at: <http://www.radcliffecardiology.com/articles/utility-optical-coherence-tomography-imaging-angiographic-co-registration-guidance>. Accessed August 3, 2015.
89. Nadkarni SK, Pierce MC, Park BH, et al: Measurement of collagen and smooth muscle cell content in atherosclerotic plaques using polarization-sensitive optical coherence tomography. *J Am Coll Cardiol* 49:1474–1481, 2007.
90. Tearney GJ, Waxman S, Shishkov M, et al: Three-dimensional coronary artery microscopy by intracoronary optical frequency domain imaging. *JACC Cardiovasc Imaging* 1:752–761, 2008.

Medical Economics and Interventional Cardiology

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KEY POINTS

- Three forms of full economic evaluations that do not assume equivalence of health outcomes are cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA).
- CEA and CUA are widely used to decide whether a medical intervention is economically attractive; CBA is used much less often for this purpose.
- CEA and CUA assess the incremental costs for a therapy or strategy to produce an incremental unit of health benefit.
- Health benefits are traditionally assessed as the number of added life years or quality-adjusted life years.
- Costs and benefits are usually assessed for a designated period, typically a lifetime time horizon that requires assessing future costs and health benefits.
- Future costs and health effects are commonly weighted in relation to the time at which they occur, and they usually receive less weight than current ones.
- Three types of medical cost studies are cost-effectiveness simulations using Markov models, observational studies, and randomized controlled trials.
- Although a scientific approach demands use of cost-effectiveness acceptability curves when assessing whether a treatment is cost-effective, thresholds may be used when policy makers seek a benchmark with which to evaluate treatments and studies.

New and expensive medical technologies and treatments have contributed to the steady increase in health care costs.[1] The past 10 years have witnessed an expansion in the diagnostic and therapeutic tools used in coronary interventions and the introduction of catheter-based interventions for noncoronary cardiac conditions.

Although percutaneous coronary intervention (PCI) remains a common major medical procedure in the United States, data suggest that the volume of PCIs is declining or expected to grow minimally in the near future.[2-4] However, there is significant expansion in the volume of noncoronary interventions, including those for peripheral arterial and structural heart diseases, and a concomitant increase in the involvement of interventional cardiologists in these procedures.[5]

Understanding basic concepts of medical economics has become a necessity because of changes in the field, an aging population, and limitations on resources and reimbursements engendered by the Patient Protection and Affordable Care Act. This chapter provides an overview of medical economics and evaluates the economics of various aspects of interventional cardiology.

MEDICAL ECONOMICS: CONCEPTS AND METHODS

A fundamental concept of economics is that resources are limited and can never satisfy all societal wants. When resources are used for health care, they are unavailable for other uses, such as education, infrastructure, and the environment. Cost is more than money required to provide a particular good or service; it is an *opportunity cost* that represents the consumption of the society's resources required to produce a good or service that could have been used for other purposes.[1]

Because opportunity cost remains a fundamental concept rather than a real measurement tool, other metrics for cost are necessary. The typical accounting price that is used in the regular market, which adds a reasonable amount of profit to the cost of production, is not clearly applicable in the U.S. medical field due to cost shifting of many other expenses, such as bad debts, rejected payment by third parties, and fees for services, including employee salaries, cost of maintenance, and expansion of services.[6] Because the addition of cost-shifting fees distorts the relationship between U.S. medical charges and medical resource consumption, the charges should not be used as a surrogate for medical costs in research and policy evaluations.[6]

Other cost concepts used in medical economics include average cost, marginal cost, incremental cost, induced cost, and indirect cost. *Average cost* is overall cost per unit; it is the total cost divided by the total number of units of production. *Marginal cost* is the cost of producing one additional (or one less) unit of product, such as a PCI or coronary bypass operation. It excludes costs that do not vary as a direct function of production (i.e., fixed costs), such as the cost of the interventional laboratory or operating room facilities.

Incremental cost is the extra cost associated with an expansion in activity of a given service. Incremental cost is particularly useful in focusing on the costs of shifting groups of patients from one diagnostic or therapeutic strategy to another, and it is essential in economic evaluations. For example, when a hospital is starting a transcatheter aortic valve replacement (TAVR) program, the incremental cost adjusts for the cost of hiring specialists who perform this procedure or training an existing interventional cardiologist, hiring a TAVR coordinator, training the catheter laboratory staff about the procedure, and new equipment for or adjustment to the existing catheter laboratory or operating room.

Induced cost (or savings) is the cost of the tests or therapies added or averted as a consequence of an initial management decision or resource use, or both. For example, interventions that may cause more complications increase the use of resources, whereas an intervention that decreases complications or resource use may reduce (save) cost.[6]

Medical Economics Terminology

Overall economic evaluations provide vital information to decision makers on the inputs and outcomes of a health or medical intervention compared with available alternatives.[7] These analyses build on the

results of clinical effectiveness studies but go beyond them to include a broader view of clinical, humanistic, and economic outcomes.[8]

Clinical outcomes are medical events that are considered meaningful by medical professionals. Humanistic outcomes include a broad array of intangible personal attributes, typically self-reported by patients, such as quality of life and spiritual well-being.[7] Economic outcomes represent the consumption and production of resources and their monetary value from the perspective of a decision maker.[7] A full economic evaluation is a study that compares one or more interventions or approaches with a defined standard of care, especially the cost of each intervention or approach in relation to the effects (i.e., benefits or returns) of each. Comparing only investment costs between interventions or approaches is considered a partial economic evaluation.[9]

Cost Measurement

A thorough economic evaluation should account for all relevant costs. It includes the costs for the new treatment or test, concomitant therapy, and treating complications and subsequent events. For example, a new treatment for acute coronary syndrome (ACS) may increase bleeding but reduce stent thrombosis or recurrent myocardial infarction (MI) and therefore the risk and cost of readmission. Fair evaluation must account for the extra cost of increased bleeding and the potential savings for decreased rates of recurrent MI.[1]

The time frame for the economic evaluation needs to be long enough to encompass all costs resulting from a particular intervention because subsequent and long-term clinical complications may be decreased or increased by a treatment or test. Although some therapies may pay for themselves with immediate savings, others may have higher costs initially but later have significant savings. Economic evaluation must have sufficient scope to account for all relevant costs, including early and late adverse events.[1] Because costs may accrue over a lifetime, a lifetime time horizon is the most inclusive, although it may not always be feasible.

Evaluation of Procedure and Hospital Costs

Evaluation of the true cost of a specific procedure and the associated hospital stay is a challenging process. In practice, it is difficult and often impractical to obtain detailed data on the resources being consumed for an intervention and to add all costs to perform a marginal or incremental cost analysis (i.e., bottom-up approach). Performing a bottom-up cost analysis (i.e., microcosting analysis) is a complex, time-consuming process that requires identification of all the inputs into a health care service and assignment of an appropriate cost to each. Even if this process is achievable for simple treatments, it becomes complicated when considering a complex interventional procedure such as a PCI and very complicated when accounting for the entire hospital stay from admission to discharge.[1] Therefore most U.S. cost studies start with an aggregated measure of costs, such as can be obtained from hospital or physician bills (i.e., top-down analysis).

To overcome the complexity, cost data in the United States are obtained mainly by one of two approaches. The first approach involves converting hospital charges (from hospital bills) to costs using the ratios of costs to charges (RCCs) included in each hospital's annual Medicare Cost Report. This report is based on annual reporting of every hospital to the Centers for Medicare and Medicaid Services (CMS) that includes details of expenses for direct patient care, overhead, capital equipment, and other expenditures related to billed charges. Although the Medicare RCCs are not designed for research, they provide a moderately standardized means of estimating cost across hospitals in the United States. Costs calculated with the RCC method also are used to recalibrate diagnosis-related group (DRG) weights by the CMS.

The method provides a valuable tool for multicenter cost research, but it has several limitations. First, the approach does not separate overhead from most other fixed costs and therefore provides an estimate of average rather than marginal cost, and it may overestimate potential cost savings. Second, due to the complexity of the instructions for reporting to the CMS, hospitals may choose to interpret the instructions differently, which results in significant variability in uncovering the hospital's actual cost of providing care. Third, the RCCs are an average of all cost-charge relationships within a large hospital revenue (ancillary) center such as the radiology, pharmacy, or laboratory departments, and the Medicare RCCs may not be particularly accurate in converting these charges to costs if the individual patient's resource consumption is not averaged appropriately. The RCC method is limited to hospitals using standardized methods of billing, which are applicable to most U.S. hospitals but no hospitals outside the United States, and it requires access to patients' bills. Physician costs are not included in this approach.[6]

The second approach depends on calculating the hospital and intervention costs from reimbursement rates for DRGs reported to the CMS by hospitals. This approach also has limitations. First, it is not sensitive to variations in resource-use intensity within a DRG because DRG reimbursement rates represent the average cost for a particular diagnosis or procedure among all patients in that DRG. Second, the CMS decides in many cases not to increase reimbursement to cover the costs of a new technology, and the cost of new technologies may therefore not be reflected in the DRG.[6] However, this approach does not require collection of hospital bills, and with some assumptions, it can be applied to any hospitalization in any health care system, which simplifies its use. By assigning DRGs to hospitalizations within studies when DRGs from hospital bills are not available, this approach can be used for international studies. Assigning costs to a DRG for hospitalization in international studies is complicated and controversial.[6,10]

Many studies estimate costs by counting only big-ticket items used, such as the number of diagnostic cardiac catheterizations, PCIs, or coronary artery bypass grafting (CABG) procedures; days in the intensive care unit (ICU); and total hospital length of stay. A unit price is then assigned to each item. The resulting linear formula (total cost $\approx \Sigma$ price $\times$ quantity) is simple and inexpensive to use, which make it desirable in clinical research.

The approach also has some significant disadvantages. First, the source of cost weights is often acquired from available unrelated economic sources external to the resource data being analyzed, and it is therefore of uncertain quality. Second, the appropriate set of big-ticket items necessary to estimate costs accurately by this method has never been rigorously defined. For example, some studies, especially multicenter clinical trials, may use the more easily obtained total hospital length of stay instead of defining specific ICU and non-ICU hospital lengths of stay, which may be more representative of accurate costs. Third, most studies treat big-ticket items similarly to preserve the desired simplicity, although they are not necessarily homogeneous. For example, by using payments according to the DRG, an uncomplicated, single-vessel PCI would typically be assigned the same price as a complex, three-vessel PCI or complex graft intervention that was complicated by abrupt closure, but the true costs of these procedures are substantially different.[6]

Evaluation of Physician Costs

Physician costs are estimated by one of two approaches. The first approach depends on acquiring the fee-for-service bills from physicians' offices. This approach has several limitations. First, most patients receive services from several physicians, and collecting bills from many offices is a far more complicated process than collecting hospital bills. Second, due to multiple services with different costs and reimbursements in physicians' offices, cost shifting is used to cover unreimbursed and underreimbursed services without the detailed report of real costs that is required by hospitals when they practice cost shifting. Using fee-for-service bills does not accurately reflect the true market price for physician services.[6]

To overcome the limitation of using physicians' bills, another approach was proposed by using the Medicare Fee Schedule based on the resource-based relative-value scale (RBRVS).[11] The RBRVS ties the price of a service to the long-term cost of providing that service.

TABLE 63-1 Types of Full Economic Assessment

Feature	Cost-Effectiveness Analysis	Cost-Utility Analysis	Cost-Benefit Analysis
Definition	Form of economic-efficiency analysis in which costs are valued in monetary terms and health benefits are valued in natural units	Variant of cost-effectiveness analysis in which health benefits are expressed on a scale that incorporates longevity and patient preferences (i.e., utilities) for the health states produced	Form of economic-efficiency analysis in which costs and outcomes (health benefits) are valued in monetary terms
Measurement	Natural units (e.g., number of added life years)	Summary measure in quality of life units (e.g., QALYs)	Summary measure in monetary units (e.g., U.S. dollars)
Results	Cost-effectiveness ratio: (C1 – C2)/(HB1 – HB2)	Cost-utility ratio: (C1 – C2)/(QALY1 – QALY2)	Net benefits: (B1 – B2) – (C1 – C2) or (B1 – B2)/(C1 – C2)

B1, Monetary value of health outcomes of alternative 1; *B2,* monetary value of health outcomes of alternative 2; *C1,* total costs of alternative 1; *C2,* total costs of alternative 2; *HB1,* health benefit of alternative 1; *HB2,* health benefit of alternative 2; *QALY1,* quality-adjusted life years of alternative 1; *QALY2,* quality-adjusted life years of alternative 2.

Depending on the data available in the report in relation to the American Medical Association's Current Procedural Terminology (CPT) classification system, physicians' costs can be estimated. This approach is not ideal, but it has the advantage of being objective and consistent, and it may represent the best available national measure of the economic value of physicians' work.[11]

Factors That Impact Cost Assessment

The different perspectives of patients, providers, health payers, and society lead to different assessments of cost. Whereas patients may consider only out-of-pocket or copayment costs, health payers consider the cost of the procedure, associated hospital costs, and whether medications are generic or nongeneric. Providers may consider cost in relation to the health benefit for an individual patient and weigh it against the public health implications of the procedure used. The cost of a health service should ideally assess the immediate cost of the strategy and consider the overall societal perspective because health care choices ultimately rest with all stakeholders in society. Societal costs include hospital costs, physician fees, outpatient testing, outpatient drug therapy costs; nonmedical direct expenses (e.g., transportation to the medical facility, child care, housekeeping); and the economic impact of lost productivity because of illness.[6,10]

Total societal cost cannot be measured effectively because each component is measured by a proxy. To eliminate some of this uncertainty, payer costs are often measured instead. However, payer costs do not represent the complete spectrum of the societal costs. Whereas CMS uses DRGs to pay hospitals regardless of the cost of service to the provider, private insurance may use a different scheme to pay providers. Payments may therefore significantly vary between payers.[10]

Time effects are important to medical cost analyses because inflation and deflation change the cost of a procedure. A common approach is to pick a base year and use the medical inflation rate to deflate all costs in subsequent years to the base year.[6,10,12]

Another important factor in determining cost is geography. The costs of material and labor inputs to medical care can vary substantially from one part of the country to another and between large urban university hospitals and small rural community hospitals. The differences in cost for medical services according to geography need to be adjusted. Several geographic adjustment indices are available, including the Medicare area wage index for adjusting DRG reimbursement and the Medicare Fee Schedule geographic adjustment factor.[6,10,12] International studies require more complex adjustments.

Analytic Methods

Several forms of economic evaluations can be performed, and each is based on the selection and measurement of health outcomes. Although the term *cost-effectiveness* is frequently used for all medical economic analyses, it is only one type of assessment. The most basic form of economic evaluation is called a *cost-consequence study*, which is a table that lists the individual economic and health outcomes of alternative interventions.

A more advanced but still basic economic form is called a *cost identification study*, which measures only the investment cost of interventions and is used to provide the data needed to better design future studies that consider the economic and health outcomes of two or more alternative therapies. Another advanced form of economic assessment is called *cost minimization analysis* (CMA), which differs from cost identification in assuming equivalence in health outcomes among alternative therapies and examines economic outcomes. Although it examines only economic outcomes, under the assumption of equivalence, a CMA is in practice a form of full economic evaluation.[7]

Three forms of full economic evaluations do not assume equivalence of health outcomes: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). Their definitions and differences are summarized in Table 63-1.[7] Whereas CEA and CUA are widely used to decide whether a medical intervention is economically attractive, CBA is used much less often because it requires measuring all health-related benefits of an intervention or approach in monetary terms without emphasis on the longevity or quality of the lives involved.[7]

The primary goal of CEA is to evaluate health care intervention options in common terms so that policy and other decision makers can be informed about the most efficient method of producing extra health benefits from among the alternative ways that health care dollars can be distributed. In CEA and CUA, the metric used to assess cost-effectiveness is the incremental cost-effectiveness ratio (ICER). An ICER is the ratio of incremental costs to incremental health benefits, or ICER = (C1 – C2)/(HB1 – HB2), in which C1 and C2 are the costs for treatment 1 and 2, respectively, and HB1 and HB2 are the health benefits of treatment 1 and 2, respectively.[1]

ICER is a ratio that has a distribution because there is uncertainty in the cost and effectiveness measurements. When patient-level data are available, it is possible to consider the uncertainty in cost and effectiveness due to the play of chance (i.e., stochastic error). To examine the confidence intervals of cost and effectiveness due to the play of chance, an approach called *bootstrap analysis* is widely used.[13] It depends on sampling the cost and effectiveness distributions concurrently, which allows multiple estimates of the ICER to be made and plotted as a pictorial four-quadrant distribution (Fig. 63-1).

The ICER defines the cost that should be assumed for gaining one unit of output. If one of the alternatives is the usual practice, the ICER can reveal how much it costs to gain a unit of outcome when moving from the usual practice to the alternative. The health benefit may be measured in any sensible unit, such as the number of MIs averted, but most economic analyses use the conventional option of measuring clinical benefits as the number of added life years (LYs) or quality-adjusted life years (QALYs).[1,14] Both approaches require estimation of life expectancy with and without the proposed intervention.

Although LYs are conceptually simple because the estimation depends only on survival, many therapies are used primarily to improve

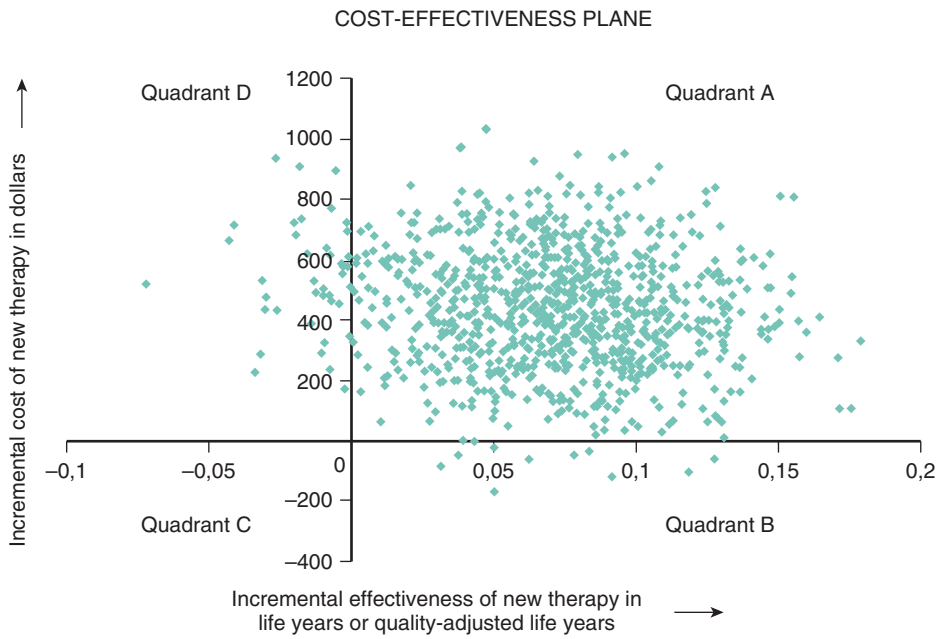

FIGURE 63-1 Distribution of cost-effectiveness. In quadrant A, the new therapy is more effective and more costly than the previous standard. In quadrant B, the new therapy dominates the standard because it is more effective and less expensive. In quadrant C, the new therapy is less effective and less expensive. In quadrant D, the new therapy is dominated by the standard because it is less effective and more expensive. *Dots* represent individual estimations of the incremental cost-effectiveness ratio from the dual bootstrap analysis.

quality of life rather than to increase longevity, and a broader measurement if QALYS is needed. To estimate QALYS, it is first necessary to estimate utility. *Utility* is the relative desirability of a particular health outcome or health state, assessed as the preference of a rater (typically a patient or member of the general public) for that outcome relative to the defined and extreme alternatives (e.g., death, excellent health). Every health state has a unique utility.

In health care economics, utility usually is scaled from 0 to 1 with a utility of 0 for death and 1 for perfect health and functioning. The relationship between utility and cost can be assessed by CUA with the use of QALYs, which is life expectancy multiplied by utility. The value of 1 year of life in excellent health is represented by 1.0 QALY (i.e., one LY multiplied by a utility of 1).[1]

Utility Assessment

Utility may be measured by patient preference methods or by surveys that have been mapped to patient preference methods. Theoretically, the best direct measure of utility is the standard gamble method because it assesses overall quality of life and risk aversion. However, this measure is difficult to obtain and may not be practical to administer in large trials.[15]

Most economic analyses derive utilities from surveys (e.g., EuroQol-5D, Health Utilities Index). Using this method, patient health states are defined by a number of explicit domains, such as physical functioning and pain. Previously measured utility weights from patients (i.e., those with the condition of interest) or the general public (i.e., those who are at risk for the condition of interest) are assigned to each possible health state.[1]

Time Horizon and Discounting

The *time horizon* of an analysis reflects the period over which clinical health benefits and costs should be considered and included in the analysis. The time frame should be the same for the clinical outcomes and costs. Although the time for many trials may be limited to a short or intermediate time horizon due to limitations in budgets and enrollment, the evaluation of cost-effectiveness from the societal perspective requires a long-term or lifetime time horizon.[16]

Assessing the cost-effectiveness over a lifetime horizon requires assessment of future costs and health benefits. Future costs and health gains are commonly weighted in relation to the time at which they occur, and future costs and health effects usually receive less weight than current ones. This process is called *discounting*.[17]

Discounting assumes that money available or spent now is more valuable than money available or spent in the future because money available now can be put to immediate use. Because costs are discounted, the benefits of health interventions must also be discounted. Discounting is not an adjustment for inflation, which is a separate consideration. Even in the absence of inflation, most individuals prefer to have an equivalent health benefit or money now rather than in the future. The discount rate captures this time preference. When data for costs are derived from different years, older costs are usually inflated to their equivalent values in more recent years to provide a consistent economic basis. If future medical inflation costs rise uniformly, future purchasing power for health care remains the same, and there is no need to adjust for medical inflation.[17]

Sensitivity Analysis

Even in the most carefully conducted cost-effectiveness studies, considerable uncertainty may remain regarding the parameters used to measure costs and health effects. Accounting for the play of chance with bootstrap analysis is not sufficient to explain the additional uncertainty or bias.

To identify and assess the degree to which uncertainty in the parameter may affect the overall results, CEAs usually perform multiple evaluations in which one or more of the parameters are varied across reasonable ranges. The ranges reflect intrinsic variability or regional variation. For example, the cost of diagnostic cardiac catheterization may be cheaper in some institutions or health care delivery settings compared with others, and to determine the cost-effectiveness of PCI in patients with stable coronary artery disease (CAD), the cost of PCI can be varied over a range to determine the maximal cost at which it remains cost-effective. This process (i.e., sensitivity analysis) enables a reasonable appraisal about the parameters that are most important in the analysis and the stability of the reference case results.[16]

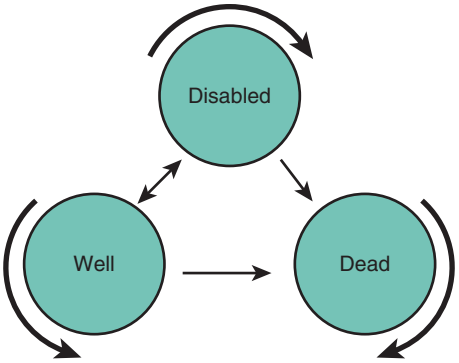

FIGURE 63-2 Movement among Markov states of health.

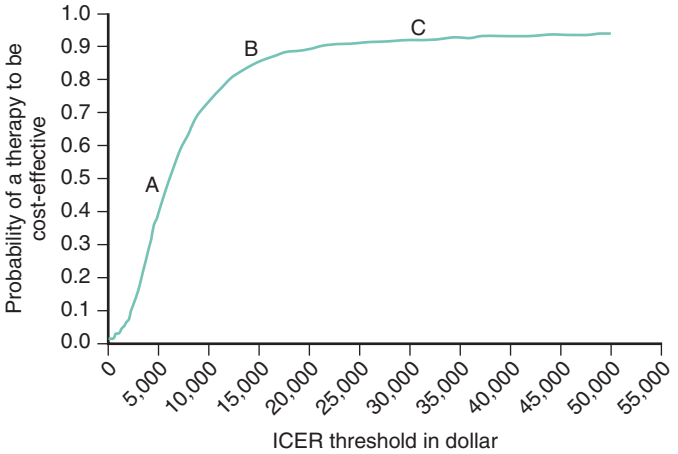

FIGURE 63-3 Cost-effectiveness acceptability curve. Points A, B, and C represent increasing willingness-to-pay thresholds. Point A is the lowest, and there is a low probability of the new therapy being considered cost-effective. Point C is the highest willingness-to-pay threshold with the highest probability of the new therapy being cost-effective. Point B is in between. *ICER,* Incremental cost-effectiveness ratio.

Sensitivity analyses have typically assessed the effect of varying selected parameters related to cost-effectiveness one at a time. A more contemporary approach, called a *Monte Carlo simulation*, permits all parameters to be varied simultaneously. These sophisticated analyses yield a cost-effectiveness acceptability curve, which accounts for uncertainty in all model estimates. The curve generated displays the likelihood that a new intervention will have a cost-effectiveness ratio that falls below a particular societal willingness to pay (see "Benchmarks in Economic Analysis").[16]

DATA SOURCES FOR ECONOMIC ANALYSIS AND DECISION MAKING

The three main types of medical cost studies are cost-effectiveness simulations using Markov models, observational studies, and randomized controlled trials (RCTs).

Simulation With Markov Models

Many economic analyses are developed as simulations. Simulations most commonly involve the construction of a decision tree to model the prognosis of a patient after the choice of a management strategy.

The Markov model is widely used in CEA because it is a convenient way of modeling prognosis for clinical problems with ongoing risks. The model assumes that the patient is always in one of a finite number of states of health referred to as *Markov states* (Fig. 63-2). Introduction of the intervention may cause the patient to move to another Markov state. The transition from one state to another represents the events of interest, and the time of this transition is referred to as a *Markov cycle*. Cumulative QALYs are calculated by assigning a utility to each health state and running the model for health cycles until death, Similarly, costs are accumulated during the Markov cycles. The incremental costs of an intervention compared with a previous standard divided by the incremental benefits yields an ICER.

Markov models are often informed by the medical literature, including RCTs when available. For example, patients with stable CAD who undergo CABG may move from being disabled by angina to being well, may remain disabled, or may die (see Fig. 63-2). Patients who die do not move to another state, whereas disabled or well patients may move from one health state to another. Assuming that the incremental utility of the well state is 1.0, that of the dead state is 0, and that of disabled states is 0.6, if the patient spends an average of 2.5 cycles in the well state and 1.25 cycles in the disabled state before entering the dead state, the utility assigned would be $(2.5 \times 1) + (1.25 \times 0.6) = 3.25$ quality-adjusted cycles. This number is the quality-adjusted life expectancy of the patient.[18]

Cost-Effectiveness Analysis With Patient-Level Data

Observational cost studies include descriptive series without an intrinsic comparison group and nonrandomized treatment comparisons. Descriptive cost studies are useful when data about cost are not readily available in the literature, and they are typically used to make sample size projections for RCTs or to inform cost-effectiveness and other health policy studies in conjunction with appropriate sensitivity analyses. Observational comparison data can be helpful in estimating the real-world cost outside the restrictions or requirements of an RCT, but they usually require statistical techniques to adjust for treatment selection bias and for bias that may be related to variations in medical costs over time, in various geographic locations, and in different practice settings.

A second major approach to economic evaluation is measurement of economic cost as an end point in an RCT. Strengths of this approach include (1) using prospective, complete data collection; (2) a well-defined protocol that measures directly the economic and clinical outcomes with few assumptions and little simulation; (3) random assignment to eliminate treatment selection bias; (4) concomitant collection of economic and clinical data that alleviates concerns about inconsistencies among data sources; and (5) collection of patient-level data, permitting estimation of stochastic error. A potential disadvantage is that RCTs mandate protocol-driven care that can deviate from usual clinical practice (i.e., extra protocol-driven angiography or mandated office follow-up visits) and that distort resource use patterns, making them unsuitable for economic analysis. Another limitation is that the high selection criteria for patients involved in the trial may render the cost analysis inapplicable to the general population.

Clinical trials usually have a time frame of weeks to several years. If the study is using a lifetime time horizon for the CEA, survival, utility, and cost must be estimated beyond the time frame of measured data.[6,10,12]

Benchmarks in Economic Analysis

Patients and their physicians wish to obtain all of the health benefits that are available from modern medical technology. However, the resources of a society are not adequate to meet this need for every individual, which forces difficult and potentially divisive choices. There is no absolute standard that can be applied to assess how much a certain society is willing to pay for medical care.

Willingness to pay may be better understood by constructing a cost-effectiveness acceptability curve (Fig. 63-3), in which a range of ICER willingness-to-pay thresholds are displayed on the x-axis, and the y-axis indicates the probability that the new therapy has an ICER

below this threshold. The curve can be constructed from Markov model simulations or from patient-level data. The curve can be used to estimate what is acceptable for a treatment.

Although from scientific standpoint cost-effectiveness acceptability curves should be used when assessing whether a treatment is cost-effective, a threshold may be used instead when policy makers seek a benchmark with which to compare treatments and studies. Wealthier countries may be willing to pay more (i.e., accept a higher threshold) for a given treatment than poorer countries.[1,19] In the United States, a cost-effectiveness ratio less than $50,000 per LY or QALY is frequently regarded as economically attractive, in part because it approximates the cost of providing chronic hemodialysis to patients with renal failure, a cost that meets willingness to pay by Medicare.[1] Conversely, a cost-effectiveness ratio greater than $100,000 per added LY or QALY is frequently regarded as economically unattractive. The range between these two benchmarks is the gray zone in which there is no consensus on whether a treatment is economically acceptable.[1]

Assigning the same ICER threshold for different treatments in wide range of diseases and for different disease burdens may not be reasonable. Some countries may assign a general threshold for most cases but allow a higher threshold for treatment that relieves a considerable burden of illness (i.e., rule of rescue). For example, in The Netherlands, the average acceptable ICER is about €20,000, but an ICER of €80,000 per QALY is acceptable for illnesses associated with a considerable burden (i.e., impact of premature death and disability).[20] Similarly, in Great Britain, the limit of an acceptable ICER varies between £20,000 and £30,000, depending on the burden of the disease.[21]

MEDICAL ECONOMICS OF CORONARY INTERVENTIONS IN STABLE CORONARY ARTERY DISEASE

The therapeutic strategies for stable CAD are optimal medical treatment (OMT) and revascularization with PCI or CABG. In the setting of stable CAD, OMT and revascularization have similar efficacy for the prevention of MI and death.[22-24] However, the impact of the strategies on patient quality of life and the costs of the options vary substantially in the short and long term. OMT carries the lowest initial cost, but it is usually less effective in relieving angina.[23] The initial cost savings may be offset by the increased rate of repeated use and subsequent clinical interventions, including hospitalizations and additional revascularization. Similarly, the initial cost of PCI is usually lower than that of CABG, but the need for repeat revascularization may increase the cost of the PCI strategy in the long term. The following sections discuss the comparative cost-effectiveness of these strategies for treating CAD.

Optimal Medical Therapy Versus Revascularization

OMT for stable CAD has significantly improved over the past few decades. Similarly, PCI has been improved with the use of bare-metal stents (BMSs) and drug-eluting stents (DESs), and CABG has been improved by increased use of the left internal mammary artery as a surgical conduit and use of the less invasive off-pump and minimally invasive keyhole techniques.

The Medicine, Angioplasty, or Surgery Study II (MASS II) randomized 611 patients to CABG, PCI, or OMT. MASS II showed a lower incidence of the primary outcome, the composite end point of overall total mortality, Q-wave MI, or refractory angina requiring revascularization, in the CABG group compared with PCI and OMT, with no significant difference found between the latter two therapeutic strategies at 5 years.[22]

CEA of MASS II showed that the event-free costs significantly favored OMT compared with PCI ($9071 OMT vs. $19,967 PCI, $P <$ .01) or with CABG ($9071 OMT vs. $18,263 CABG, $P <$ .01) and favored CABG compared with PCI ($18,263 CABG vs. $19,967.00 PCI, $P =$ .01). The event-free plus angina-free costs significantly favored OMT compared with PCI ($16,553 OMT vs. $25,831 PCI, $P =$ .04) or with CABG ($16,553 OMT vs. $24,614 CABG, $P <$ .001). There was no significant difference between CABG and PCI ($25,831 PCI vs. $24,614 CABG, $P >$ .05).[25]

The Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial randomized 2368 patients with type 2 diabetes and heart disease to undergo prompt revascularization with OMT or OMT alone.[24] There was no significant difference in the mortality rates between patients undergoing prompt revascularization and those undergoing medical therapy. Although there was no difference between patients undergoing PCI and OMT in freedom from major adverse cardiovascular events (MACEs), CABG was associated with fewer MACEs than OMT.[24]

CEA of the BARI 2D trial showed that revascularization was associated with significantly higher costs compared with OMT. The 4-year costs were higher for CABG ($80,900 CABG vs. $60,600 OMT, $P <$ .0001) and PCI ($73,400 PCI vs. $67,800, $P <$ .02). Using the $50,000/LY benchmark, OMT was more cost-effective than PCI ($600/LY), and CABG was probably more cost-effective than OMT ($47,000/LY).[26]

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, which randomized 2287 patients with stable CAD to PCI with OMT or OMT alone, showed that PCI was not associated with a reduction in the risk of death, MI, or other MACEs when added to OMT.[23] The COURAGE trial showed that although PCI was associated with an incremental benefit for the first 12 to 24 months in the key domains of physical limitations, frequency of angina, and quality of life, the benefit disappeared by 36 months.[27]

CEA of the COURAGE trial showed that PCI was associated with an added cost of approximately $10,000 per patient without a significant gain in LYs or QALYs. The ICER for PCI varied from slightly more than $168,000 to slightly less than $300,000 per LY or QALY gained, and PCI was therefore not considered cost-effective.[28]

Drug-Eluting Stents Versus Bare-Metal Stents in Stable Multivessel Disease

The use of BMSs improved outcomes compared with balloon angioplasty but was associated with a high rate of in-stent restenosis (ISR), which prompted development of DESs. The presumed impact of reducing restenosis rate was proved in multiple RCTs and a meta-analysis of 17 RCTs.[29-31] The meta-analysis showed that the introduction of DESs significantly reduced the incidence of restenosis without a significant impact on the incidence of death, MI, or stent thrombosis compared with BMSs.[31]

A prospective economic analysis of the Sirolimus-Eluting Balloon-Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions (SIRIUS) trial, which compared sirolimus-eluting stents (SESs) with BMSs, showed that use of an SES was associated with an initially higher cost of $2881 per patient but that the additional cost attenuated over 1 year to $309 due to the significant reductions in repeat revascularization, with an ICER of $1650 per repeat revascularization avoided.[32] Similarly, CEA of the Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent (TAXUS IV) trial showed that the use of a paclitaxel-eluting stent (PES) compared with a BMS was associated with a 12.2% reduction in target-vessel revascularization (TVR), resulting in a 1-year cost difference of $572 in favor of DES per patient, with an ICER of $4678 per TVR avoided and $47,798 per QALY gained.[33]

The Basel Stent Kosten Effektivitäts Trial (BASKET), which randomized 826 consecutive patients to a first-generation DES (i.e., SES and PES) or third-generation BMS, showed that use of a DES was associated with higher total costs at 6 months (€10,544 DES vs. € 9639 BMS, $P <$ .0001) and at 18 months (€11,808 DES vs. €10,450 BMS), with an unattractive ICER of €64,732 to avoid one MACE (i.e., cardiac death, MI, or TVR). However, analysis of different subgroups showed that although the chance of finding an attractive ICER was 1.6% for low-risk patients, it was more than 87.4% likely for high-risk patients.[34] Results of this trial suggested that a DES might be more cost-effective for patients at higher risk for restenosis (i.e., those with small vessels,

stenting of a CABG graft) than for low-risk patients with large coronary arteries.

A real-world registry CEA comparing costs of care over 3 years for BMS patients with those of DES patients showed that although costs were $1846 higher per patient for DES, the cost difference was completely offset by lower TVR-related costs at 3 years.[35] Even after adding the cost of clopidogrel use, the ICER per TVR avoided ranged from $4703 to $6379 over 3 years, making the use of DES economically attractive.[35]

Overall, reduction in the cost of existing DESs over time makes DES use a more attractive option than BMS long term. However, the cost-effectiveness of subsequent generations of DES compared with earlier generations must be assessed.

Balloon Angioplasty Versus Coronary Artery Bypass Grafting in Stable Multivessel Disease

CABG was introduced in 1968, and it was the only revascularization option until the introduction of balloon angioplasty in 1979. Although balloon angioplasty appeared effective, its role in the treatment of CAD compared with CABG remained in question.

The Bypass Angioplasty Revascularization Investigation (BARI) randomized 1829 patients with multivessel CAD to percutaneous transluminal coronary balloon angioplasty (PTCA) or CABG. Of these patients, 41% had three-vessel disease. The results showed that although there was no significant difference in mortality with similar 10-year survival rates (71.0% PTCA vs.73.5% CABG, $P = .18$), PTCA was associated with substantially higher subsequent revascularization rates (76.8% PTCA vs. 20.3% CABG, $P < .001$).[36]

The BARI Substudy of Economics and Quality of Life (SEQOL), which evaluated economic outcomes for 934 of the 1829 patients enrolled in BARI, showed only a 5% difference in total discounted costs at 5 years between PTCA and CABG ($56,225 PTCA vs. $58,889 CABG).[37] Although PTCA was more expensive than CABG for three-vessel disease ($60,918 PTCA vs. $59,430 CABG), the 5-year cost was significantly lower for PTCA in patients with two-vessel disease ($52,390 PTCA vs. $58,498 CABG).[37] At the 12-year follow-up, the difference in cumulative costs was no longer significant ($120,750 PTCA vs. $123,000 CABG, $P = .55$), with CABG yielding an ICER of $14,300 per LY added compared with PTCA at 12 years.[37]

Although the exclusive use of PTCA is somewhat antiquated in the current stent era, BARI established that balloon angioplasty could be an acceptable economic alternative for patients with one- or two-vessel disease. CABG was a more cost-effective option for patients with three-vessel disease.

Bare-Metal Stents Versus Coronary Artery Bypass Grafting in Stable Multivessel Disease

A relatively high rate of restenosis is associated with PTCA. The use of BMSs is associated with lower rates of restenosis and revascularization compared with balloon angioplasty.[38] The increasingly routine use of left internal mammary artery grafts in CABG is also associated with better outcomes.[39] Many trials have compared BMSs with CABG in patients with multivessel disease.

The Arterial Revascularization Therapies Study (ARTS I) randomized 1205 patients with multivessel CAD to PCI with BMS or CABG. Although there was no difference in overall freedom from death, stroke, or MI (18.2% BMS vs. 14.9% CABG, $P = .14$; RR = 1.22; 95% confidence interval [CI], 0.95 to 1.58), PCI with BMS was associated with a much higher incidence of TVR (30 vs. 8.8%, $P < .001$).[40] Despite this finding, a cost estimation analysis of ARTS I showed that PCI with BMS was associated with a cost savings of €2779 (€11,117 BMS vs. €13,896 CABG) at 1 year that was somewhat attenuated at 3 years to €1798 (€14,302 BMS vs. €16,100 CABG), likely due to the initial high hospitalization and procedural costs of CABG.[40]

The Surgery or Stent (SoS) trial randomized 988 patients with typical angina and multivessel disease to PCI with BMS or CABG. Economic analysis of the trial showed higher initial hospitalization costs with CABG and higher follow-up costs with PCI. The total cost of the procedure with a total 1-year follow-up was higher with CABG in the ACS subgroup ($6435 PCI vs. $8870 CABG) and non-ACS subgroup ($5069 PCI vs. $7487 CABG).[41]

Although the data demonstrate that the cost of CABG is higher than PCI in the short term, CABG is associated with substantial improvement in outcomes compared with BMS in the treatment of multivessel disease.[40,41] Unfortunately, a formal and complete CEA comparing PCI plus BMS with CABG has not been reported in the literature.

Drug-Eluting Stents Versus Coronary Artery Bypass Grafting in Stable Multivessel Disease

Although the use of BMSs significantly reduced the rates of restenosis compared with PTCA, the rates of clinically salient ISR with BMSs remained a problem. Introduction of DESs reduced ISR rates to between 4.5% and 5%, and their use was associated with a significant decrease in the incidence of TVR compared with BMSs.[29,30] It was unclear how their use compared with CABG, whose major advantage over PTCA and PCI with BMS was in the rate of revascularization for clinically salient restenosis. Many RCTs were conducted to compare the outcomes of the two strategies.

PCI with DES and CABG were compared in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial.[42] It showed that PCI with the paclitaxel-eluting Taxus stent was associated with significantly higher rates of major adverse cardiovascular and cerebrovascular events at 12 months compared with CABG (17.8% DES vs. 12.4% for CABG, $P = .002$), in large part due to an increased rate of TVR (13.5% DES vs. 5.9% CABG, $P < .001$).[42]

CEA of the SYNTAX trial[43] showed that among patients with three-vessel or left main CAD, PCI was economically more attractive in the first year for patients with low and moderate angiographic complexity (SYNTAX score <32) because CABG was associated with a $3590 higher cost per patient at 1 year in the two subgroups. This cost reflected a $5693 higher initial hospitalization cost with CABG and a $2282 higher cost of follow-up with PCI; the latter resulted mainly from more frequent revascularization procedures and higher outpatient medication costs with PCI. CABG seemed to be a more attractive option among patients with high angiographic complexity (SYNTAX score >32); the total 1-year costs were similar for CABG and PCI, and the ICER for CABG was $43,486 per QALY gained.[43]

The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial showed higher incidence of the composite end point of death, MI, or stroke among diabetic patients undergoing PCI with DES compared with CABG at 5 years (26.6% DES vs. 18.7% CABG, $P = .05$), with a significantly higher incidence of TVR with PCI as early as 1 year (12.6% DES vs. 4.8% CABG, $P < .001$).[44]

CEA of the FREEDOM trial showed that initial procedural costs were higher with CABG ($8622 per patient). Over the next 5 years, even accounting for higher follow-up costs with PCI, the cumulative 5-year costs were higher with CABG ($3641 per patient). However, when the analysis extended the modest gains in survival with CABG during the trial period to a lifetime horizon, CABG was projected to be the more economically attractive option compared with PCI with DES, with substantial gains in life expectancy and quality-adjusted life expectancy (ICER <$10,000 per LY or QALY).[45]

Results from real-world registries demonstrated similar results. The American College of Cardiology Foundation and Society of Thoracic Surgeons (ACCF-STS) Database Collaboration on the Comparative Effectiveness of Revascularization Strategies Trial (ASCERT) compared 86,244 Medicare patients who underwent CABG with 103,549 Medicare patients who underwent PCI and showed that although there was no significant difference in mortality rates between the groups at 1 year (6.24% CABG vs. 6.55% PCI; RR = 0.95; 95% CI, 0.90 to 1.00),

CABG was associated with a lower mortality rate at 4 years (16.4% CABG vs. 20.8% PCI; RR = 0.79; 95% CI, 0.76 to 0.82).[46]

CEA of the ASCERT study[47] showed that in the first year, CABG was more costly and less effective than PCI, with a higher cost by $10,951 during the initial hospitalization and by $9906 at the end of first year.[47] At 4 years, the average total costs were still higher for CABG by $7825 ($32,428 CABG vs. $24,623 PCI). Unlike the RCT data, the average total costs over a lifetime were higher for CABG by $6105 ($88,125 CABG vs. $82,020 PCI). However, using the common threshold of $50,000, CABG often is a cost-effective strategy, with an ICER of $48,135 per LY gained.[47] Although ASCERT had almost 200,000 patients, it was not randomized and was subject to treatment selection bias, which can affect the clinical outcome data.

Although CABG is associated with higher initial and short-term costs, it seems to be a cost-effective long-term option compared with BMS or DES use, especially for high-risk patients with high angiographic complexity (SYNTAX score >32) or diabetes.

MEDICAL ECONOMICS OF CORONARY INTERVENTIONS IN ACUTE CORONARY SYNDROME

Reperfusion in ST-Elevation Myocardial Infarction

Management of ST-elevation myocardial infarction (STEMI) witnessed major changes after the introduction of PCI. Although thrombolysis was once considered the mainstay therapy, primary PCI has become the standard of care based on multiple trials that compared the two strategies. A meta-analysis of 22 pooled RCTs comparing PCI with thrombolysis showed that primary PCI was associated with a significant reduction in 30-day mortality rates for patients treated early and those who were treated more than 4 hours after symptom onset.[48] PCI was associated with a higher early reperfusion rate and a higher proportion of patients achieving grade 3 flow as defined in the Thrombolysis in Myocardial Infarction (TIMI) trial.[49]

Economic analysis of the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) trial showed that although there was no difference in 1-year outcomes between the two reperfusion strategies, costs were lower for primary PCI. The thrombolysis strategy in the CAPTIM trial included the use of rescue PCI as needed.[50] Similarly, results of the Swedish Early Decision Reperfusion Study (SWEDES) and a subsequent Norwegian study showed that although there was no difference in clinical outcomes, primary PCI was a more cost-effective strategy. The SWEDES trial showed that PCI was associated with higher initial costs due to procedural and medication costs, but they were offset by lower hospitalization costs. Early discharge of low-risk patients who received primary PCI also helped to reduce total costs of care.[51,52]

Primary PCI is a cost-effective strategy only if resources are readily available. For example, in a hospital with an existing catheterization laboratory with night and weekend coverage that admitted 200 patients with acute MI (AMI) each year, PCI was associated with cost savings of less than $30,000 per QALY compared with thrombolysis.[53] If the hospital did not have the available resources, the costs to build a new catheterization laboratory, staff it with around-the-clock coverage, and accept initial low volumes of patients would not be cost-effective. Transporting every patient from non–PCI-capable hospitals to PCI-capable facilities was more cost-effective, with a $2750 saving per QALY.[54]

Early Invasive Versus Early Conservative Strategies for Non–ST-Elevation Myocardial Infarction Acute Coronary Syndrome

The expansion of PCI use led to a gradual shift in the management of non–ST-elevation myocardial infarction (NSTEMI). Initially, many patients were treated medically, with intervention reserved for those with recurrent ischemia, but a more aggressive approach with early revascularization began to emerge as an alternative. Timing of the procedure also shifted. The shift correlated with a change in the definition of an early invasive strategy in trials comparing early invasive and conservative approaches, such as 7 days in the Framingham and Fast Revascularization During Instability in Coronary Artery Disease II (FRISC II) trial and 2 days in the Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI 18) trial.

The FRISC II trial compared an early invasive strategy with an early noninvasive strategy in 2457 patients with unstable CAD. The early invasive strategy was associated with a significant reduction the composite end point of death or AMI (10.4% vs.14.1%, $P = .005$). There were also reductions in readmission (37% vs. 57%, $P < .001$) and revascularization after the initial admission with the early invasive strategy (7.5% vs. 31%, $P < .01$).[55]

Economic analysis of FRISC II showed that at the end of 1 year, the early invasive strategy was associated with a $3511 (23,876 Swedish koruna [SEK]) higher cost compared with the noninvasive arm. The ICER for choosing the invasive instead of the noninvasive strategy was substantially higher, with $206,470 (1,404,000 SEK) per avoided death and $94,852 (645,000 SEK) per avoided death or AMI.[56] However, what was called an early invasive approach in this trial was not associated with an early intervention. The intervention was done within 1 week and was associated with a longer hospital stay (12 vs. 8 days).

The TACTICS-TIMI 18 trial randomized 2220 patients with unstable angina or NSTEMI to an early invasive strategy with routine catheterization and revascularization within 4 to 48 hours or to a conservative or "selective invasive" strategy, with catheterization performed only if the patient had objective evidence of recurrent ischemia or a positive stress test result. All patients were provided with appropriate medical therapy. The early strategy was associated with a significant reduction in the composite end point of death or AMI (7.3% vs. 9.5%, $P < .05$; OR = 0.74; 95% CI, 0.54 to 1.00).[57]

Economic analysis of the TACTICS-TIMI 18 trial showed that the early invasive treatment arm had higher initial costs ($15,714 vs. $14,047) but lower follow-up costs up to 6 months ($6098 vs. $7180) and similar cumulative 6-month costs ($19,780 vs. $19,111). The early invasive strategy was shown to be cost-effective, with an estimated ICER of $13,000 per LY gained.[58] Data showed that adapting an early invasive approach with the intervention done in the first 48 hours was a very economically attractive option.

Antiplatelet Therapy

Glycoprotein IIb/IIIa Inhibitors

The benefit of antiplatelet therapy in the setting of ACS was first established with aspirin. Aspirin, an inhibitor of platelet aggregation through inhibition of thromboxane A_2, was found to be as effective as streptokinase in reducing mortality rates when used alone, and better outcomes were achieved by using both in combination in the setting of STEMI.[59] The trial demonstrated the importance of platelet aggregation in the setting of ACS and the potential benefit of using more potent platelet-activation inhibitors. This led the introduction of intravenous glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors in the management of ACS.

Many trials have evaluated the clinical and economic impact of using GP IIb/IIIa inhibitors in the setting of ACS and after coronary interventions. The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial randomized 2197 patients with ACS and undergoing coronary intervention (i.e., balloon angioplasty or directional atherectomy) within 72 hours of presentation to tirofiban or placebo. Use of tirofiban was associated with a significant reduction in the composite end point of death, MI, or TVR at 2 days (8% tirofiban vs. 12% placebo, $P = .002$). This difference was not statistically significant at 30 days (10.3% tirofiban vs. 12.2% placebo, $P = .16$).[60] Economic evaluation of RESTORE showed that the cost of tirofiban use was not significantly higher than placebo at 30 days ($12,446 ± $5814 tirofiban vs. $12,402 ± $6147 placebo, $P = .87$).[61]

The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial randomized 10,948 patients with ischemic chest pain to receive a bolus and infusion of eptifibatide or placebo. The use of eptifibatide was associated with a reduction in the incidence of a composite end point of death and AMI at 30 days (14.2% eptifibatide vs. 15.7% placebo, $P = .04$).[62] An economic evaluation of the 3522 U.S. patients enrolled in PURSUIT showed that the use of eptifibatide was associated with a nonstatistically significant $372 cost advantage. The estimated life expectancy was 15.96 years for eptifibatide and 15.85 years for placebo, an incremental difference of 0.111. The ICER for eptifibatide therapy was $16,491 per LY gained and $19,693 per QALY gained.[63]

The use of GP IIb/IIIa inhibitors proved to be beneficial in the setting of elective coronary intervention. The Evaluation of Platelet IIb/IIIa Inhibitor in Stenting (EPISTENT) trial randomized 2399 patients to stenting with abciximab, stenting with placebo, or balloon angioplasty with abciximab. Adding abciximab to stenting was associated with a significant reduction in the incidence of death (1% stent plus abciximab vs. 2.4% stent alone, $P = .037$; HR = 0.43; 95% CI, 0.19 to 0.97) and the composite end point of death and MI (5.3% stent plus abciximab vs. 11.0% stent alone, $P < .001$; HR = 0.46; 95% CI, 0.32 to 0.67) at 30 days.[64] Compared with stenting plus placebo, the incremental 1-year costs of stenting plus abciximab was $58, with a corresponding ICER of $5291 per LY gained.[64]

The use of GP IIb/IIIa inhibitors has been an economically attractive option in the setting of ACS and after elective PCI. However, their use has markedly decreased since the introduction of adenosine diphosphate receptor inhibitors (discussed later). Concomitant use of both agents has not been evaluated from an economic standpoint.

P2Y12 Receptor Antagonists

The benefit of dual antiplatelet therapy (DAPT) was established by data showing that the combination of aspirin and ticlopidine was associated with higher levels of platelet inhibition than aspirin alone in patients with CAD treated with PCI.[65] However, ticlopidine use was associated with many side effects. Subsequently, clopidogrel, a P2Y12 receptor antagonist, was studied in many clinical trials and proved to be an effective option for DAPT with fewer side effects than ticlopidine. However, the use of clopidogrel was associated with substantial interpatient variability and a delayed onset of action. The reduced pharmacologic response in some patients to clopidogrel was associated with an increased risk of adverse clinical events, including MI and stent thrombosis. This limitation led to the introduction of the more potent antiplatelet inhibitors prasugrel and ticagrelor as alternatives to clopidogrel.

Several trials have evaluated the economics of using an oral P2Y12 receptor antagonist after PCI. The PCI-CURE substudy of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial showed that the use of clopidogrel was associated with a 31% reduction in cardiovascular death or MI ($P = .002$).[66] CEA of CURE-PCI showed that clopidogrel was associated with a higher average cost at 1 year of $253 to $423. For patients who underwent PCI during the initial hospitalization, the difference was substantially less and ranged from $155 lower to $90 higher with clopidogrel. Clopidogrel proved to be a very attractive option, with an ICER of $2856 to $4775 per LY without PCI and $935 per LY for the early PCI subgroup.[67]

Although clopidogrel was established as a clinically effective and cost-effective strategy for PCI, the role of the novel adenosine diphosphate receptor antagonists remained in question. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) randomized 13,608 patients with moderate- or high-risk ACS to receive prasugrel or clopidogrel at the time of PCI. The study showed that prasugrel use was associated with a significant reduction in the combined end point of cardiovascular death, nonfatal MI, or nonfatal stroke (9.9% prasugrel vs. 12.1% clopidogrel, $P < .001$) and a significant reduction in urgent TVR (2.5% vs. 3.7%, $P < .001$) and stent thrombosis (1.1% vs. 2.4%, $P < .001$). Patients receiving prasugrel had significantly higher rates of major bleeding (2.4% prasugrel vs. 1.8% clopidogrel, $P < .03$).[68]

CEA of the TRITON-TIMI 38 trial showed that over 14.7 months of follow-up, prasugrel was associated with a net savings of $221 per patient compared with clopidogrel. This was attributed to the lower rate of rehospitalization involving PCI. Prasugrel was associated with life expectancy gains of 0.102 years (95% CI, 0.030 to 0.180), primarily because of the decreased rate of nonfatal MI. Prasugrel was shown to be a dominant strategy, with an ICER of $9727 per LY gained.[69] This comparison was done between prasugrel and the brand rather than generic clopidogrel, but prasugrel is likely an economically attractive alternative.

The Platelet Inhibition and Patient Outcomes (PLATO) trial randomized 18,624 patients with moderate- or high-risk ACS to receive ticagrelor or clopidogrel upstream or at the time of PCI. The use of ticagrelor was associated with a significant reduction in the composite end point of death from vascular causes, MI, or stroke (9.8% ticagrelor vs.11.7% clopidogrel, $P < .001$; HR = 0.84; 95% CI, 0.77 to 0.92). The use of ticagrelor was associated with no increased risk of major bleeding (11.6% ticagrelor vs.11.2% clopidogrel, $P = .43$).[70]

Economic evaluation of PLATO showed that although ticagrelor use was associated with a higher cost of €362, it was balanced by a QALY gain of 0.13 compared with generic clopidogrel at 1 year. Use of ticagrelor was an economically attractive option, with an ICER of €2753 per QALY gained and €2372 per LY gained.[71]

The use of clopidogrel as a second antiplatelet agent with aspirin remains attractive clinically and economically. It has clinical and economic advantages over ticagrelor and prasugrel.

Antithrombotic Use in Acute Coronary Syndrome

The benefit of using unfractionated heparin (UFH) in addition to antiplatelet therapy to reduce the incidence of death and recurrent MI in the setting of ACS has been well established.[72,73] However, the use of UFH is associated with an unpredictable anticoagulant response due to its neutralization by protein binding and activated platelets. Discontinuation of UFH is associated with an increased incidence of cardiac events.[74] Several studies were therefore performed to demonstrate the benefit of more predictable anticoagulation using enoxaparin or low-molecular-weight heparin, anti-Xa inhibitors, and direct thrombin inhibitors.

Antithrombotic Use in Non–ST-Elevation Myocardial Infarction

The first comparison between UFH and enoxaparin in the setting of non-STEMI ACS was the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events (ESSENCE) trial. The trail randomized 3171 patients with non-STEMI ACS to receive enoxaparin or continuous intravenous UFH. The use of enoxaparin was associated with a significant decrease in the incidence of the composite end point of death, MI, or recurrent angina at 30 days (19.8% enoxaparin vs. 23.3% UFH, $P = .016$) and the need for revascularization at 30 days (27.1% enoxaparin vs. 32.2% UFH, $P = .001$). Enoxaparin was associated with an increase in all bleeding but a nonsignificant difference in the incidence of major bleeding.[74] Economic evaluation of the ESSENCE trial showed that the use of enoxaparin was associated with a net cumulative cost savings of $1172 ($P = .04$) and was therefore cost-effective.[75]

The fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial randomized 20,078 NSTEMI ACS patients to fondaparinux or enoxaparin and reported no significant difference in the composite end point of death, MI, or refractory ischemia at 9 days (5.8% fondaparinux vs. 5.7% enoxaparin; HR = 1.01; 95% CI, 0.90 to 1.13), but fondaparinux did significantly reduce major bleeding events at 9 days (2.2% fondaparinux vs. 4.1% enoxaparin, $P < 0.001$, HR = 0.52).[76] Economic evaluation showed that using fondaparinux instead of enoxaparin was associated with a cost savings of $547 per patient at 180 days, and a long-term CEA found fondaparinux to be the dominant therapy.[77]

The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial randomized 13,819 patients with ACS to one of three

antithrombotic regimens: UFH or enoxaparin plus a GP IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin alone. Results showed that bivalirudin alone compared with UFH plus a GP IIb/IIIa inhibitor was associated with a noninferior rate of the composite end point of death, MI, or unplanned revascularization (7.8% vs. 7.3%, $P = .32$; RR = 1.08; 95% CI, 0.93 to 1.24) and significantly reduced rates of major bleeding (3.0% vs. 5.7%, $P < .001$; RR = 0.53; 95% CI, 0.43 to 0.65). There was no difference in any of the outcomes between the use of UFH or enoxaparin plus a GP IIb/IIIa inhibitor and that of bivalirudin plus a GP IIb/IIIa inhibitor.[78] Economic evaluation of the U.S. cohort of the ACUITY trial showed that despite the higher drug cost of bivalirudin, the cumulative hospital stay costs were lowest with bivalirudin monotherapy (mean difference range, $184 to $1081, $P <$ .001 for overall comparison), with cost savings extending up to 30 days (mean difference range, $123 to $938, $P = .005$). Savings primarily resulted from less major and minor bleeding with bivalirudin ($8658/event and $2282/event, respectively).[79]

In the medical management of non-STEMI ACS, the use of more predictable anticoagulation with enoxaparin and fondaparinux is associated with cost savings compared with UFH. During PCI, the use of bivalirudin alone seems to be a more attractive option than the combined use of UFH or enoxaparin with a GP IIb/IIIa inhibitor.

Antithrombotic Use in ST-Elevation Myocardial Infarction

Data comparing enoxaparin and UFH in the setting of STEMI comes from the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction 25 (EXTRACT-TIMI 25) study. EXTRACT-TIMI 25 randomly assigned 20,506 patients with STEMI who were scheduled to undergo fibrinolysis to receive enoxaparin throughout the index hospitalization or weight-based UFH for at least 48 hours. The use of enoxaparin was associated with a significant reduction in the incidence of the composite end point of death, nonfatal MI, or urgent revascularization (11.7% enoxaparin vs. 14.5% heparin, $P < .001$).[80] CEA of EXTRACT-TIMI 25 showed that enoxaparin use in STEMI was associated with a higher cost at 30 days ($102) and 1 year ($1207). However, patients receiving enoxaparin gained an average of 0.12 LYs compared with patients given UFH. Enoxaparin was shown to be an economically attractive option, with an ICER of $5700 per LY gained.[81]

The Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial randomized 3602 patients with STEMI who were seen within 12 hours after the onset of symptoms and who were undergoing primary PCI to treatment with heparin plus a glycoprotein IIb/IIIa inhibitor or treatment with bivalirudin alone. Similar to the findings in the ACUITY trial, the use of bivalirudin alone was associated with reduced 30-day rate of the composite end point of major bleeding and MACEs, including death, MI, TVR, and stroke (9.2% vs. 12.1%, $P = .005$; RR = 0.76; 95% CI, 0.63 to 0.92),; lower rate of major bleeding (4.9% vs. 8.3%, $P < .001$; RR = 0.60; 95% CI, 0.46 to 0.77); lower rate of 30-day cardiac death (1.8% vs. 2.9%, $P = .03$; RR = 0.62; 95% CI, 0.40 to 0.95); and death from all causes (2.1% vs. 3.1%, $P = .047$; RR = 0.66; 95% CI, 0.44 to 1.00).[82]

Economic evaluation of the HORIZONS-AMI trial showed that the use of bivalirudin alone was associated with a lifetime savings of £267 (£12,843 bivalirudin vs. £13,110 heparin plus GP IIb/IIIa). Probabilistic analysis showed that bivalirudin use was associated with higher quality-adjusted survival at lower costs, suggesting that bivalirudin alone may be dominant, with cost-effectiveness being better than £20,000 per QALY gained.[83] However, a single-center experience presented at the 2014 American College of Cardiology meeting demonstrated improvement in outcomes with the use of heparin monotherapy plus bailout GP IIb/IIIa inhibitors compared with bivalirudin monotherapy. This finding was unique in that HORIZONS-AMI did not use a treatment arm with heparin alone. It stands to reason that heparin monotherapy may be as effective or more effective than bivalirudin monotherapy at a decreased cost.

The How Effective Are Antithrombotic Therapies in Primary PCI (HEAT-PPCI) trial, which randomly assigned 1917 patients undergoing emergency angiography to UFH or bivalirudin, showed that the use of bivalirudin compared with heparin alone was associated with a higher incidence of the primary composite end point of death, MI, CVA, or TVR (8.7% bivalirudin vs. 5.7% UFH, $P = .01$; RR = 1.52, 95% CI, 1.09 to 2.13) without changing the incidence of major bleeding (3.5% bivalirudin vs. 3.1% UFH, $P = .59$; RR = 1.15; 95% CI, 0.70 to 1.89).[84] Cost analysis of the trial has not been reported, but UFH use is expected to be more cost-effective and even dominant compared with bivalirudin because UFH use is associated with lower costs and better outcomes without increasing the risk of complications.

Peripheral Vascular Interventions

Admissions for peripheral artery disease (PAD) have been increasing and are responsible for approximately 20% of all U.S. hospital admissions. Analysis of more than 2 million hospital admissions for PAD between 2001 and 2007 showed that the choice of treatment has dramatically changed, with a 78% increase in endovascular procedures and a concomitant decrease in open bypass and amputations.[85] The trend was associated with a change in the distribution of cases among different specialties involved in performing them. Between 1998 and 2005, there was a sixfold drop in peripheral procedures performed by interventional radiologists (5.6% of all cases in 2005), with a threefold increase for interventional cardiologists (29% of all cases) and a twofold increase for vascular surgeons (43% of all cases).[86]

The number of interventional laboratories capable of peripheral vascular interventions is rapidly growing, with many fellowship programs offering additional training in these techniques. Advances in technology, uses of BMSs and atherectomy, and intravascular imaging have helped to increase success rates and reduce complications. Peripheral interventions are expected to grow by an average of 8% per year over the next 4 years.[4,5]

Peripheral Artery Disease Treatment

Many factors may affect the cost of vascular interventions. In a study assessing the cost of peripheral procedures at the Brigham and Women's Hospital from 1990 through 1995, the cost of these interventions was higher with advanced age ($1345, $P = .02$), CAD ($1287, $P = .05$), and female gender ($1461, $P = .03$). Complications were associated with a substantial increase in cost, with an additional cost for fatal systemic complications of $11,675 ($P = .004$) and for nonfatal systemic complications of $9345 ($P < .001$).[87]

The extent and severity of PAD substantially influence the cost of treatment. Whereas treatment of a patient with stage IIa PAD by Fontaine criteria (i.e., pain-free walking distance of more than 200 m) costs about $650 per year, treatment of a patient with stage IV PAD (i.e., ischemic tissue necrosis) costs $9353 per year. Similarly, critical leg ischemia (i.e., PAD stages III and IV) is on average $4478 more expensive than the treatment of intermittent claudication (i.e., PAD stage II disease).[87,88] This association also holds true for the costs of a specific therapeutic or invasive procedure. For example, the costs for percutaneous transluminal angioplasty (PTA) are much greater for patients with critical ischemia and tissue necrosis than for patients with disabling claudication due to higher complication rates and longer hospital stays.[89] Amputation is about twice as expensive as a limb-salvage strategy with interventional or surgical methods and for acute and chronic limb-threatening ischemia.[90]

Noninvasive Therapy

The use of antiplatelet agents was shown to be effective in reducing the risk of vascular occlusion in a wide range of patients with PAD. A meta-analysis of 8000 patients from 46 randomized trials of antiplatelet therapy versus control and 14 randomized trials comparing one antiplatelet regimen with another showed that antiplatelet therapy produced a highly significant ($P < .0001$) reduction in vascular occlusion, with the largest absolute reductions among patients at highest risk of occlusion and smaller but still significant absolute reductions among lower-risk patients. Antiplatelet therapy for patients with PAD

produced a significant 25% reduction ($P = 0.002$) in the incidence of vascular events (i.e., nonfatal MI, nonfatal stroke, or vascular death).[91]

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, which randomized 15,603 patients with clinically evident cardiovascular disease or multiple risk factors for cardiovascular disease to receive clopidogrel plus low-dose aspirin or low-dose aspirin alone, showed no significant difference in the composite end point of MI, stroke, or cardiac death.[92] However, a subgroup analysis of 9478 patients with manifest cardiovascular disease (i.e., prior MI, stroke, or symptomatic PAD) in the CHARISMA trial showed a significant reduction in the incidence of the composite end point of cardiovascular death, MI, or stroke with the use DAPT (7.3% vs. 8.8%, $P < .01$; HR = 0.83, 95% CI, 0.72 to 0.96) and a reduction in hospitalizations for ischemia (11.4% vs. 13.2%, $P = .008$; HR = 0.86; 95% CI, 0.76 to 0.96).[93]

Economic evaluation of the CHARISMA subgroup showed that DAPT use was associated with a $2607 higher cost and with a projected life expectancy increased by an average of 0.072 years. The use of DAPT therefore appeared to be an economically attractive option, with an ICER of $36,343 per LY gained.[94]

Vasoactive agents, including cilostazol, naftidrofuryl oxalate, pentoxifylline, and inositol nicotinate, are used for symptomatic relief in patients with intermittent claudication. Review and analysis of the results of 26 RCTs showed that naftidrofuryl oxalate and cilostazol were effective treatments, with significant improvement in the logarithmic mean of maximal walking distance from 0.181 to 0.762 and 0.108 to 0.337, respectively, for this patient population. Naftidrofuryl oxalate, however, seems to be the only treatment that is likely to be considered cost-effective, with an ICER of about £6070 per QALY gained compared with no vasoactive drug, whereas cilostazol was associated with an ICER of more than £20,000 per QALY gained compared with no vasoactive drug.[94]

Percutaneous Transluminal Angioplasty Versus Bypass Surgery

The first data on the comparative cost-effectiveness of PTA versus bypass surgery came from the Revascularization for Femoropopliteal Disease trial, which studied the impact of both strategies on 65-year-old men with disabling claudication or chronic critical limb ischemia due to femoropopliteal stenosis. Initial angioplasty increased quality-adjusted life expectancy by 2 to 13 months for patients with disabling claudication and by 1 to 4 months for patients with chronic critical ischemia and resulted in decreased lifetime expenditures compared with bypass surgery in both groups. Using a maximum threshold cost of $50,000 per QALY, PTA was cost-effective compared with vein bypass for lesions that could be treated, with a better than 30% 5-year patency.[89]

The Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial randomized 452 patients with severe limb ischemia due to infrainguinal disease to receive a surgery-first or an angioplasty-first strategy. After 1 year, the two strategies did not differ significantly in amputation-free survival (71% bypass vs. 68% PTA; adjusted HR = 0.73; 95% CI, 0.49 to 1.07).[95] However, the 5-year follow-up assessment of the BASIL trial showed that bypass surgery was associated with better overall survival (47% bypass vs. 41% PTA, $P < .009$; adjusted HR = 0.61; 95% CI, 0.50 to 0.75) and a nonsignificant difference in amputation-free survival (38% bypass vs. 37% PTA, $P = .108$; adjusted HR = 0.85; 95% CI, 0.5 to 1.07).[96] Economic assessment showed that for the first year, the hospital costs associated with a surgery-first strategy were $8469 higher ($34,378 bypass vs. $25,909 PTA). However, at the 5-year follow-up and due to increased costs subsequently incurred by the need for repeat revascularization (including surgery in the PTA patients), the difference decreased to $5521 ($45,322 bypass vs. $39,801 PTA) and was no longer significant.

Although the bypass strategy was associated with better survival, it was not economically attractive, with an ICER of $184,492 per QALY gained.[96] Consistent with the disparate economic findings, clinical practice for this patient population varies greatly with regard to angioplasty or bypass selection.

Advanced Endovascular Interventions

Although PTA alone was originally introduced as a treatment alternative to surgical revascularization, subsequent development of stent technology demonstrated a lower incidence of target-lesion revascularization (TLR).[34,97,98] Drug-coated balloons (DCBs) have emerged as a revascularization strategy that holds the promise of reducing the number of TLRs further while avoiding stent-related risks such as ISR and stent fracture and maintaining all therapeutic options for subsequent intervention.[99] Starting in 2014, DESs and DCBs became available for commercial use in the United States and are expected to be widely used.

Two studies compared the economics of the three modalities. A British economic study compared PTA with no bailout stenting, PTA with bailout DESs, DCBs, primary BMSs, primary DESs, endovascular brachytherapy, stent grafts, and cryoplasty in patients with intermittent claudication and critical leg ischemia. The cost and QALY were favorable for DCBs compared with all other strategies for intermittent claudication (cost, £12,668 vs. £13,032 to £17,578; QALY, 6.120 vs. 5.931 to 6.081) and critical limb ischemia (cost, £49,890 vs. £54,775 to £58,097; QALY, 3.402 vs. 2.988 to 3.297). Using £100,000 as a higher cutoff for the calculation, the use of DCBs seemed to be more economically attractive because of lower lifetime costs and greater effectiveness. The probability of DCBs being cost-effective was at least 58.3% for patients with intermittent claudication and at least 72.2% for patients with critical leg ischemia.[100]

Another economic study analyzed results for a cohort of 2406 patients from 13 trials. It assessed the economic impact of BMS, DES, or DCB use compared with PTA alone based on the 2013 reimbursement rates of U.S. Medicare and the German statutory sickness funds. Results showed TLR rates of 14.3%, 19.3%, 28.1%, and 40.3% for DCB, DES, BMS, and PTA strategies, respectively. The drug-eluting strategies had a lower projected budget impact over 24 months compared with BMS and PTA in the U.S. Medicare ($10,214 DCB, $12,904 DES, $13,114 PTA, $13,802 BMS) and German public health care systems (€3,619 DCB, €3,632 DES, €4,026 BMS, €4,290 PTA).[101] Clinical trials are evaluating the efficacy of these drug-coated products in the vascular periphery.

MEDICAL ECONOMICS OF STRUCTURAL CARDIAC INTERVENTIONS

Structural heart disease is the field of interventional cardiology that may witness the greatest growth in the next 10 years.[5] The field of structural interventional cardiology was first developed with transcatheter valvuloplasty of the mitral valve, followed by the introduction of closure devices for atrial septal defect (ASD) and patent foramen ovale (PFO). Transcatheter aortic valve replacement (TAVR) and new transcatheter techniques to manage mitral regurgitation are expected to increase the volume of structural procedures by 30% over the next decade.[5] This growth reflects the projected increase in the incidence of aortic and mitral valve disease due to aging of the population and greater penetration of these therapeutic methods for a broader population. Analysis of three large population-based epidemiologic studies found that the overall prevalence of aortic and mitral valve disease was estimated to be 2.5%, but the rate was less than 1% for those younger than 54 years, 4% to 8% for those between 65 and 74 years, and 12% to 14% for those older than 75 years old.[102]

Approval of the Sapien transcatheter heart valve (Edwards Lifesciences, Irvine, CA) in 2007 and the CoreValve (Medtronic, Minneapolis, MN) shortly thereafter in Europe led to the performance of more than 60,000 TAVR procedures outside of the United States in 2011.[4] In the United States, the Sapien valve was approved in 2011, and the CoreValve was approved in 2014. The annual TAVR volume is expected to grow from 2000 in 2012 to 25,000 after 2015, especially after TAVR was shown to be a viable option for inoperable and operable but high-risk patients.[4]

Transcatheter Versus Surgical Closure of Secundum Atrial Septal Defects in Adults

Transcatheter ASD closure was shown to be a feasible option for the management of secundum ASD in adults.[103] Outcome analysis of a cohort of 718 ASD closures performed between 1988 and 2005, which included 383 surgical ASD closures and 335 transcatheter ASD closures, showed no difference in mortality rates at 5 years between the two strategies (5.3% transcatheter vs. 6.3% surgical, $P = 1.00$), but transcatheter intervention was associated with a higher reintervention rate at 5 years (7.9% vs. 0.3%, $P = .0038$).[103] CEA of this cohort showed that the 5-year costs were $15,304 for surgical closure and $11,060 for the transcatheter alternative. At 5 years, transcatheter closure was marginally more effective than surgery (4.683 ± 0.379 LY vs. 4.618 ± 0.638 LY).[104] Whenever feasible, transcatheter ASD closure seems to be the dominant strategy over surgical closure.

Transcatheter Aortic Valve Replacement

An estimated 3.4% of the population older than 75 years has severe aortic stenosis, corresponding to 350,000 patients in the United States alone.[105] Forty percent of these patients do not get surgical intervention because they are considered to be inoperable or at very high surgical risk.

TAVR was developed as an alternative to surgical aortic valve replacement (SAVR). TAVR treats aortic stenosis by displacing and functionally replacing the native valve with a bioprosthetic valve delivered on a catheter (i.e., Sapien valve) or a trileaflet porcine pericardial valve on a self-expanding nitinol frame (CoreValve) through the femoral artery (i.e., transfemoral approach) or the left ventricular apex (i.e., transapical placement). It is estimated that there are approximately 102,558 TAVR candidates in North America and 189,836 TAVR candidates in Europe.[105]

Transcatheter Aortic Valve Replacement Versus Medical Therapy in Inoperable Patients

Symptomatic severe aortic stenosis in the absence of definitive treatment leads to progressive symptoms, functional decline, and death.[106] In patients not considered candidates for SAVR, medical therapy was not effective in slowing the expected outcomes. The introduction of TAVR offered an alternative for this patient population.

Evidence supporting the use of TAVR in patients with severe aortic stenosis who are not surgical candidates comes from Cohort B of the Placement of Aortic Transcatheter Valve (PARTNER) trial, which randomized 358 patients with aortic stenosis who were not considered suitable surgical candidates to medical management (including balloon valvuloplasty) or TAVR. The trial found an impressive absolute 20% reduction in the 1-year mortality rate for TAVR compared with standard therapy in this population (30.7% TAVR vs. 50.7% standard therapy, $P < .001$; HR = 0.55; 95% CI, 0.40 to 0.74). However, TAVR was associated with a higher incidence of major strokes (5.0% vs. 1.1%, $P = .06$) and major vascular complications (16.2% vs. 1.1%, $P < .001$).[106]

Economic evaluation of the PARTNER Cohort B data showed that TAVR was associated with a mean cost of $42,806 for the initial procedure and $78,542 for the hospitalization. Follow-up costs through 12 months were lower with TAVR compared with standard therapy ($29,289 vs. $53,621). The cumulative 1-year costs remained higher for TAVR ($106,076 vs. $53,621). TAVR increased discounted life expectancy by 1.6 years (1.3 QALYs) at an incremental cost of $79,837. TAVR was associated with an ICER of $50,200 per LY gained and $61,889 per QALY gained.[107]

A cost stimulation model based on the same cohort data for an estimated 10-year time horizon showed that TAVR was cost-effective at 24 months, with an ICER of £18,500 ($31,450) per QALY gained.[108] Although TAVR in this group was associated with a considerable increase in cost, it was also associated with an acceptable ICER per LY and a potentially acceptable ICER per QALY over time.

The U.S. trial evaluating the self-expanding CoreValve compared with standard therapy in extreme-risk patients yielded similar improvements in outcomes with significant reductions in the incidence of death and stroke (26.0% CoreValve vs. 43.0% standard therapy, $P < .0001$).[109] Economic analysis of CoreValve use in this population is expected in the near future.

Transcatheter Aortic Valve Replacement Versus Surgical Aortic Valve Replacement in High-Risk Patients

Because TAVR offered a less invasive approach for aortic valve replacement, the question of its applicability and effectiveness in high-risk surgical patients came to the forefront. Cohort A of the PARTNER trial tried to answer this by randomizing 699 high-risk patients with severe aortic stenosis to undergo TAVR (by a transfemoral or transapical approach) or SAVR. The results showed that TAVR was noninferior to SAVR in the primary end point of death at 1 year (24.2% TAVR vs. 26.8% SAVR, $P = .44$). The rates of major stroke were not statistically different at 1 year (5.1% TAVR vs. 2.4%, SAVR, $P = .07$). At 30 days, major vascular complications were significantly more frequent with TAVR (11.0% TAVR vs. 3.2% SAVR, $P < .001$), and MACEs (including major bleeding) were more frequent after SAVR (9.3% TAVR vs. 19.5% SAVR, $P < .001$).[110]

CEA of Cohort A of the PARTNER trial compared SAVR with TAVR using a transfemoral approach (TF-TAVR) or transapical approach (TA-TAVR). In the TF-TAVR cohort, the overall admission costs were not significantly different between groups ($73,219 TAVR vs. $74,067 SAVR), and the 12-month costs were marginally lower for TF-TAVR (mean difference, −$1250; 95% CI, −$18,132 to $13,867). Life expectancy and quality-adjusted life expectancy were slightly higher with TF-TAVR, making TF-TAVR economically dominant compared with SAVR in 55.7% of replicates, with an ICER of $50,000 per QALY gained in 70.9%.[111]

In the TA-TAVR cohort, the total admission costs remained higher with TA-TAVR ($90,919 TA-TAVR vs. $79,024 SAVR). The 12-month cost was slightly higher with TA-TAVR ($100,504 TA-TAVR vs. $98,434 SAVR), with a mean difference of $2,070 (95% CI, −$9,960 to $13,499). Life expectancy was similar for the TA-TAVR and SAVR groups, whereas quality-adjusted life expectancy tended to be less with TA-TAVR. TA-TAVR was economically dominated by SAVR in the base case and economically attractive in only 7.1% of replicates. TF-TAVR seems to be an economically attractive alternative to SAVR for high-risk surgical patients, but this is not the case for TA-TAVR.

Data from the U.S. trial comparing CoreValve TAVR with SAVR in high-risk patients showed that CoreValve use was associated with a significant reduction in mortality (14.2% CoreValve TAVR vs. 19.1% SAVR, $P < .001$ for noninferiority, $P = .04$ for superiority).[112] Economic evaluation of CoreValve use in this population is expected in the near future.

Transcatheter Aortic Valve Replacement Versus Surgical Aortic Valve Replacement in Intermediate-Risk Patients

SAVR is the standard of care for patients with severe aortic stenosis and intermediate or average surgical risk. Randomized trials such as the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) and PARTNER II trials are comparing the effectiveness and cost-effectiveness of TAVR and SAVR for intermediate-risk patients.[113]

Data comparing the costs of both procedures come from a single-center study performed at the Erasmus Medical Center in The Netherlands that compared CoreValve TAVR with SAVR. Despite a shorter hospital length of stay with TAVR, the cost of the TAVR procedure and patient follow-up was higher, resulting in higher in-hospital (€40,802 TAVR vs. €33,354 SAVR, $P = .01$) and total costs for TAVR (€46,217 TAVR vs. €35,511 SAVR, $P = .009$).[114]

Percutaneous Mitral Valve Repair

Data comparing percutaneous mitral valve repair with mitral valve surgery come from the Endovascular Edge-to-Edge Repair Study II

(EVEREST II), which randomly assigned 279 patients with moderately severe or severe (grade 3+ or 4+) mitral regurgitation in a ratio of 2 to 1 to percutaneous repair with the MitraClip (Abbott Vascular, Santa Clara, CA) or conventional surgery for repair or replacement of the mitral valve. Surgical repair was associated with higher rates of freedom from death, from surgery for mitral valve dysfunction, and from grade 3+ or 4+ mitral regurgitation at 12 months (55% MitraClip vs. 73% mitral surgery, $P = .007$). The results reflected the increased need for definitive surgery after use of the MitraClip (20% MitraClip vs. 2% surgery). There was no difference in death (6% in each group) or freedom from grade 3+ or 4+ mitral regurgitation (21% MitraClip vs. 20% surgery). Patients' quality of life improved from baseline to 12 months in the two study groups, but surgery was associated with a transient decrease in the quality of life at 30 days.[115]

CEA of EVEREST II showed that the potential cost-effectiveness of the MitraClip compared with mitral valve surgery depended primarily on the MitraClip price and early procedural success. Economic assessment using the study price of $18,000 showed that the clip strategy reduced costs by $2200 per patient, making it economically dominant. Using a clip price of $26,200 (i.e., approximate European price), the overall costs were higher with the clip strategy by $6192, and the ICER was unfavorable (>$400,000 per QALY gained). In a sensitivity analysis limited to patients with early procedural success, the QALY gain was larger, the cost offset with the clip was greater, and cost-effectiveness was more favorable (i.e., dominant at a MitraClip price of $18,000 and about $54,000 per QALY gained at a price of $26,200).[116] The MitraClip may be an economically reasonable option if the equipment cost falls over time.

REFERENCES

1. Mark DB, Hlatky MA: Medical economics and the assessment of value in cardiovascular medicine: part I. *Circulation* 106(4): 516–520, 2002.
2. Epstein AJ, Polsky D, Yang F, et al: Coronary revascularization trends in the United States, 2001-2008. *JAMA* 305(17):1769–1776, 2011.
3. Jones WS, Patel MR, Holleran SA, et al: Trends in the use of diagnostic coronary angiography, percutaneous coronary intervention, and coronary artery bypass graft surgery across North Carolina. *Am Heart J* 162(5):932–937, 2011.
4. Leon M: *Sweeping changes in the dynamic interventional global landscape*. Presented at the Transcatheter Cardiovascular Therapeutics meeting. San Francisco, November 10, 2011. Available at: <http://www.tctmd.com>. Accessed March 17, 2015.
5. Faxon DP, Williams DO: The changing face of interventional cardiology. *Circ Cardiovasc Interv* 5(3):325–327, 2012.
6. Mahoney EM, Chu H: Cost-effectiveness analysis alongside clinical trials: statistical and methodologic issues. In Weintraub WS, editor: *Cardiovascular health care economics*, Totowa, NJ, 2003, Humana Press, pp 123–156.
7. Pelletier KR, Herman PM, Metz RD, Nelson CF: Health and medical economics applied to integrative medicine. *Explore* 6(2):86–99, 2010.
8. Gunter MJ: The role of the ECHO model in outcomes research and clinical practice improvement. *Am J Manag Care* 5(4 Suppl): S217–S224, 1999.
9. Drummond MF, O'Brien B, Stoddart GL, Torrence GW: *Methods for the economic evaluation of health care programmes*, ed 2, Oxford, UK, 1997, Oxford University Press.
10. Gold MR, Siegel JE, Russell LB, et al: *Cost-effectiveness in health and medicine*, New York, 1996, Oxford University Press.
11. Hsiao WC, Braun P, Dunn D, et al: Results and policy implications of the resource-based relative-value study. *N Engl J Med* 319(13):881–888, 1988.
12. Nease RF, Jr: Introduction to cost-effectiveness analysis. In Weintraub WS, editor: *Cardiovascular health care economics*, Totowa, NJ, 2003, Humana Press, pp 111–121.
13. Weintraub WS, Cohen DJ: The limits of cost-effectiveness analysis. *Circ Cardiovasc Qual Outcomes* 2(1):55–58, 2009.
14. Wright JC, Weinstein MC: Gains in life expectancy from medical interventions—standardizing data on outcomes. *N Engl J Med* 339(6):380–386, 1998.
15. Torrance GW: Measurement of health state utilities for economic appraisal. *J Health Econ* 5(1):1–30, 1986.
16. Claxton K, Sculpher M, Drummond M: A rational framework for decision making by the National Institute for Clinical Excellence (NICE). *Lancet* 360(9334):711–715, 2002.
17. Torgerson DJ, Raftery J: Economic notes. Discounting. *BMJ* 319(7214):914–915, 1999.
18. Sonnenberg FA, Beck JR: Markov models in medical decision making: a practical guide. *Medical Decis Making* 13(4):322–338, 1993.
19. Gilder SS: London letter. *Can Med Assoc J* 104(6):473–481, 1971.
20. Simoens S: How to assess the value of medicines? *Front Pharmacol* 1:115, 2010.
21. Devlin N, Parkin D: Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. *Health Econ* 13(5):437–452, 2004.
22. Hueb W, Lopes NH, Gersh BJ, et al: Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 115(9):1082–1089, 2007.
23. Boden WE, O'Rourke RA, Teo KK, et al: Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 356(15):1503–1516, 2007.
24. Group BDS, Frye RL, August P, et al: A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 360(24):2503–2515, 2009.
25. Vieira RD, Hueb W, Hlatky M, et al: Cost-effectiveness analysis for surgical, angioplasty, or medical therapeutics for coronary artery disease: 5-year follow-up of medicine, angioplasty, or surgery study (MASS) II trial. *Circulation* 126(11 Suppl 1):S145–S150, 2012.
26. Hlatky MA, Boothroyd DB, Melsop KA, et al: Economic outcomes of treatment strategies for type 2 diabetes mellitus and coronary artery disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial. *Circulation* 120(25):2550–2558, 2009.
27. Weintraub WS, Spertus JA, Kolm P, et al: Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med* 359(7):677–687, 2008.
28. Weintraub WS, Boden WE, Zhang Z, et al: Cost-effectiveness of percutaneous coronary intervention in optimally treated stable coronary patients. *Circ Cardiovasc Qual Outcomes* 1(1):12–20, 2008.
29. Holmes DR, Jr, Leon MB, Moses JW, et al: Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation* 109(5):634–640, 2004.
30. Stone GW, Ellis SG, Cox DA, et al: One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation* 109(16):1942–1947, 2004.
31. Roiron C, Sanchez P, Bouzamondo A, et al: Drug eluting stents: an updated meta-analysis of randomised controlled trials. *Heart* 92(5):641–649, 2006.
32. Cohen DJ, VanHout B, Juliard JM, et al: Economic outcomes after coronary stenting or balloon angioplasty in the BENESTENT II trial: the US perspective. *Circulation* 96:455A, 1997.
33. Bakhai A, Stone GW, Mahoney E, et al: Cost effectiveness of paclitaxel-eluting stents for patients undergoing percutaneous coronary revascularization: results from the TAXUS-IV trial. *J Am Coll Cardiol* 48(2):253–261, 2006.
34. Kaiser C, Brunner-La Rocca HP, Buser PT, et al: Incremental cost-effectiveness of drug-eluting stents compared with a third-generation bare-metal stent in a real-world setting: randomised Basel Stent Kosten Effektivitats Trial (BASKET). *Lancet* 366(9489):921–929, 2005.
35. Schafer PE, Sacrinty MT, Cohen DJ, et al: Cost-effectiveness of drug-eluting stents versus bare metal stents in clinical practice. *Circ Cardiovasc Qual Outcomes* 4(4):408–415, 2011.
36. BARI investigators: The final 10-year follow-up results from the BARI randomized trial. *J Am Coll Cardiol* 49(15):1600–1606, 2007.
37. Hlatky MA, Boothroyd DB, Melsop KA, et al: Medical costs and quality of life 10 to 12 years after randomization to angioplasty or bypass surgery for multivessel coronary artery disease. *Circulation* 110(14):1960–1966, 2004.
38. Nordmann AJ, Hengstler P, Leimenstoll BM, et al: Clinical outcomes of stents versus balloon angioplasty in non-acute coronary artery disease: a meta-analysis of randomized controlled trials. *Eur Heart J* 25(1):69–80, 2004.
39. Karthik S, Fabri BM: Left internal mammary artery usage in coronary artery bypass grafting: a measure of quality control. *Ann Roy Coll Surg Engl* 88(4):367–369, 2006.
40. Serruys PW, Ong AT, van Herwerden LA, et al: Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol* 46(4):575–581, 2005.
41. Zhang Z, Spertus JA, Mahoney EM, et al: The impact of acute coronary syndrome on clinical, economic, and cardiac-specific health status after coronary artery bypass surgery versus stent-assisted percutaneous coronary intervention: 1-year results from the Stent or Surgery (SoS) trial. *Am Heart J* 150(1):175–181, 2005.
42. Serruys PW, Morice MC, Kappetein AP, et al: Percutaneous coronary intervention versus coronary artery bypass grafting for severe coronary artery disease. *N Engl J Med* 360(10):961–972, 2009.
43. Cohen DJ, Lavelle TA, Van Hout B, et al: Economic outcomes of percutaneous coronary intervention with drug-eluting stents versus bypass surgery for patients with left main or three-vessel coronary artery disease: one-year results from the SYNTAX trial. *Catheter Cardiovasc Interv* 79(2):198–209, 2012.
44. Farkouh ME, Domanski M, Sleeper LA, et al: Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 367(25):2375–2384, 2012.
45. Magnuson EA, Farkouh ME, Fuster V, et al: Cost-effectiveness of percutaneous coronary intervention with drug eluting stents versus bypass surgery for patients with diabetes mellitus and multivessel coronary artery disease: results from the FREEDOM trial. *Circulation* 127(7):820–831, 2013.
46. Weintraub WS, Grau-Sepulveda MV, Weiss JM, et al: Comparative effectiveness of revascularization strategies. *N Engl J Med* 366(16):1467–1476, 2012.
47. Zhang ZEF, Kolm P, Grau-Sepulveda M, et al: Cost-effectiveness of revascularization strategies: a preliminary study from ASCERT. *Circulation* 126:A18630, 2012.
48. Boersma E, Primary Coronary Angioplasty vs. thrombolysis Group: Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J* 27(7):779–788, 2006.
49. Huynh T, Perron S, O'Loughlin J, et al: Comparison of primary percutaneous coronary intervention and fibrinolytic therapy in ST-segment-elevation myocardial infarction: bayesian hierarchical meta-analyses of randomized controlled trials and observational studies. *Circulation* 119(24):3101–3109, 2009.
50. Machecourt J, Bonnefoy E, Vanzetto G, et al: Primary angioplasty is cost-minimizing compared with pre-hospital thrombolysis for patients within 60 min of a percutaneous coronary intervention center: the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) cost-efficacy sub-study. *J Am Coll Cardiol* 45(4):515–524, 2005.
51. Aasa M, Henriksson M, Dellborg M, et al: Cost and health outcome of primary percutaneous coronary intervention versus thrombolysis in acute ST-segment elevation myocardial infarction—results of the Swedish Early Decision Reperfusion Study (SWEDES) trial. *Am Heart J* 160(2):322–328, 2010.
52. Selmer R, Halvorsen S, Myhre KI, et al: Cost-effectiveness of primary percutaneous coronary intervention versus thrombolytic therapy for acute myocardial infarction. *Scand Cardiovasc J* 39(5):276–285, 2005.
53. Lieu TA, Gurley RJ, Lundstrom RJ, et al: Projected cost-effectiveness of primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 30(7):1741–1750, 1997.
54. Concannon TW, Kent DM, Normand SL, et al: Comparative effectiveness of ST-segment-elevation myocardial infarction regionalization strategies. *Circ Cardiovasc Qual Outcomes* 3(5): 506–513, 2010.
55. Wallentin L, Lagerqvist B, Husted S, et al: Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. FRISC II Investigators. Fast Revascularisation during Instability in Coronary artery disease. *Lancet* 356(9223): 9–16, 2000.
56. Janzon M, Levin LA, Swahn E: Cost-effectiveness of an invasive strategy in unstable coronary artery disease; results from the FRISC II invasive trial. The Fast Revascularisation during InStability in Coronary artery disease. *Europ Heart J* 23(1):31–40, 2002.
57. Cannon CP, Weintraub WS, Demopoulos LA, et al: Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 344(25):1879–1887, 2001.
58. Mahoney EM, Jurkovitz CT, Chu H, et al: Cost and cost-effectiveness of an early invasive vs conservative strategy for the treatment of unstable angina and non-ST-segment elevation myocardial infarction. *JAMA* 288(15):1851–1858, 2002.
59. International Study of Infarct Survival Collaborative Group: Randomised trial of intravenous streptokinase, oral aspirin,

both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 2(8607):349–360, 1988.
60. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. The RESTORE Investigators. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation* 96(5):1445–1453, 1997.
61. Weintraub WS, Culler S, Boccuzzi SJ, et al: Economic impact of GPIIB/IIIA blockade after high-risk angioplasty: results from the RESTORE trial. Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis. *J Am Coll Cardiol* 34(4):1061–1066, 1999.
62. PURSUIT Trial Investigators: Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med* 339(7):436–443, 1998.
63. Mark DB, Harrington RA, Lincoff AM, et al: Cost-effectiveness of platelet glycoprotein IIb/IIIa inhibition with eptifibatide in patients with non-ST-elevation acute coronary syndromes. *Circulation* 101(4):366–371, 2000.
64. Topol EJ, Mark DB, Lincoff AM, et al: Outcomes at 1 year and economic implications of platelet glycoprotein IIb/IIIa blockade in patients undergoing coronary stenting: results from a multicentre randomised trial. EPISTENT investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lance* 354(9195):2019–2024, 1999.
65. Rupprecht HJ, Darius H, Borkowski U, et al: Comparison of antiplatelet effects of aspirin, ticlopidine, or their combination after stent implantation. *Circulation* 97(11):1046–1052, 1998.
66. Mehta SR, Yusuf S, Peters RJ, et al: Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 358(9281):527–533, 2001.
67. Mahoney EM, Mehta S, Yuan Y, et al: Long-term cost-effectiveness of early and sustained clopidogrel therapy for up to 1 year in patients undergoing percutaneous coronary intervention after presenting with acute coronary syndromes without ST-segment elevation. *Am Heart J* 151(1):219–227, 2006.
68. Wiviott SD, Braunwald E, McCabe CH, et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 357(20):2001–2015, 2007.
69. Mahoney EM, Wang K, Arnold SV, et al: Cost-effectiveness of prasugrel versus clopidogrel in patients with acute coronary syndromes and planned percutaneous coronary intervention: results from the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with Prasugrel-Thrombolysis in Myocardial Infarction TRITON-TIMI 38. *Circulation* 121(1):71–79, 2010.
70. Wallentin L, Becker RC, Budaj A, et al: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 361(11):1045–1057, 2009.
71. Nikolic E, Janzon M, Hauch O, et al: Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study. *Eur Heart J* 34(3):220–228, 2013.
72. Theroux P, Ouimet H, McCans J, et al: Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 319(17):1105–1111, 1988.
73. Oler A, Whooley MA, Oler J, Grady D: Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina: A meta-analysis. *JAMA* 276(10):811–815, 1996.
74. Cohen M, Demers C, Gurfinkel EP, et al: A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events study group. *N Engl J Med* 337(7):447–452, 1997.
75. Mark DB, Cowper PA, Berkowitz SD, et al: Economic assessment of low-molecular-weight heparin (enoxaparin) versus unfractionated heparin in acute coronary syndrome patients: results from the ESSENCE randomized trial. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events [unstable angina or non-Q-wave myocardial infarction]. *Circulation* 97(17):1702–1707, 1998.
76. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes I, Yusuf S, Mehta SR, et al: Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 354(14):1464–1476, 2006.
77. Sculpher MJ, Lozano-Ortega G, Sambrook J, et al: Fondaparinux versus enoxaparin in non-ST-elevation acute coronary syndromes: short-term cost and long-term cost-effectiveness using data from the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators (OASIS-5) trial. *Am Heart J* 157(5):845–852, 2009.
78. Stone GW, McLaurin BT, Cox DA, et al: Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 355(21):2203–2216, 2006.
79. Pinto DS, Stone GW, Shi C, et al: Economic evaluation of bivalirudin with or without glycoprotein IIb/IIIa inhibition versus heparin with routine glycoprotein IIb/IIIa inhibition for early invasive management of acute coronary syndromes. *J Am Coll Cardiol* 52(22):1758–1768, 2008.
80. Antman EM, Morrow DA, McCabe CH, et al: Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 354(14):1477–1488, 2006.
81. Marcoff L, Zhang Z, Zhang W, et al: Cost effectiveness of enoxaparin in acute ST-segment elevation myocardial infarction: the ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction 25) study. *J Am Coll Cardiol* 54(14):1271–1279, 2009.
82. Stone GW, Witzenbichler B, Guagliumi G, et al: Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 358(21):2218–2230, 2008.
83. Schwenkglenks M, Toward TJ, Plent S, et al: Cost-effectiveness of bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitor in the treatment of acute ST-segment elevation myocardial infarction. *Heart* 98(7):544–551, 2012.
84. Shahzad A, Kemp I, Mars C, et al: Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet* 2014.
85. Hong MS, Beck AW, Nelson PR: Emerging national trends in the management and outcomes of lower extremity peripheral arterial disease. *Ann Vasc Surg* 25(1):44–54, 2011.
86. Eslami MH, Csikesz N, Schanzer A, Messina LM: Peripheral arterial interventions: trends in market share and outcomes by specialty, 1998-2005. *J Vasc Surg* 50(5):1071–1078, 2009.
87. Jansen RM, de Vries SO, Cullen KA, et al: Cost-identification analysis of revascularization procedures on patients with peripheral arterial occlusive disease. *J Vasc Surg* 28(4):617–623, 1998.
88. Kugler CF, Rudofsky G: The challenges of treating peripheral arterial disease. *Vasc Med* 8(2):109–114, 2003.
89. Hunink MG, Wong JB, Donaldson MC, et al: Revascularization for femoropopliteal disease: a decision and cost-effectiveness analysis. *JAMA* 274(2):165–171, 1995.
90. Singh S, Evans L, Datta D, et al: The costs of managing lower limb-threatening ischaemia. *Eur J Vasc Endovasc Surg* 12(3):359–362, 1996.
91. Antiplatelet Trialists' Collaboration: Collaborative overview of randomised trials of antiplatelet therapy—II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. *BMJ* 308(6922):159–168, 1994.
92. Bhatt DL, Fox KA, Hacke W, et al: Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 354(16):1706–1717, 2006.
93. Bhatt DL, Flather MD, Hacke W, et al: Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol* 49(19):1982–1988, 2007.
94. Chen J, Bhatt DL, Dunn ES, et al: Cost-effectiveness of clopidogrel plus aspirin versus aspirin alone for secondary prevention of cardiovascular events: results from the CHARISMA trial. *Value Health* 12(6):872–879, 2009.
95. Adam DJ, Beard JD, Cleveland T, et al: Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet* 366(9501):1925–1934, 2005.
96. Bradbury AW, Adam DJ, Bell J, et al: Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. *J Vasc Surg* 51(5 Suppl):5S–17S, 2010.
97. Duda SH, Bosiers M, Lammer J, et al: Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. *J Endovasc Ther* 13(6):701–710, 2006.
98. Dake MD, Ansel GM, Jaff MR, et al: Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. *Circ Cardiovasc Interv* 4(5):495–504, 2011.
99. Werk M, Albrecht T, Meyer DR, et al: Paclitaxel-coated balloons reduce restenosis after femoro-popliteal angioplasty: evidence from the randomized PACIFIER trial. *Circ Cardiovasc Interv* 5(6):831–840, 2012.
100. Kearns BC, Michaels JA, Stevenson MD, Thomas SM: Cost-effectiveness analysis of enhancements to angioplasty for infrainguinal arterial disease. *Br J Surg* 100(9):1180–1188, 2013.
101. Pietzsch JB, Geisler BP, Garner AM, et al: Economic analysis of endovascular interventions for femoropopliteal arterial disease: a systematic review and budget impact model for the United States and Germany. *Catheter Cardiovasc Interv* 84(4):546–554, 2014.
102. Nkomo VT, Gardin JM, Skelton TN, et al: Burden of valvular heart diseases: a population-based study. *Lancet* 368(9540):1005–1011, 2006.
103. Kotowycz MA, Therrien J, Ionescu-Ittu R, et al: Long-term outcomes after surgical versus transcatheter closure of atrial septal defects in adults. *JACC Cardiovasc Interv* 6(5):497–503, 2013.
104. Mylotte D, Quenneville SP, Kotowycz MA, et al: Long-term cost-effectiveness of transcatheter versus surgical closure of secundum atrial septal defect in adults. *Int J Cardiolo* 172(1):109–114, 2014.
105. Osnabrugge RL, Mylotte D, Head SJ, et al: Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol* 62(11):1002–1012, 2013.
106. Leon MB, Smith CR, Mack M, et al: Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 363(17):1597–1607, 2010.
107. Reynolds MR, Magnuson EA, Wang K, et al: Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the placement of aortic transcatheter valves (PARTNER) trial (Cohort B). *Circulation* 125(9):1102–1109, 2012.
108. Watt M, Mealing S, Eaton J, et al: Cost-effectiveness of transcatheter aortic valve replacement in patients ineligible for conventional aortic valve replacement. *Heart* 98(5):370–376, 2012.
109. Popma JJ, Adams DH, Reardon MJ, et al: Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol* 63(19):1972–1981, 2014.
110. Smith CR, Leon MB, Mack MJ, et al: Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 364(23):2187–2198, 2011.
111. Reynolds MR, Magnuson EA, Lei Y, et al: Cost-effectiveness of transcatheter aortic valve replacement compared with surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results of the PARTNER (Placement of Aortic Transcatheter Valves) trial (Cohort A). *J AmColl Cardiol* 60(25):2683–2692, 2012.
112. Adams DH, Popma JJ, Reardon MJ, et al: Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 370(19):1790–1798, 2014.
113. Gadey G, Reynolds MR: Cost-effectiveness considerations in transcatheter management of valvular heart disease. *Can J Cardioy* 30(9):1058–1063, 2014.
114. Osnabrugge RL, Head SJ, Genders TS, et al: Costs of transcatheter versus surgical aortic valve replacement in intermediate-risk patients. *Ann Thorac Surg* 94(6):1954–1960, 2012.
115. Feldman T, Foster E, Glower DD, et al: Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 364(15):1395–1406, 2011.
116. Reynolds MR, Galper B, Apruzzese P, et al: Cost effectiveness of the MitraClipcompared with mitral valve surgery: 12-month results from the EVEREST II randomized controlled trial (abstract). *J Am Coll Cardiol* 60:B229, 2012.

Quality of Care in Interventional Cardiology

64

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KEY POINTS

- With increasing state and federal regulations, direct patient access to publicly available information about the quality of care, and pressures from payers for cost-efficiency, the delivery of care in the cardiac catheterization laboratory is being examined closely.
- Efforts to improve the quality of medical care in the United States started more than 150 years ago and new initiatives such as public reporting were incorporated into the Patient Protection and Affordable Care Act of 2010.
- Donabedian's triad of three domains—structure, process, and outcomes—provides a conceptual framework for evaluating the quality of medical care. Catheterization laboratory personnel should understand the existing structural elements, processes, and outcomes.
- Each catheterization laboratory should develop a framework of quality to ensure that the right patient gets the right procedure with the right execution and the right outcome on a daily basis.
- The framework should include the specific elements and activities that constitute the building blocks of quality.
- Public reporting increases transparency and is part of the proposed mechanisms to tie reimbursement to quality care. Reporting must occur in a fair, accurate, and meaningful way that benefits patients but minimizes unintended negative consequences.

Quality is everyone's responsibility.

W. Edwards Deming[1]

Interventional cardiology has grown rapidly since its inception more than 30 years ago. Invasive cardiovascular procedures have become the cornerstone for evaluation and management of many cardiovascular diseases, especially coronary artery disease. Since the start of interventional cardiology, there have been efforts to measure and evaluate the quality of care.

Considerable attention has been focused on the cardiac catheterization laboratory because these procedures are widely used, easily identified with claims data, expensive, and associated with important complications. Attention continues to intensify because of increasing state and federal regulations, requests for public reporting of hospital and physician data, consumer pressures for care of the highest quality, and pressure from payers for cost-efficient care and appropriate use of diagnostic cardiac catheterization and percutaneous coronary interventions (PCIs). There is also growing awareness that the quality of health care is compromised by preventable medical errors, absence of evidence-based standards in many areas, lack of emphasis on disease prevention, inadequate personal responsibility for maintaining health, and disparities in health care delivery related to race, gender, income, and insurance status.

Numerous government and private agencies in the United States have been involved in the development of quality measures and dissemination of data (Table 64-1). Report cards on cardiac operations and PCIs for hospitals and individual physicians exist in some states.[2,3] Interest in these reports continue to increase as data have emerged showing that patients fail to receive up to 45% of the tests and treatments recommended by evidence-based guidelines.[4] In an attempt to promote quality and improve outcomes, pay-for-performance programs, in which providers receive financial incentives for achieving certain benchmark goals in patient care, were developed.[5] With payment reform and Centers for Medicare and Medicaid Services (CMS) demonstration projects such as bundled payment care initiatives, there will be increasing focus on the efficient delivery of percutaneous procedures as part of a complete episode of care over a specified time period (e.g., 30 to 90 days).[6]

Although there are no formal national standards with which to judge the quality of cardiac catheterization laboratories, some states have used clinical practice guidelines and expert consensus documents published by the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the Society for Cardiovascular Angiography and Interventions (SCAI) to develop quality standards.[7-9] Although these documents were never intended to serve as state or national standards, they have become the de facto basis for licensure regulations imposed by state health departments in an attempt to improve quality. To understand the current status of quality efforts in the cardiac catheterization laboratory, it is helpful to examine some of the major events that form the history of quality efforts in U.S. health care.

QUALITY EFFORTS IN U.S. MEDICINE

Despite concerns about the state of American medicine, there have been profound improvements during the past 150 years. The American Medical Association (AMA) was founded in 1847, in part to address the disorganized and poor quality of health care in the United States. As a precursor of future efforts, the American College of Surgeons established the Hospital Standardization Program in 1917, promoting five basic patient care standards and surveying health care organizations to determine their acceptability for accreditation. In 1952, several other organizations collaborated with the American College of Surgeons to form the Joint Commission on Accreditation of Hospitals, now called The Joint Commission.[10]

A structure for organizing quality standards in health care was proposed by Avedis Donabedian in 1966 with the publication of an article that provided a broad definition of quality. It recommended evaluations in three areas: structure, process, and outcome.[11] This format was widely adapted and is still in use today.

During this early period, quality was often assessed by random chart audits or outcome-oriented chart surveys to evaluate metrics such as the use of blood products in surgical cases. Audit requirements were later minimized in favor of hospital-wide quality assurance programs designed to detect care that was thought to be outside acceptable standards. Physician profiles reflecting the number of procedures performed, indications, and complications were compared with grouped data from similar physicians to identify outliers with the hope that they could be persuaded to change their practice habits by colleagues, the hospital, or other agencies.[12]

About 1990, a technique developed primarily for industry, called *continuous quality improvement* (CQI), was advocated by The Joint Commission. Compared with quality assurance programs, CQI tries to improve overall performance rather than identifying poor performers.[13-15] CQI has become a central activity for all health care organizations.

TABLE 64-1 Organizations Involved in the Assessment of Quality Care

Organization	Mission, Goals, and Focus	Website
Agency for Healthcare Research and Quality (AHRQ)	Lead federal agency charged with improving the quality, safety, efficiency, and effectiveness of health care for all Americans	www.ahrq.gov
National Guideline Clearinghouse (NGC)	An initiative of AHRQ that is a public resource for evidence-based clinical practice guidelines	www.guideline.gov
Centers for Medicare and Medicaid Services (CMS)	Host for Hospital Compare, which reports the process of care, risk-adjusted outcomes, and patient satisfaction measures for all hospitals in the United States	www.medicare.gov/hospitalcompare
Centers for Medicare and Medicaid Services (CMS)	Host for Physician Compare, which helps consumers find and choose physicians and other health care professionals enrolled in Medicare and will report several provider metrics in the future	www.medicare.gov/physiciancompare
Department of Health and Human Services (DHHS)	Provides links to hundreds of sites on the Internet that contain reliable health care information and links to many government and nongovernment sources of information on health care quality	www.healthfinder.gov
The Joint Commission	Provides accreditation to hospital and other health care facilities; provides quality care and hospital quality measures for public reporting through the ORYX reporting program	www.jointcommission.org
National Committee for Quality Assurance (NCQA)	A private, 501(c)(3) not-for-profit organization dedicated to improving health care quality; operates the Healthcare Effectiveness Data and Information Set (HEDIS), a tool used by more than 90% of America's health plans to measure performance on important dimensions of care and service	www.ncqa.org
The American Health Quality Association (AHQA)	An educational, not-for-profit national membership association dedicated to health care quality through community-based, independent quality evaluation and improvement programs	www.ahqa.org
National Quality Forum (NQF)	Sets national priorities and goals for performance improvement and endorses national consensus standards for measuring and publicly reporting on performance	www.qualityforum.org
American Medical Association (AMA)	AMA-sponsored Physician Consortium for Performance Improvement (PCPI) enhances quality of care and patient safety through development, testing, and maintenance of evidence-based clinical performance measures and measurement resources for physicians	www.ama-assn.org
American College of Cardiology Foundation (ACCF)	In collaboration with other professional organizations, develops clinical practice guidelines, expert consensus documents, and other quality programs, including Guidelines Applied in Practice (GAP) to assist with guideline application in clinical practice and Hospital to Home (H2H), an effort to improve the transition from inpatient to outpatient status for those with cardiovascular disease	www.cardiosource.org
American Heart Association (AHA)	In collaboration with other professional organizations, develops clinical practice guidelines, expert consensus documents, and other quality programs, including Get With the Guidelines, a hospital-based quality-improvement program to ensure consistent treatment according to evidence-based guidelines, and Mission: Lifeline, a national, community-based initiative to improve systems of care for patients with ST-elevation myocardial infarction	www.my.americanheart.org
The Leapfrog Group	A voluntary program organized by large employers to promote big leaps in health care safety, quality, and customer value	www.leapfroggroup.org

As quality efforts by the medical profession were maturing, state and federal agencies were becoming interested in regulating health care, developing standards, and promoting high-quality medical care. By the late 1800s, many states required physician licensure and mandated educational standards for physicians. The National Board of Medical Examiners was founded in 1915 to provide a nationwide examination that licensing authorities could accept and use to judge candidates for licensure.

As the medical field expanded and specialty training became available, it was recognized that some type of certification process for specialists was necessary. To establish a uniform system, the American Board of Medical Specialties was formed in 1933. There are now 24 specialty boards that certify physicians, and this process has evolved to one of continuous professional development and lifelong learning through a Maintenance of Certification program requiring ongoing measurement of six core competencies.[16] Controversy has accompanied the Maintenance of Certification program, and it continues to evolve as several groups attempt to determine the optimal strategy.[17]

One of the first federal quality initiatives was the formation of the U.S. Food and Drug Administration (FDA) in 1906. With the enactment of Social Security in 1935 and Medicare in 1965, the Federal government became more involved in setting requirements for the delivery of health care funded by federal dollars.

To monitor the care of Medicare patients, Congress enacted rules called *Conditions of Participation*, which required hospitals to provide certain services and conduct reviews to determine the appropriateness of hospital admissions. In 1972, amendments to the Social Security Act created the Professional Standards Review Organization program to promote hospital efficiency and eliminate unnecessary hospital use. This program failed to meet expectations and was unpopular because many thought it emphasized cost containment rather than quality.[12] It was abandoned and replaced by other peer review organizations.[18]

At the same time, substantial changes in hospital reimbursement occurred, with a shift to a cost-per-case system based on assignment to a diagnosis-related group (DRG). The peer review organizations were responsible for validating correct assignment to a DRG and for monitoring hospital admissions, readmissions, surgical procedures, complications, and hospital deaths. Peer review organizations emphasized quality but focused more on outcome metrics than structure and process metrics, and they were not without their critics.[19]

As the amount of Medicare spending increased, the federal government became more involved in monitoring and controlling payments

to physicians and hospitals. Before 1989, physician payments for services within the Medicare program were based on usual and customary charges for services by similar physicians in the previous year. Substantial changes in Medicare payments to physicians occurred as a result of the Budget Reconciliation Act of 1989, which redirected payments based on costs rather than charges. Costs were determined for the actual work involved, the overhead required to provide the service, and malpractice costs, with all three elements further adjusted for geographic differences in cost. This caused major changes in practice patterns, which had positive and negative effects on the quality of care.

Additional federal funding led to the formation of the Agency for Health Care Policy and Research, which had a turbulent history and narrowly escaped being eliminated in 1995, only to be reauthorized in 1999 with a new mandate and new name: the Agency for Healthcare Research and Quality (AHRQ). Many other quality initiatives and programs were developed by professional organizations and government agencies over the next 10 years with various degrees of success.

Several quality initiatives were proposed as part of the Patient Protection and Affordable Care Act (PPAHA public law 111-148) of 2010. In addition to sweeping changes in the delivery of health care, several provisions in this legislation specifically targeted the quality of health care, including establishment of a Patient-Centered Outcomes Research Institute, formation of a Medicare Innovation Center with $10 billion to fund payment reform and quality improvement pilots, and development of new systems linking payment to quality outcomes. The initiatives in the PPAHA and other progressive efforts promote a major transformation of the American health care delivery system through realignment of payment incentives to reward quality rather than quantity of care.

It is important for interventional cardiologists to understand this history as they interact with many parts of the developing quality infrastructure, such as The Joint Commission, board certification, maintenance of certification, increased transparency from public reporting, and payment reforms.

QUALITY IN INTERVENTIONAL CARDIOLOGY

But even though Quality cannot be defined, you know what Quality is.

Robert M. Persig[20]

Definition

Quality is something everyone wants in health care, but it is not easily defined. Patients, physicians, payers, and government have different perspectives on the elements that contribute to high-quality health care. Patients frequently place greater emphasis on the interaction and time they have with their physician rather than on issues such as adherence to practice guidelines. In contrast, payers and government agencies are likely to place more emphasis on adherence to performance measures and on reductions in unnecessary procedures and costs.

The potential to deliver high-quality care in the cardiac catheterization laboratory centers on the core values promoted by the Institute of Medicine (IOM). In its report, *Crossing the Quality Chasm,* quality is defined as "the degree to which health care systems, services, and supplies for individuals and populations increase the likelihood for desired health outcomes in a manner consistent with current professional knowledge."[21] The IOM further states that health care should be safe, effective, evidence based, timely, equitable, and patient centered.

Several definitions of quality have been proposed, reflecting the complexity of the health care system and its heterogeneous stakeholders. The RAND Corporation defines quality care as "providing patients with appropriate services in a technically competent manner, with good communications, shared decision making, and cultural sensitivity."[22]

An increasingly popular operational definition of quality is based on error reduction and the recognition that there are three major types of errors in health care: underuse, overuse, and misuse.[23] *Underuse* is a failure to provide a medical intervention when it is likely to produce a favorable outcome for a patient. *Overuse* is the use of a test or therapy even though its benefits do not justify the potential harm or costs. *Misuse* occurs when a therapy or diagnostic test is used in the wrong way or for the wrong purpose.

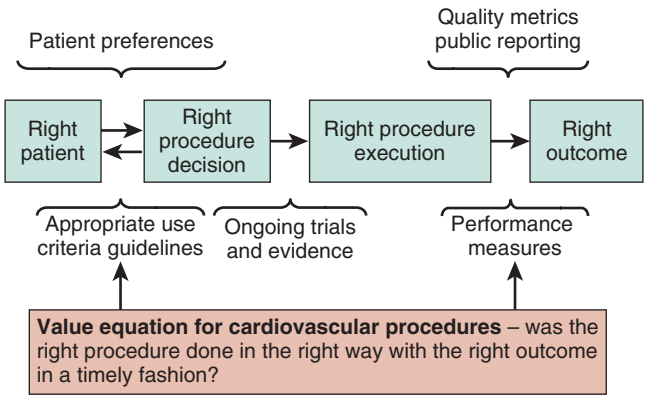


FIGURE 64-1 Conceptual model and quality framework for high-quality interventional procedures.

However quality is defined for interventional cardiologists, a structure for evaluating and measuring quality is needed to continually improve patient care (Fig. 64-1).[24] The structure suggested provides a framework of quality into which recognized building blocks of quality can be placed and used in everyday workflow. The building blocks include specific elements and activities:

- Quality and case reviews are performed on a regular basis by all members of the patient care team in the catheterization laboratory (e.g., cardiologists, nurses, technologists) and by cardiac surgeons, noninvasive cardiologists, and others if necessary.
- Clinical practice guidelines, data standards, performance measures, and appropriate use criteria are incorporated into daily practice.
- The CQI process is used as a tool to evaluate variations in practice and improve performance in the cardiac catheter laboratory.
- Data are submitted to clinical registries such as the CathPCI Registry of the National Cardiovascular Data Registry (NCDR) to benchmark patient outcomes rather than using volume standards or administrative databases.
- Data from the NCDR and other local information are used to create dashboards for easy and understandable display of trends.

For invasive procedures, the decision to perform the procedure (i.e., right patient and right procedure) may be measured with appropriate use criteria and clinical practice guidelines. A quality health care environment ensures that the patient is receiving the correct treatment for his or her condition. If the patient receives flawless and efficient delivery of the wrong treatment, quality cannot exist. Patient preference is solicited as part of shared decision making along with the clinical recommendation. Execution of the right procedure is influenced by clinical practice guidelines, performance measures, and the best available evidence, but it also includes the operator's skill and experience as assessed by board certification and maintenance of certification, case reviews, and other peer review activities.

The right clinical result can be assessed by performance and outcome measures, some of which are publicly reported. In this fashion, the interventional practice of a facility and an operator may be evaluated, which provides the basis for determining the value of different practices.

Therapeutic Development and Quality

Quality in health care has its origin in the cycle of therapeutic development (Fig. 64-2).[25] The model starts with a hypothesis derived from basic scientific research, animal research, or other observations. It progresses to early clinical research with small, nonrandomized, and

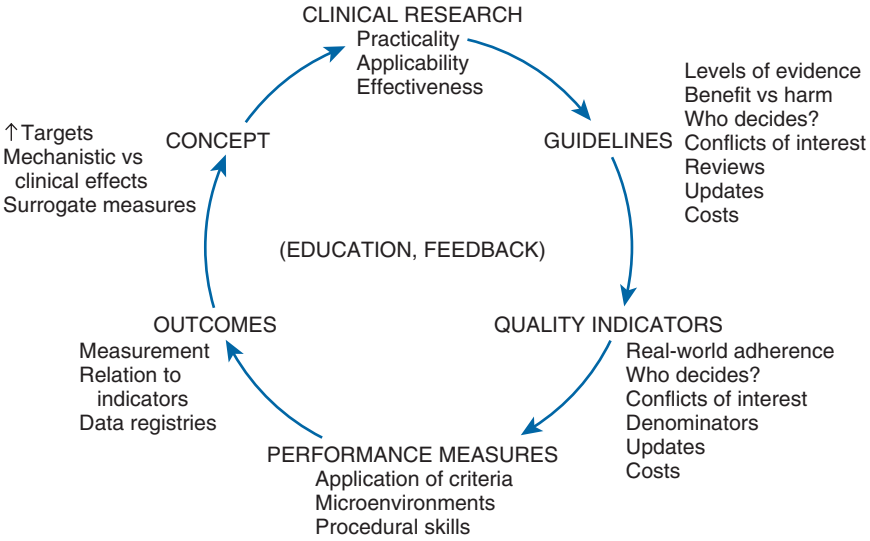


FIGURE 64-2 Model for the integration of quality into the cycle of therapeutic development. Concepts from the basic research laboratory eventually leads to clinical studies. After well-conducted clinical research is completed, clinical practice guidelines are developed, leading to quality indicators and then performance measures intended to elevate the level of care and improve patient outcomes. (From Califf RM, Peterson ED, Gibbons RJ, et al: Integrating quality into the cycle of therapeutic development. *J Am Coll Cardiol* 40[11]:1895-1901, 2002.)

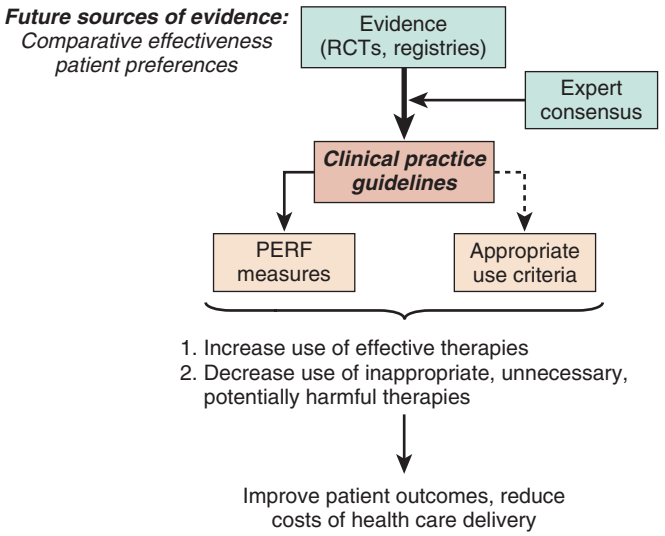


FIGURE 64-3 The building blocks of quality. Performance measures and appropriate use criteria are derived from clinical practice guidelines. PERF, Performance; RCT, randomized controlled trial. (From Antman EM, Peterson ED: Tools for guiding clinical practice from the American Heart Association and the American College of Cardiology: what are they and how should clinicians use them? *Circulation* 119:1180-1185, 2009.)

unblinded case series and eventually leads to a large, randomized, blinded, and well-designed clinical trial.

After one or more well-performed clinical trials provide clear information about a clinical question, the substrate is established for a clinical practice guideline. All available evidence and opinions are used to produce the clinical practice guidelines for medical conditions and therapeutic procedures (e.g., PCI guidelines). The appropriate use criteria and performance measures are then derived from clinical practice guidelines (Fig. 64-3).

BUILDING BLOCKS OF QUALITY

Clinical Practice Guidelines

The IOM defines *guidelines* as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."[26] For almost 20 years, the AHA, ACCF, and subspecialty organizations have collaborated to develop clinical practice guidelines in cardiology. Guidelines can improve the quality of cardiovascular care and enhance the use of evidence-based therapies, leading to better patient outcomes, improved cost-effectiveness, and identification of knowledge gaps that require further research.

After a thorough review of the evidence, guideline recommendations are developed with a designated level of evidence in a structured format (Fig. 64-4). To remain relevant and be embraced by clinicians, clinical practice guidelines must incorporate new evidence in a timely fashion. Guidelines are updated as new and important data are published. Guideline recommendations can be synthesized into algorithms, which can be used to develop quality indicators by specifying the clinical circumstances under which a technology or treatment should or should not be used. Class I and III guideline recommendations with level A evidence identify recommendations that can be considered for the development of a quality measure.

Unfortunately, the process is not as straightforward as it seems because of the many treatment considerations for which reasonable uncertainty exists. A challenge to the development of quality indicators occurs when attempting to define which patients qualify for a particular indicator. In one study involving Medicare patients, less than half of all patients with an acute myocardial infarction (AMI) qualified for a particular quality measure because of a long list of exclusions.[27] If a large number of patients are excluded from a particular quality measure, it may not be a meaningful reflection of the care provided by a physician or a facility. Determining how well a provider or an institution meets specified quality indicators is one way to gauge the quality of the health care delivered. Clinical practice guidelines and performance measures do not consider cost and value in their deliberations.[28]

Performance Measures

Performance measures are derived from clinical practice guidelines. A *quality indicator* is a variable, such as primary PCI performed in patients with ST-segment elevation myocardial infarction (STEMI) within 90 minutes if PCI is immediately available. In contrast, *performance measures* must have a well-defined numerator and denominator and have appropriate and specified reasons to exclude patients from the tabulation within the measure.

Performance measure selection involves evaluating the strength of evidence supporting the measure, defining the importance of the outcome most likely to be achieved by adherence to it, and assessing the association between adherence to the performance measure and a

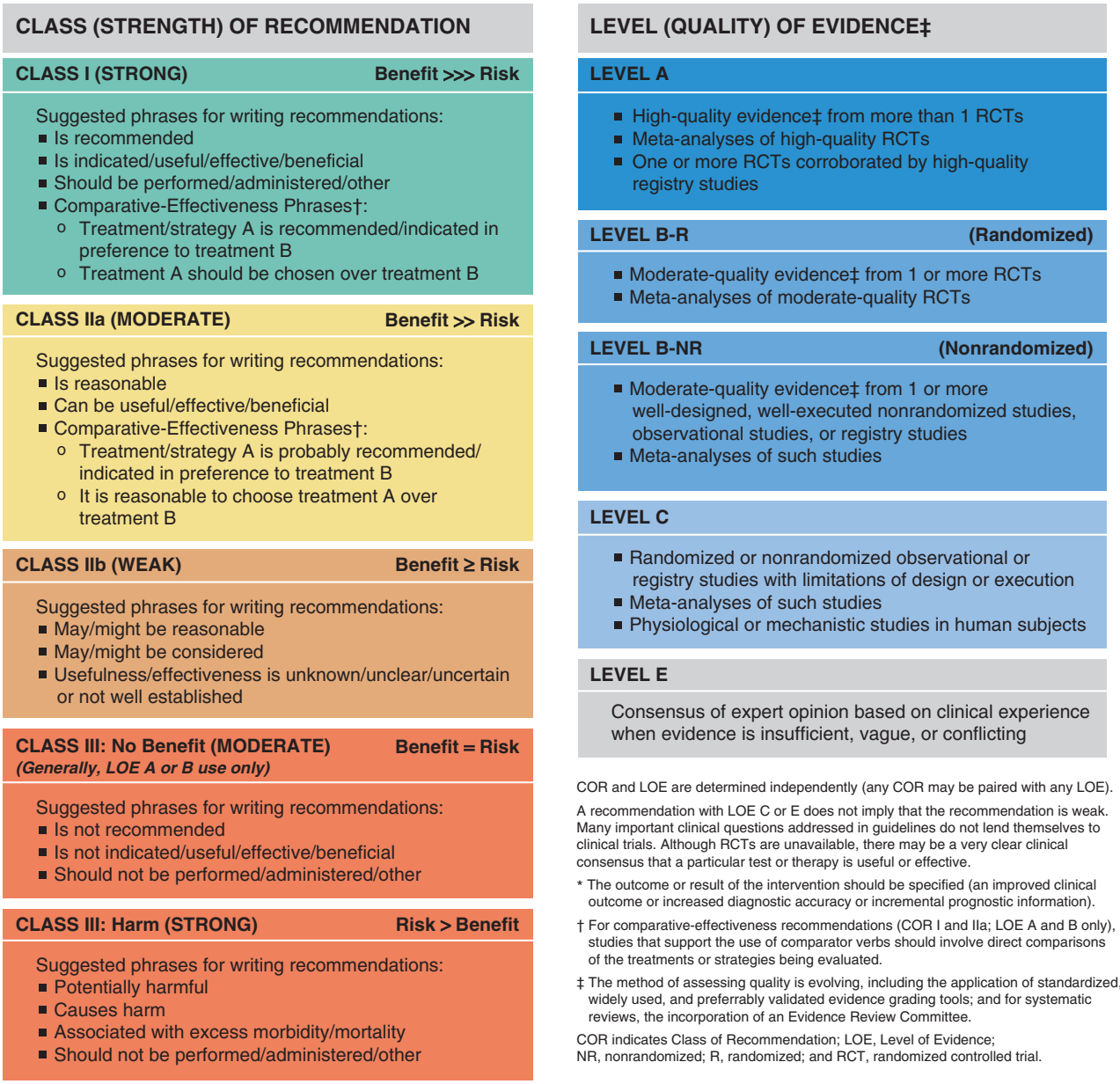


FIGURE 64-4 Classification of recommendations and level of evidence used in the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) clinical practice guidelines. Definitions of treatment recommendations and levels of evidence are shown. (From American Heart Association: Methodology manual and policies from the ACCF/AHA Task Force on Practice Guidelines. Available at http://assets.cardiosource.com/Methodology_Manual_for_ACC_AHA_Writing_Committees.pdf [accessed March 25, 2015].)

clinically important outcome. Using the earlier example, the corresponding performance measure would be the proportion of eligible patients with STEMI who arrive at a PCI-capable hospital and receive primary PCI within 90 minutes of arrival. Guideline recommendations that clearly specify the patient population appropriate for a specified treatment or the optimal timing of a treatment are ideal for translation into performance measures.

A detailed description of the methodology for the selection and creation of American College of Cardiology and American Heart Association (ACC/AHA) performance measures has been published.[29] Similar to quality measures, class I guideline recommendations identify potential patient care decisions that could be considered for a performance measure. Performance measures represent mandatory elements of clinical care, whereas failure to adhere to a performance measure represents inadequate or inferior care. Other important attributes to consider in the development of a performance measure are the cost associated with implementing the measure, availability of reimbursement for the therapy or intervention, and the cost of collecting data required for the measure (Table 64-2).

Performance measures set a threshold for acceptable performance. This leads to questions regarding who determines the threshold and how the threshold level of performance is determined because it is unlikely that 100% compliance will be achieved for every performance measure. One method for defining thresholds is to establish achievable benchmarks of care.[30] Adherence to a performance measure is determined in a large sample, and the rate of adherence in the top 10% of facilities or physicians is set as the achievable benchmark. Using this method avoids establishing unreasonable goals that might paradoxically lead to inappropriate actions to achieve the established goal. Table 64-3 lists current performance measures in cardiology.

TABLE 64-2 American College of Cardiology and American Heart Association (ACC/AHA) Attributes for Satisfactory Performance Measures

Measures for Improving Patient Outcomes
Evidence based
Interpretable
Actionable
Measure Design
Denominator precisely defined
Numerator precisely defined
Validity
Face validity
Content validity
Construct validity
Reliability
Measure Implementation
Feasibility
Reasonable effort
Reasonable cost
Reasonable time period for collection

Modified from Spertus JA, Eagle KA, Krumholtz HM, et al: American College of Cardiology and American Heart Association methodology for the selection and creation of performance measures for quantifying and quality of cardiovascular care. *J Am Coll Cardiol* 45(7):1147-1156, 2005.

TABLE 64-3 American College of Cardiology Foundation and American Heart Association Performance Measure Sets

Topic	Publication Date	Partnering Organizations
Chronic heart failure	2005	ACC, AHA: inpatient measures ACC, AHA, PCPI outpatient measures
Chronic stable coronary artery disease	2005	ACC, AHA, PCPI
Hypertension	2005	ACC, AHA, PCPI
ST- and non–ST-myocardial infarction	2006	ACC, AHA
Cardiac rehabilitation	2007	AACVPR, ACC, AHA
Atrial fibrillation	2008	ACC, AHA, PCPI
Primary prevention of cardiovascular disease	2009	ACCF, AHA
Peripheral artery disease	2010	ACCF, AHA, ACR, SCAI, SIR, SVM, SVN, SVS
Percutaneous coronary intervention	2013	ACCF, AHA, SCAI, AMA

ACC, American College of Cardiology; *ACCF,* American College of Cardiology Foundation; *AHA,* American Heart Association; *PCPI,* AMA's Physician Consortium for Performance Improvement; *AACVPR,* American Association of Cardiovascular and Pulmonary Rehabilitation; *ACR,* American College of Radiology; *SCAI,* Society for Cardiovascular Angiography and Interventions; *SIR,* Society for Interventional Radiology; *SVM,* Society for Vascular Medicine; *SVN,* Society for Vascular Nursing; *SVS,* Society for Vascular Surgery.

There is interest in developing composite performance measures.[31] A composite performance measure is the combination of two or more measures into a single index. Composite measures reduce the information burden by distilling the available indicators into a summary with which to examine multiple dimensions of performance and facilitate comparisons. The Society of Thoracic Surgeons developed and validated a composite measure for coronary artery bypass grafting (CABG) comprising five process measures and six outcome measures, all of which are endorsed by the National Quality Forum (NQF) (Table 64-4).[32,33] The NQF has endorsed ACC/AHA and NCDR performance measures, potentially affecting future payment models. However, there are challenges to this approach. Details of an important individual measure can be diluted in the overall composite, and methods for deriving the composite must be transparent to prevent it from being perceived as a black box.

TABLE 64-4 Individual Measures and Domains Included in the Society of Thoracic Surgeons Composite Score

Operative Care Domain
Use of at least one internal mammary artery graft
Perioperative Medical Care Domain
Preoperative beta-blockers
Discharge beta-blockers
Discharge antiplatelet medication
Discharge antilipid medication
Risk-Adjusted Mortality Domain
Operative mortality
Risk-Adjusted Major Morbidity Domain
Prolonged ventilation (>24 hr)
Deep sternal wound infection
Permanent stroke
Renal insufficiency
Reoperation

From O'Brien SM, Shahian DM, DeLong ER, et al: Quality measurement in adult cardiac surgery: part 2—statistical considerations in composite measure scoring and provider rating. *Ann Thorac Surg* 83(4 Suppl):S13-S26, 2007.

A detailed list of performance measures has been published for PCI.[34] Eleven measures encompassing the triad of structure, process, and outcome were identified; six are considered performance measures, and five were recommended as quality metrics for self-improvement (Table 64-5). The measures identified as performance measures include comprehensive documentation of the indication for the procedures, assessment of candidacy for dual-antiplatelet therapy, postprocedural optimal medical therapy, patient referral to cardiac rehabilitation, regional or national PCI registry participation, and annual hospital PCI volume. Individual operator volume was identified as a quality metric. In addition to these measures, national agencies such as the CMS have identified potential outcome measures for PCI.

Outcome Measures

The ultimate goal of performance measures is to identify care opportunities that are likely to improve outcomes for patients and thereby the quality of care. Among interventional cardiologists, there is general agreement regarding the outcome measures of importance, and they have been used in many trials. Death and freedom from major adverse cardiac events such as AMI, stroke, bleeding, and target-lesion or target-vessel revascularization are all important, relatively easy to quantify, and have been used in many trials. Improvements in symptoms and quality of life also are important but are more subjective and challenging to quantify, and collecting these data may involve additional cost and effort.

Many outcome measures require risk adjustment to compare outcomes at the provider level in a fair manner, but adjusting for the effects of comorbid medical conditions, severity of the underlying disease, and socioeconomic status is imperfect. This is a huge challenge when analyses are restricted to administrative claims data, which often have inferior data quality and lack the necessary clinical covariables for risk adjustment. Because of the challenges in measuring outcomes, especially some long-term outcomes at the provider level, it is often easer to assess quality by adhering to performance measures as surrogates of actual quality on the assumption that a high level of adherence to performance measures results in better outcomes. In addition to traditional outcome measures, new measures, such as 30-day readmission after a PCI, have been implemented by CMS, with financial penalties

TABLE 64-5 2013 Performance Measures for Adults Undergoing Percutaneous Coronary Intervention

Performance Measure	Description*
Comprehensive documentation of indications for PCI†	Percentage of patients age ≥18 years for whom PCI is performed with comprehensive documentation of the procedure, which includes at a minimum the following elements: • Priority (e.g., acute coronary syndrome, elective, urgent, emergency or salvage) • Presence and severity of angina symptoms (e.g., Canadian Cardiovascular Society classification system) • Use of antianginal medical therapies within 2 weeks before the procedure, if any • Presence, results, and timing of noninvasive stress test, fractional flow reserve, or intravascular ultrasound, if performed • Significance of angiographic stenosis (i.e., quantitative or qualitative) on coronary angiography for treated lesion
Appropriate indication for elective PCI‡	Percentage of patients age ≥18 years for whom elective PCI is performed in a native coronary artery who have an appropriate indication for the procedure that suggests the overall benefits outweigh its risks
Assessment of candidacy for dual-antiplatelet therapy†	Percentage of patients age ≥18 years for whom PCI is performed who have documentation in the medical record that an assessment of candidacy for initiation and duration of dual-antiplatelet therapy was performed before the procedure
Use of embolic protection devices in the treatment of saphenous vein bypass graft disease‡	Percentage of patients age ≥18 years for whom saphenous vein graft PCI is performed who received an embolic protection device during the procedure
Documentation of preprocedural glomerular filtration rate and contrast dose used during the procedure‡	Percentage of patients age ≥18 years for whom PCI is performed who have preprocedural estimated glomerular filtration rate or an indication that the patient is on dialysis and the administered contrast dose documented in the catheterization report or procedure notes
Radiation dose documentation‡	Percentage of patients age ≥18 years for whom PCI is performed who have the administered radiation dose documented in the catheterization report or procedure notes
Postprocedural optimal medical therapy composite†	Percentage of patients age ≥18 years for whom PCI is performed who are prescribed optimal medical therapy at discharge
Cardiac rehabilitation patient referral†	Percentage of patients age ≥18 years for whom PCI is performed who have been referred to an outpatient cardiac rehabilitation or secondary prevention program
Regional or national PCI registry participation†	Participation in a national or multisystem geographic regional PCI registry that provides regular performance reports based on benchmarked data
Annual operator PCI volume‡	Average annual volume of PCIs performed by an operator over the previous 2 calendar years
Annual hospital PCI volume†	Annual volume of PCIs performed by a hospital over the previous calendar year

From Nallamothu BK, Tommaso CL, Anderson HV, et al: ACC/AHA/SCAI/AMA-Convened PCPI/NCQA 2013 performance measures for adults undergoing percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures, the Society for Cardiovascular Angiography and Interventions, the American Medical Association-Convened Physician Consortium for Performance Improvement, and the National Committee for Quality Assurance. *J Am Coll Cardiol* 63(7):722-745, 2014.
PCI, Percutaneous coronary intervention.
*Comprehensive information on these measures, including measure exceptions, is provided by the complete ACC/AHA/AMA-PCPI/NCQA/SCAI performance measurement specifications through the PCPI website (http://www.ama-assn.org/apps/listserv/x-check/qmeasure.cgi?submitPCPI).
†These measures are designated *performance measures,* which are process, structure, efficiency, or outcome measures that have been developed with ACCF/AHA methodology, including the process of public comment and peer review, and they have been designated as performance measures by the ACC/AHA Task Force on Performance Measures. Measures are intended for internal quality improvement and may be considered for purposes of public reporting or other forms of accountability.
‡These measures are designated *quality metrics,* which are measures developed to support self-assessment and quality improvement at the provider, hospital, or health care system level. These valuable tools to aid clinicians and hospitals in improving quality of care and enhancing patient outcomes but may not meet all specifications of formal performance measures and are therefore not appropriate for any use other than internal quality improvement.

imposed for high readmission rates, and these measures are NQF approved.

Appropriate Use Criteria

Although clinical practice guidelines provide a foundation for summarizing evidence-based cardiovascular care, there are many gaps in current knowledge and wide variation in practice patterns. The variability in the use of cardiovascular procedures raises questions of overuse or underuse. Realizing that clinical practice guidelines do not cover all possible clinical situations, appropriate use criteria (AUC) have been developed for cardiovascular imaging procedures and coronary revascularization.[35]

AUC should serve as a supplement to clinical practice guidelines and performance measures. They are intended to assist patients and clinicians but are not intended to diminish the acknowledged difficulty or uncertainty of clinical decision making and cannot substitute for sound clinical judgment and practice experience. The AUC allow assessment of use patterns for a test or procedure. Comparing use patterns across a large subset of provider's patients can allow assessment of a provider's management strategies with those of his or her peers. Ideally, measurement of the AUC in clinical practice would allow improvement of indications for procedures and stimulate discussions with patients as part of shared decision making.

The process of AUC development is well defined.[36] First, the AUC writing group combines specific clinical characteristics to create prototypical patient scenarios. Second, a technical panel is created from nominations by relevant professional societies, provider-led organizations, and health policy and payer communities. To preserve objectivity, the technical panels do not include a majority of individuals whose livelihood is tied to the technology under study. Third, the technical panel is provided with summaries of the relevant evidence from the literature and practice guidelines, and each member of the panel then independently assigns an appropriateness rating to each scenario. A numeric score is assigned to each scenario, with a score of 7 to 9 indicating *appropriate*, 4 to 6 indicating *may be appropriate*, and 1 to 3 indicating *rarely appropriate* indications to perform that test or procedure. Fourth, the technical panel meets as a group to discuss the initial ratings and the benefits and risks of the test or procedure in the context of the potential benefits to patients' outcomes, with an implicit understanding of the associated resource use and costs. After the group meeting, the individual panel members again rate each scenario for the final ranking. Fifth, the final appropriateness ratings are summarized using an established rigorous methodology.[36]

The current terms of *appropriate*, *may be appropriate*, and *rarely appropriate* replaced the original terms of *appropriate*, *uncertain*, and *inappropriate* used in the RAND methodology.[37] The terminology was changed to provide a better characterization of the ratings in the context of real-world decision making and clinical uncertainty and to provide a better focus on the aim of the AUC in measuring overall clinical practice trends rather than adjudicating individual cases.

Impact of Guidelines, Performance Measures, and Appropriate Use Criteria

Relatively few studies assess the extent to which guidelines are applied by clinicians in daily practice. Using data from the NCDR collected between 2001 and 2004, it was shown that 64% of patients undergoing PCI had a class I indication, 21% class IIa, 7% were class IIb, and 8% were rated class III.[38] The clinical success of a PCI was directly related to the class of indication. *Clinical success*, defined as less than 25% residual stenosis without MI, same-admission bypass surgery, or death, was attained for 92.8% of patients with a class I indication, 91.7% of those with a class IIa indication, 89% of those with a class IIb indication, and only 85.5% of those with a class III indication.

Unfortunately, other studies have evaluated the extent to which guidelines are followed in clinical practice with disappointing results. For example, Lopes and colleagues examined a large cohort of patients from three randomized, double-blind clinical trials to determine whether patients with atrial fibrillation were being treated with antithrombotic therapy in accordance with accepted guidelines.[39] Only 13.5% of the patients in these trials were receiving indicated prophylactic antithrombotic therapy with warfarin. Similarly, data from the Worcester Heart Attack Study and the Global Registry of Acute Coronary Events (GRACE) show an increase in the use of guideline-recommended medications (i.e., beta-blockers, angiotensin-converting enzyme inhibitors, aspirin, and lipid-lowering agents) over time, but only about 60% of patients are receiving these medications.[40,41] These findings are not unusual, and other studies have documented that guideline recommendations are followed for a disappointingly small portion of inpatients and outpatients.[42]

Care providers may not be using guidelines to a greater extent in daily practice because of the sheer number of guidelines and their length, because they are comfortable with tried and true approaches to managing disease, because they desire to avoid standardized and rigid order sets that do not apply to all patients and are perceived as "cookbook" medical therapy, and because some patients have unique clinical issues with no specific guideline recommendations available or, when available, are based more on expert consensus rather than on data from multiple randomized trials.[43]

Tricoci and colleagues evaluated 16 current ACC/AHA guideline documents.[44] Of 2711 separate guideline recommendations, a median of 11% were based on level A evidence, compared with a median of 48% that were based on level C evidence, and only 19% of class I recommendations were based on level A evidence. Expert consensus was used more frequently for imaging recommendations, whereas recommendations for revascularization procedures were more commonly based on level A or level B evidence.

These limitations exist in the United States and other countries. The Reassessing European Attitudes About Cardiovascular Treatment (REACT) survey obtained responses from 754 physicians, each with more than 10 years' experience, in five European countries to assess whether physicians' perceptions of coronary heart disease management matched their treatment practices and whether their perceptions of patients' awareness was an accurate reflection of their patients' understanding.[45] In the survey, physicians were asked to identify the most common barriers that prevented them from implementing guideline recommendations. The most common barrier, cited by 38% of the respondents, was lack of time (Fig. 64-5).

The potential effect of decision-maker bias regarding the recommendation for coronary artery revascularization has been examined.[46] Using the New York State database, the treatment decision (i.e., CABG, PCI, medical therapy, or no treatment) made by the cardiologist performing the cardiac catheterization was compared with the treatment recommendation from the relevant ACC/AHA guideline document. Guideline-supported indications for CABG applied to 13% of the study patients, indications for PCI indications to 59% of patients, and indications for CABG or PCI applied to 17% of patients. For the patients with an indication for CABG, the cardiologist recommended CABG for 53% and PCI for 34%. Among patients with indications for PCI, 94% were recommended for PCI, and among patients with indications for CABG or PCI, the cardiologist recommended PCI for 93% and CABG for 5%. Treatment recommendations also varied, depending on whether the catheterization laboratory did or did not offer PCI. These findings show the potential effect of decision bias on the application of guideline recommendations for coronary revascularization.

Considerable geographic variation in the use of PCI within the Medicare population has been documented in other large surveys

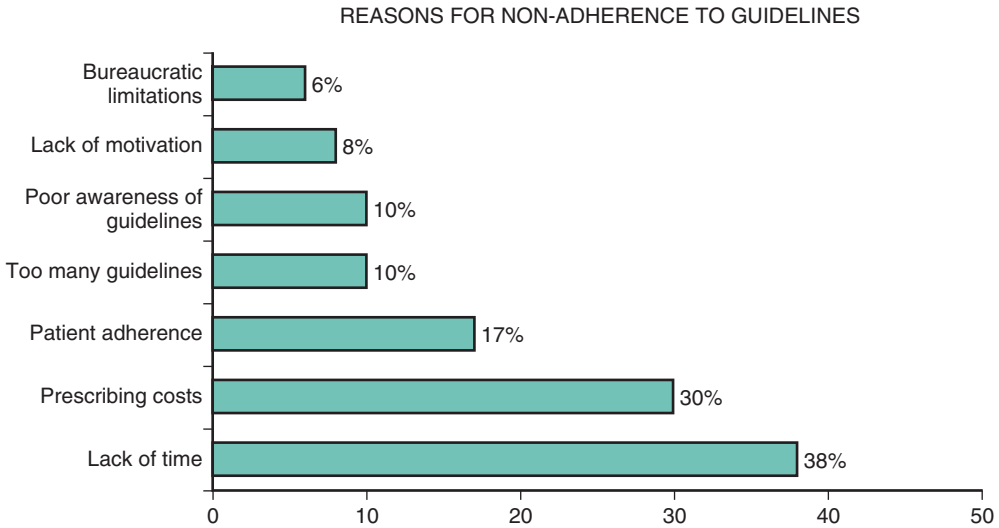


FIGURE 64-5 Barriers cited by physicians that prevent guideline implementation. (Modified from Hobbs FD, Erhardt L: Acceptance of guideline recommendations and perceived implementation of coronary heart disease prevention among primary care physicians in five European countries: the Reassessing European Attitudes about Cardiovascular Treatment (REACT) survey, *Fam Pract* 19[6]:596-604, 2002.)

(Fig. 64-6).[47] Variation in cardiologists' propensity to make treatment recommendations is also affected by several nonclinical factors.[48] In a survey of 598 cardiologists, several nonclinical reasons to recommend cardiac catheterization, including protection from malpractice litigation, were identified (Table 64-6).

With the goal of improving outcomes for patients with cardiovascular disease, it is important to emphasize that some studies show a positive relationship between adherence to performance measures and clinical outcomes.[49] However, this relationship is not necessarily strong and does not completely explain all of the variations. An analysis of the National Registry of Myocardial Infarction (NRMI) database, showed that only 6% of the hospital-level variations in 30-day death rates after AMI could be attributed to differences in the use of performance measures.[50]

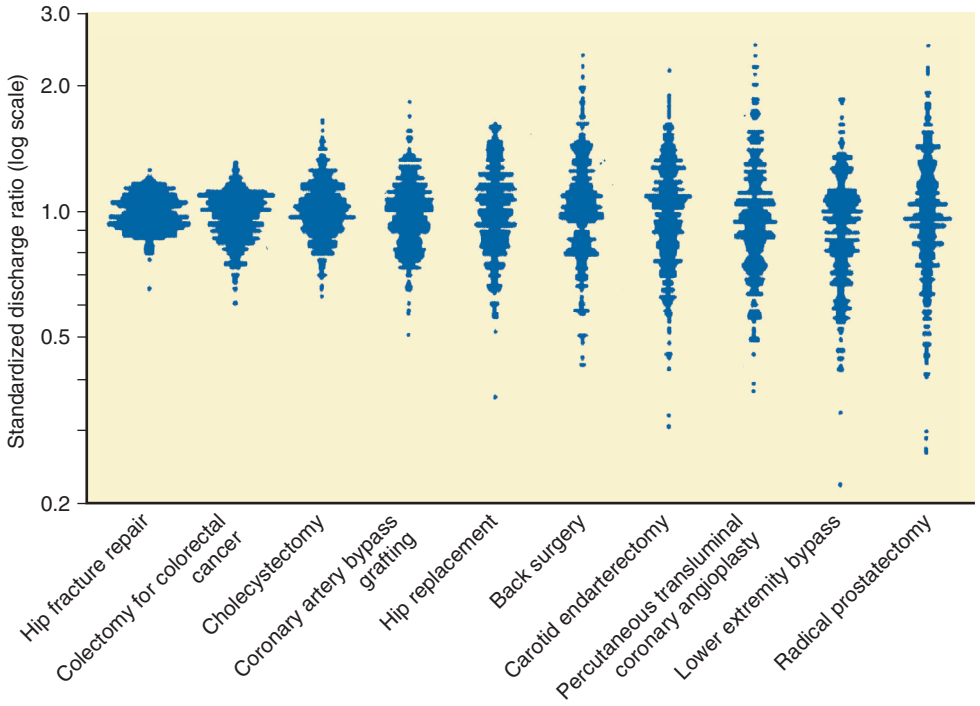


FIGURE 64-6 Regional variations in 10 common surgical procedures are plotted. Each *dot* represents the ratio of the actual number of procedures performed to the average number in each of the 306 hospital referral regions in the United States. Little variation is seen per region for hip fracture repair *(far left)*. However, there is considerable and largely unexplained regional variation in the use of percutaneous transluminal coronary angioplasty. (From Center for the Evaluative Clinical Sciences: Dartmouth atlas of health care: cardiac surgery. Available at http://www.dartmouthatlas.org/downloads/reports/Cardiac_report_2005.pdf [accessed March 25, 2015].)

TABLE 64-6 Nonclinical Reasons for Recommending Cardiac Catheterization

Reason*	Frequently *n* (%)	Sometimes *n* (%)	Rarely *n* (%)	Never *n* (%)	Association With CSI (*P* Trend)
The patient is expected to undergo the procedure.	9 (1.5)	91 (15.6)	271 (46.4)	213 (36.5)	
Mean CSI	*51.5*	*49.7*	*49.8*	*49.9*	*0.99*
Colleagues would do so in the same situation.	22 (3.8)	134 (23.3)	240 (41.7)	180 (31.3)	
Mean CSI	*52.7*	*50.1*	*50.2*	*48.7*	*0.02*
You wanted to satisfy the expectations of the referring physician.	11 (1.9)	156 (26.9)	257 (44.2)	157 (27)	
Mean CSI	*52.6*	*50.0*	*49.3*	*50.3*	*0.90*
You wanted to prevent a possible malpractice suit.	16 (2.7)	123 (21.1)	245 (42.0)	200 (34.3)	
Mean CSI	*51.8*	*50.5*	*50.1*	*48.8*	*0.02*
Doing so would enhance the financial stability of your practice.	2 (0.3)	3 (0.5)	46 (7.9)	532 (91.3)	
Mean CSI	*49.7*	*55.9*	*51.1*	*49.7*	*0.22*

From Lucas FL, Sirovich BE, Gallagher PM, et al: Variation in cardiologists' propensity to test and treat: is it associated with regional variation in utilization? *Circ Cardiovasc Qual Outcomes* 3(3):253-260, 2010.

CSI, Cardiac intensity score.

*Consider your own cardiac catheterization recommendations. A cardiologist sometimes recommends cardiac catheterization for other than purely clinical reasons. During the past 12 months, how often has each of these reasons led you to recommend cardiac catheterization for a patient?

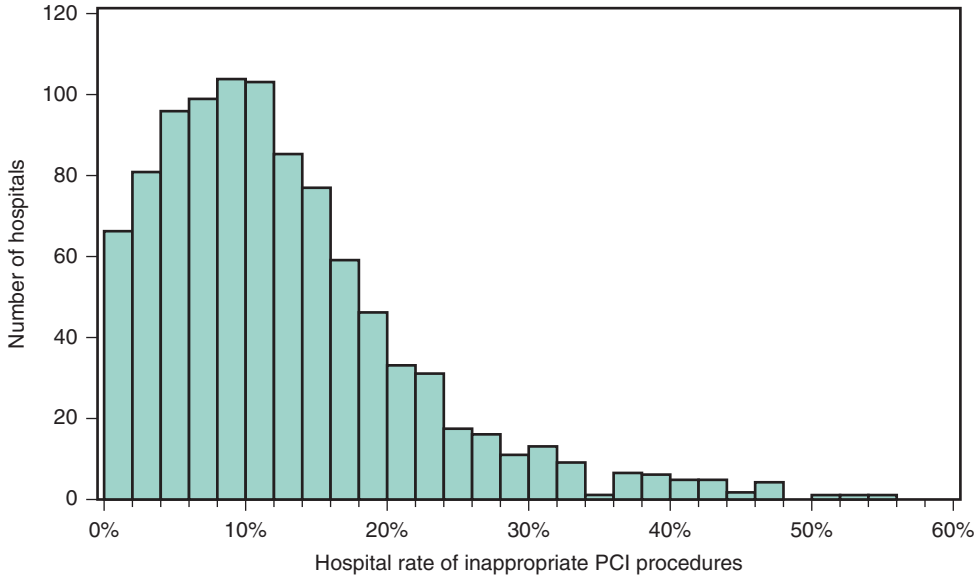


FIGURE 64-7 Hospital-level variations in the rate of inappropriate percutaneous coronary intervention (PCI) procedures. (From Chan PS, Patel MR, Klein LW, et al: Appropriateness of percutaneous coronary intervention. *JAMA* 306:53-61, 2011.)

In 2011, Chan and associates reported the appropriateness ratings for more than 500,000 PCI procedures from the NCDR and documented that most urgent PCIs were appropriate, whereas approximately 12% of elective PCIs, comprising only 30% of the overall database, were deemed inappropriate.[51] However, there was substantial hospital-level variation in cases deemed inappropriate (Fig. 64-7). These data have increased the focus on developing systematic ways to capture the information needed for AUC reporting.

Studies that attempt to validate the AUC are being performed. For example, a retrospective analysis of 1625 patients with 3 years of follow-up showed a relationship between the appropriateness rating and clinical outcome.[52] Revascularization (i.e., PCI or CABG) was performed only in 69% of patients deemed appropriate, but those who were appropriately revascularized had a lower adjusted hazard ratio (hazard ratio = 0.61; 95% confidence interval, 0.42 to 0.88) for death or acute coronary syndrome at 3 years compared with medically treated patients. In contrast, 14% of the study cohort had an inappropriate rating for revascularization, but despite this, 45% underwent revascularization. Although the difference did not reach statistical significance, patients undergoing inappropriate revascularization had a 14.2% incidence of an adverse outcome during follow-up, compared with 9.4% of patients who did not undergo an inappropriate revascularization.

These data provide some early validation of the AUC and demonstrate opportunities to reduce overuse and underuse of coronary revascularization.[24] Unfortunately, some payers are challenging and denying payment for individual cases rated rarely appropriate without an interactive review. This should be considered a misuse of the AUC, and the ACC and SCAI professional societies are providing leadership in responding to these types of challenges.

Quality Assurance and Continuous Quality Improvement

Quality assurance is a process that is based largely on the retrospective review of selected outcomes to determine discrepancies between practice and recommended standards of care.[53] It can be likened to inspecting the final product as it comes off the assembly line. Criteria are established to identify an acceptable product, and items not meeting these criteria are judged as flawed or damaged and rejected before leaving the factory. This process maintains a certain level of product quality, with only acceptable products reaching the market.

Applied to the clinical environment, quality assurance seeks to identify outliers in some aspect of clinical care. Identified outliers often provide an opportunity to improve, but if that fails, they can be denied further participation in clinical care (Fig. 64-8, *A*). The structured quality assurance process may promote a level of defensiveness among health care providers because the process often focuses on determining who is at fault if something goes wrong—the so-called bad apple concept.[54]

The CQI process provides an alternative approach with which specific problems are first identified, followed by the formulation of a solution by various stakeholders. This is validated by reevaluation of the process after the solution is implemented (see Fig. 64-8, *B*). For example, a facility may have an excessive number of patients with groin hematomas after PCI. Patients with hematomas are unhappy, have a prolonged hospitalization, and cost the facility more in resources. A CQI project could be initiated to reduce the number of patients with hematomas. It would require participation of all individuals involved, including physicians, catheter laboratory personnel, nursing staff in the recovery area, and others who interact with the patient. Each step in the process is carefully examined, opportunities for improvement are identified, and appropriate steps are taken to address defects in the process. The new process is initiated, and the results are assessed by determining whether the number of patients with hematomas has been reduced.

The CQI process has become a vital and expected component of a quality cardiovascular program, with the goals of reducing variation and improving overall performance.[55] Several models for CQI exist. One model frequently used is the Plan-Do-Study-Act (PDSA) model, and an alternative is the Focus-Analyze-Develop-Execute (FADE) model (Figs. 64-9 and 64-10). Many of these systems have been adopted from manufacturing and industry. The core actions of these models and most CQI programs include the following:

- Collection of data containing relevant patient variables that allow assessment of clinical processes, performance, and outcomes
- Feedback of performance and outcome information to the clinicians, with risk adjustment, if necessary, and benchmarking of the data
- Implementation of appropriate interventions to reduce wasteful and inefficient variations in care and improve performance
- Use of an iterative process to assess the effectiveness of changes

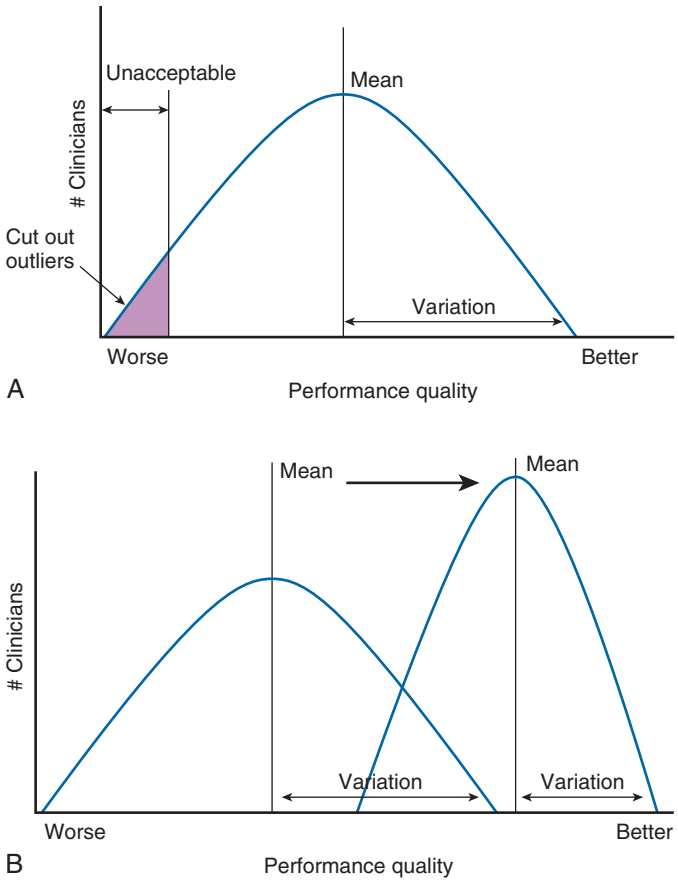


FIGURE 64-8 **A,** The goal of the quality assurance approach is to identify outliers that are unacceptable and should be excluded. **B,** The goal of the continuous quality improvement approach is to identify opportunities for practice improvement and develop methods to respond to these opportunities and improve overall practice.

- Answers to two questions: How am I doing compared with others? Am I getting better?

Despite the emphasis on the importance of CQI efforts, relatively few studies have formally examined the results or improvements in outcomes related to CQI. Moscucci and colleagues reported the results of a statewide CQI PCI initiative in Michigan.[56] It involved the use of a wide range of CQI strategies that relied on quarterly feedback reports to clinicians on their adherence to process and performance measures, along with reports of crude and risk-adjusted outcomes. The program resulted in a demonstrable decrease in bleeding, transfusion requirements, vascular complications, and contrast use, which reduced the rate of contrast nephropathy. In a temporal observational study at the Mayo Clinic, Rihal and coworkers identified the benefit of CQI intervention for PCI delivery, showing improvements in clinical and economic outcomes.[57]

Unfortunately, there are several barriers to the implementation of CQI programs. Lack of hospital administrative and financial supports, the time and expense of internal data collection, and a deficit of physician leadership frequently hamper CQI efforts.[58]

Benchmarking

Another essential building block of the quality framework is the process of benchmarking. A *benchmark* is a standard by which something can be measured or judged. Only by the collection of data can clinicians or hospitals compare, or benchmark, their care and outcomes with those of their peers and with national standards. Major strides in quality improvement require benchmarking coupled with changes in the systems of care and engagement of local clinical leaders and administrative support.[59]

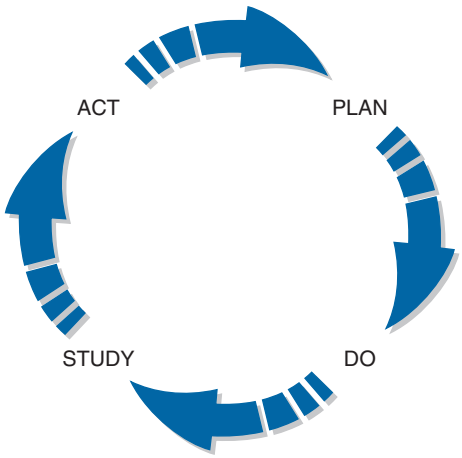


FIGURE 64-9 The Plan-Do-Study-Act (PDSA) model for continuous quality improvement.

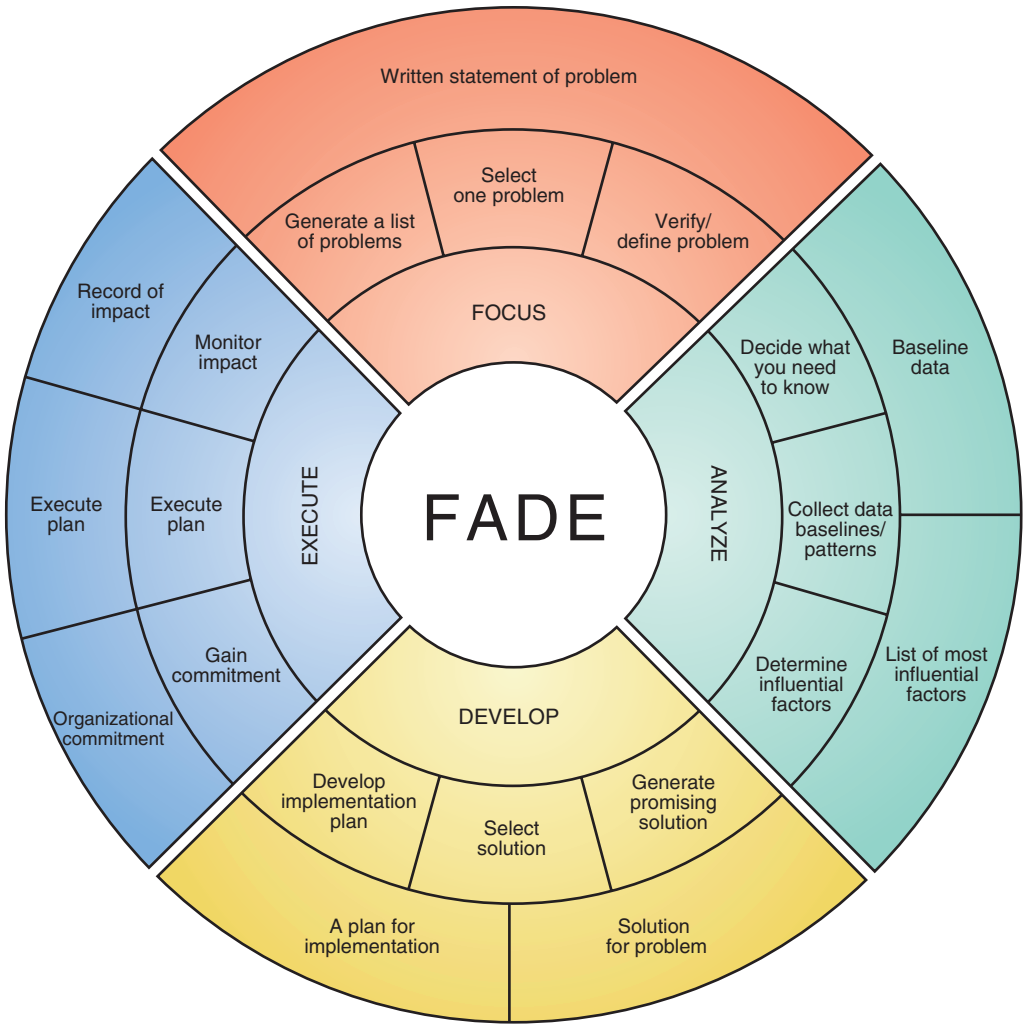
The NCDR was developed to assist facilities in the collection of data for use in benchmarking and quality improvement. Collection of laboratory data with benchmarking against state or national data is an important structural element to assess clinical outcomes. Examples include the NCDR's CathPCI Registry, Acute Coronary Treatment and Intervention Outcomes Network–Get With the Guidelines (ACTION-GWTG) Registry of myocardial infarction, Society of Thoracic Surgeons Database, and Northern New England Cardiovascular Disease Study Group.[33,60,61] Participation in these programs provides caregivers with standardized tools for data collection, defined data elements and definitions, and validated risk-adjustment models for patient outcomes, such as mortality.

In addition to tracking outcomes, data reports help to assess adherence to guidelines and performance measure recommendations and can serve as a focus for quality improvements within an institution. The reports include regional benchmarking (i.e., comparison with similar hospitals) and national benchmarking against all participating facilities. Sample sections of a benchmark report from the CathPCI and ACTION-GWTG registries are shown in Figures 64-11 and 64-12. Feedback with benchmarking is intended to be used by hospitals and practices to target areas for improvement around which CQI efforts can be developed.[55] Benchmarking data are available to individual operators with their personal NCDR reports (i.e., dashboards) with relevant benchmarks.

Peer Review

One of the most challenging components of the quality framework is peer review. Catheterization laboratory directors are under increasing pressure to document the quality of care in their laboratories. Government agencies, aggregate purchasers of health care services, and accrediting organizations are commonly request outcome data and other evidence of peer review activities.[62,63] Although representative of only a small number of operators, several highly publicized examples have suggested the overuse of coronary stents, highlighting the need for local peer review.[63a,63b]

The primary goal of peer review is to improve patient care by analyzing physician performance and providing meaningful feedback to



FOCUS: Define and verify the process to be improved

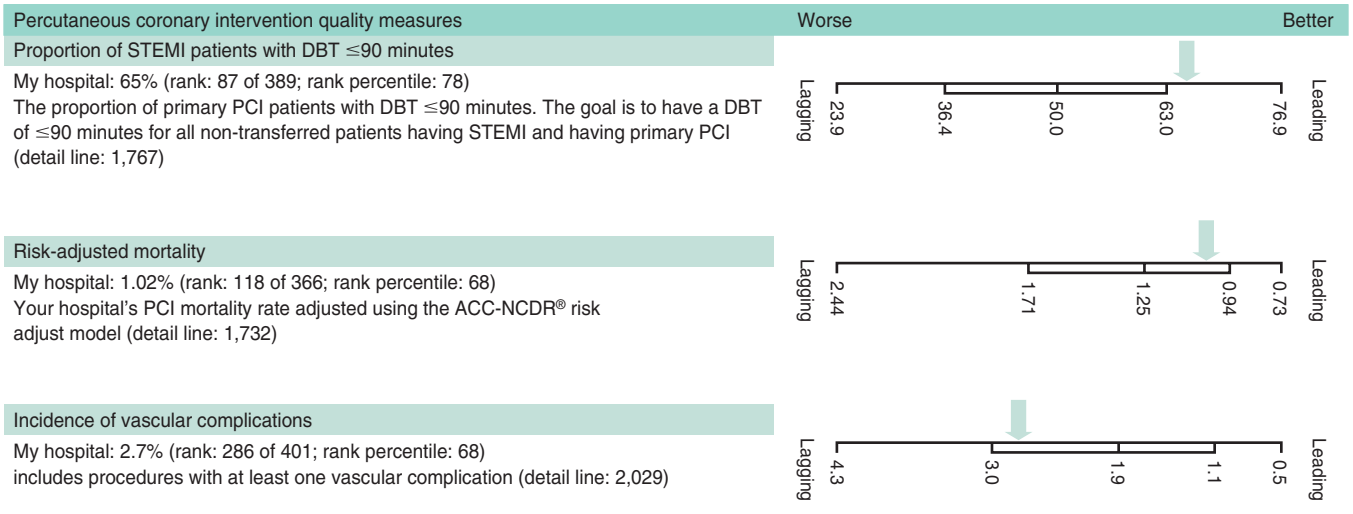
ANALYZE: Collect and analyze data to establish baselines, identify root causes and point toward possible solutions

DEVELOP: Based on the data, develop action plans for improvement, including implementation, communication, and measuring/monitoring.

EXECUTE: Implement the action plans, on a pilot basis as indicated.

EVALUATE: Install an ongoing measuring/monitoring system to ensure success.

FIGURE 64-10 The Focus-Analyze-Develop-Execute and Evaluate (FADE) model is used to reduce variation and improve overall performance. (Courtesy Organizational Dynamics Institute, Wakefield, MA.)



ACC-NCDR® = American College of Cardiology National Cardiovascular Data Registry; DBT = door to balloon time; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

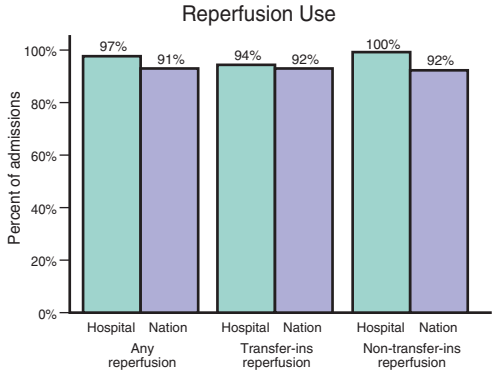
FIGURE 64-11 Sample from the executive summary of a report from the CathPCI Registry, a source of cardiovascular data from the National Cardiovascular Data Registry (NCDR).

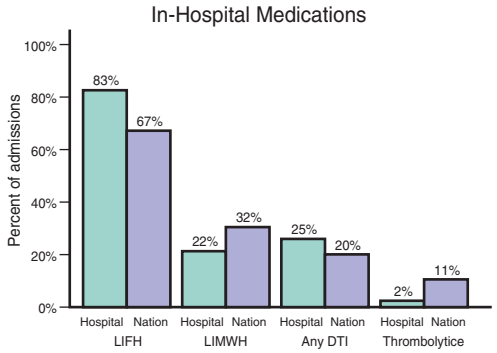
ACTION Registry -GWTG

Table 6: STEMI - Reperfusion Use

ACTION Registry-GWTG™ Report: Q1/10
* Confidential Information *

	Hospital		Like Hospitals	Nation	Top 10%
	Last Ctr	Last 12 mo			
Overall reperfusion, %[1]	97%	97%	94%	92%	96%
# of admissions reperfused	30	123	9,324	20,938	2,375
Transfers-in, % reperfused	100%	94%	94%	93%	96%
Non-transfer-ins, % reperfused	95%	99%	94%	92%	97%
Contraindicated reperfusion, %	21%	21%	12%	12%	10%
# of admissions	8	33	1,310	2,987	275
Any thrombolytic, %[2]	0%	2%	13%	11%	13%
# of admissions	-	3	1,210	2,507	328
Door to needle time, overall[3]					
# of admissions	-	-	41	245	3
Median (minutes)	-	-	29	23	56
<=30 minutes, %	-	-	51%	64%	33%
Primary PCI, overall, %[2]	97%	94%	83%	82%	85%
# of admissions	30	120	8,208	18,666	2,094
Door to balloon, non-trans. in %[4]	69%	64%	72%	73%	67%
# of admissions	20	71	5,085	11,679	1,213
Median (minutes)	51	55	60	61	56
<=90 minutes, %	95%	96%	91%	89%	96%
1st door to balloon, trans. in %[4, 5]	31%	36%	28%	27%	33%
# of admissions	9	40	1,968	4,214	591
Median (minutes)	115	99	113	114	105
<=90 minutes, %	44%	35%	24%	23%	30%
<=120 minutes, %	56%	73%	57%	56%	65%
Rescue PCI[5]					
# of admissions	-	2	489	906	128
Median (minutes)	-	133	181	187	183





[1]Patients receiving thrombolytics or primary PCI, among non-contraindications
[2]Among non-contraindications
[3]Among patients receiving thrombolytics therapy, excluding transfer-in patients
[4]Among patients receiving primary PCI that is not rescue or facilitated
[5]For transfer-in patients, time is calculated from arrival at the ref. hospital to PCI

FIGURE 64-12 Sample page of a report from the Acute Coronary Treatment and Intervention Outcomes Network–Get with the Guidelines (ACTION-GWTG) Registry.

physicians.[64-66] The term *peer review* encompasses two clinical processes. Local peer review should occur in every laboratory as part of the quality framework. In that context, it is a patient-centered undertaking that should be positive, nonthreatening, and helpful to operators, but it also should identify and correct variations from accepted practice. Peer review programs should be individualized for each institution's catheterization laboratory and should remain flexible to accommodate change.[67]

Conflicts of interest are common among competing physicians, who may perceive a financial advantage to adjudicate adversely another physician's care.[68] For peer review to be successful, there should be a formal method of oversight for perceived conflicts of interest within the peer review process. This can frequently be difficult, especially at smaller facilities. An independent facility accreditation process, such as offered by Accreditation for Cardiovascular Excellence (ACE) may be helpful.[69] Court decisions have confirmed that physicians have a legal responsibility to perform peer review. Members of peer review committees and their peer review activities are protected under state laws from discovery in lawsuits. Although antitrust laws cover peer review activities by a hospital medical staff, some actions that physicians or hospitals engage in may have an anticompetitive effect and violate federal antitrust laws. These laws prohibit efforts by one group of physicians to suppress competition from other physicians by preventing their entry into the relevant market (i.e., hospital) or excluding or restricting their professional activities.[70]

The second form of peer review (i.e., professional review activity) is specifically defined in federal law. It consists of an evaluation by the review bodies at hospitals, professional medical societies, or other entities to determine the professional competence of individual physicians through a formal review process that may result in restriction or termination of professional privileges and that requires due process.[71] Several publications from the SCAI define the best practices for this type of activity in the cardiac catheterization laboratory.[72-75]

JUDGING QUALITY IN INTERVENTIONAL CARDIOLOGY

The building blocks of quality fit into Donabedian's triad, a conceptual framework that has been used extensively.[11] The three domains (i.e., structure, process, and outcome) each identify a major area containing multiple metrics that can be assessed to determine the program's quality.

Structure

Structure refers to the physical components of health care delivery. For the cardiac catheterization laboratory, structural measures include the training, experience, and board certification of the physicians performing procedures; training and competency records for laboratory staff; adequacy of diagnostic and therapeutic equipment; appropriate maintenance and calibration logs for equipment; educational opportunities

TABLE 64-7 Structure, Process, and Outcome Measures in the Cardiac Catheterization Laboratory

Structural Indicators
Personnel Indicators
Credentialing (training and certification) of physicians and staff
Reappointment criteria for physicians
Functioning peer-review process for operators
Staff development and continuing education
Equipment Indicators
Fluoroscopic image quality
Quality of stored images and stability of the image archive
Maintenance schedule for equipment
Evaluation of new equipment and disposables
Laboratory time lost or rescheduling because of equipment failure or problems
Electrical safety systems
Organizational Indicators
Internal methods for tracking and comparing procedural data
Laboratory use (e.g., hours/day, procedures/laboratory/day, laboratory time/procedure)
Total full-time equivalents per procedure
Disposable equipment costs per procedure; total costs per procedure and per operator
Personnel costs per procedure
Delay time between procedures
Adherence to Occupational Safety and Health Administration (OSHA) guidelines
Procedure fluoroscopy and cine-angiography times
Radiation dosage to personnel
Radiation protection practices
Radiographic contrast use per case
In-hospital delays for procedures
Outpatient waiting times for procedures
Outpatient waiting times for procedure starts
Process Indicators
Indications for procedures or adherence to appropriate use criteria
Indications for hospital admissions
Length of stay after procedures (i.e., total for laboratory and per physician)
Quality of angiographic studies
Quality (correctness) of study interpretation
Precautions for patients with renal insufficiency, contrast allergy, latex allergy, or other conditions
Outcome Indicators
Success rates for percutaneous coronary interventions
Risk-adjusted outcomes, especially mortality, emergency bypass surgery, and coronary perforation
Satisfaction surveys (e.g., patient, family, referring physician)
Frequency of coronary angiograms showing no significant disease

Modified from Heupler FA, Al-Hani AJ, Dear WE, et al: Guidelines for continuous quality improvement in the cardiac catheterization laboratory. *Cathet Cardiovasc Diagn* 30(3):191-200, 1993.

for the staff; and internal methods used for tracking procedural data (Table 64-7).

To assess the knowledge base of interventional cardiologists, the American Board of Internal Medicine (ABIM) has administered an additional qualification examination for board certification in interventional cardiology since 1999. Maintenance of certification is required after 10 years. Other requirements include maintenance of a valid certification in internal medicine or cardiovascular disease, documentation of adequate procedure volumes (e.g., 100 cases over 2 years), evidence of participation in a quality improvement project, and completion of self-evaluation modules for medical knowledge and practice performance. Hospitals and payers frequently adopt a requirement for board certification, but there are no data to prove that board-certified physicians provide a higher quality of care than those who are not board certified. For other laboratory personnel, structural measures can include requirements for all technologists to be registered cardiovascular invasive specialists and to maintain certification in advanced cardiac life support.

Important structural components include education in the form of cardiac catheterization conferences, which provide a forum for discussing difficult management issues, and morbidity and mortality reviews as part of a peer review quality improvement program.[73] To be effective, these programs must emphasize improvement of performance rather than identifying individual physicians as potential one-time outliers. Collection of laboratory data with benchmarking against state or national data is important for assessing clinical outcomes. Examples include the NCDR's CathPCI Registry and ACTION-GWTG registry of myocardial infarction.[60,76] Participation in these programs provides caregivers with standardized tools for data collection, including relevant data elements and definitions, and for validated risk-adjustment of patient outcomes, such as mortality rates. In addition to tracking outcomes, the data reports help to assess adherence to guidelines and performance measures and can serve as a focus for quality improvements within an institution.

Process

Process measures assess how the system works and how health care is delivered (see Table 64-7). An example in interventional cardiology is the door-to-balloon (DTB) time for patients with STEMI. To achieve an optimal DTB time, many steps spanning several hospital departments and services are necessary. The emergency department triages the patient with a possible STEMI, an electrocardiogram is obtained to confirm the diagnosis, and appropriate treatment is started. The interventional team is alerted, the cardiac catheter laboratory is prepared, the patient is transported to the laboratory, and the culprit artery is opened.[77] A flaw in any step increases the DTB time and the possibility of failure.

Realizing that DTB times were suboptimal in many facilities, the Door-to-Balloon Alliance was launched in late 2006 with the goal of achieving a DTB time of 90 minutes or less for at least 75% of non-transferred patients.[78] Several process measures that improved DTB times were adopted and tracked, resulting in significant improvement in national DTB times (Fig. 64-13).[79]

Other examples of process measures are collecting data to determine the appropriateness of performing a PCI and collecting data that allow assessment of performance measures. Proper patient selection for PCIs is receiving increasing scrutiny by all health care stakeholders because there is wide variation in the use of PCIs (see Fig. 64-6).[47] Assessing the appropriateness of a PCI involves understanding the patient's history, clinical presentation, and physical findings; noninvasive testing to determine ischemia severity; assessment of left ventricular function; and interpretation of coronary angiographic findings.

Appropriate use criteria have been developed to determine whether coronary revascularization is a reasonable approach for a given clinical circumstance (Fig. 64-14).[80] Although acceptable indications in addition to the AUC exist, measuring the degree of adherence to the clinical situations covered by the criteria is valuable for assessing the quality of patient selection. Application and assessment of appropriateness of care require collection of the relevant clinical variables. Because of evolving information about fractional flow reserve and revascularization from randomized controlled trials, the revascularization AUC are updated every 2 to 3 years.

Outcomes

The third component of Donabedian's triad is *outcome*, which is the final product or result of previous actions. Outcomes are tangible measures such as procedural risk-adjusted mortality rates and other adverse outcomes such as vascular complications, bleeding, stroke, contrast nephropathy, cardiac tamponade, periprocedural AMI, and the rate of emergency CABG (see Table 64-7). Measuring outcomes as quality indicators is attractive because of the implied association

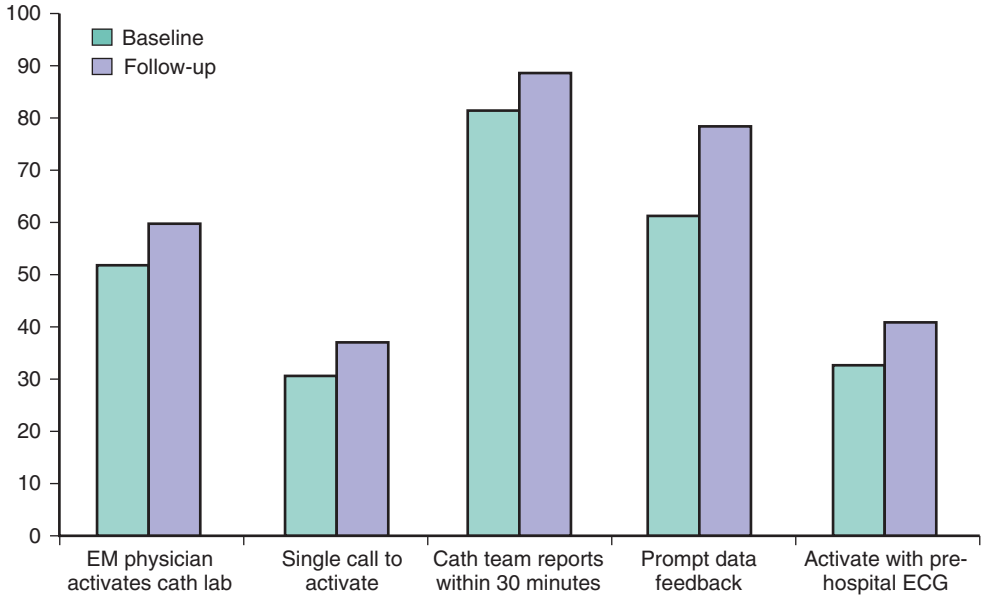


FIGURE 64-13 Percentage of Door-to-Balloon Alliance hospitals reporting use of recommended strategies at baseline and in follow-up surveys. *cath lab,* Catheterization laboratory; *ECG,* electrocardiogram; *EM,* emergency medicine. (From Bradley EH, Nallamothu BK, Herrin J, et al: National efforts to improve door-to-balloon time results from the Door-to-Balloon Alliance. *J Am Coll Cardiol* 54[25]:2423-2439, 2009.)

REVASCULARIZATION APPROPRIATENESS FOR PATIENTS WITH LOW-RISK FINDINGS ON NONINVASIVE STUDIES (PATIENTS WITHOUT PRIOR BYPASS SURGERY)

Low risk findings on noninvasive study — Noninvasive testing

Symptoms / Med. Rx					
Class III or IV Max Rx	U	A	A	A	A
Class I or II Max Rx	U	U	A	A	A
Asymptomatic Max Rx	I	I	U	U	U
Class III or IV No/min Rx	I	U	A	A	A
Class I or II No/min Rx	I	I	U	U	U
Asymptomatic No/min Rx	I	I	U	U	U
Coronary Anatomy	CTO of 1 vz.; no other disease	1-2 vz. disease; no prox. LAD	1 vz. disease of prox. LAD	2 vz. disease with prox. LAD	3 vz. disease; no left main

Symptom level and medical therapy

Burden of CAD

FIGURE 64-14 Presentation of the coronary revascularization appropriate use criteria (AUC) for patients with low-risk findings on noninvasive studies. The burden of coronary artery disease is shown on the bottom of the table. The symptom class and degree of medical therapy is shown on the vertical axis. *A,* Appropriate; *CAD,* coronary artery disease; *CTO,* chronic total occlusion; *I,* inappropriate; *LAD,* left anterior descending coronary artery; *Max,* maximal; *Med. Rx,* medical therapy; *Prox,* proximal; *U,* uncertain; *vz.,* vessel. (From Patel MR, Dehmer GJ, Hirshfeld JW, et al: ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 53[6]:530-553, 2009.)

TABLE 64-8 National Cardiovascular Data Registry CathPCI Risk Score System

Variable	SCORING RESPONSE CATEGORIES				Total Points*	Risk of Inpatient Mortality (%)
	<60 yr	≥60, <70 yr	≥70, <80 yr	≥80 yr		
Age	0	4	8	14	5	0.1
Cardiogenic shock	No	Yes	—	—	10	0.1
	0	25	—	—	15	0.2
Prior CHF	No	Yes	—	—	20	0.3
	0	5	—	—	25	0.6
Peripheral vascular disease	No	Yes	—	—	30	1.1
	0	5	—	—	35	2.0
Chronic lung disease	No	Yes	—	—	40	3.6
	0	4	—	—	45	6.3
GFR	<30	30-60	60-90	>90	50	10.9
	18	10	6	0	55	18.3
NYHA functional class IV	No	Yes	—	—	60	29.0
	0	4	—	—	65	42.7
PCI status (STEMI)	Elective	Urgent	Emergent	Salvage	70	57.6
	12	15	20	38	75	71.2
PCI status (no STEMI)	Elective	Urgent	Emergent	Salvage	80	81
	0	8	20	42	85	89.2
					90	93.8
					95	96.5
					100	98.0

From Peterson ED, Dai D, DeLong ER, et al: Contemporary mortality risk prediction for percutaneous coronary intervention: Results from 588,398 procedures in the National Cardiovascular Data Registry. *J Am Coll Cardiol* 55(18):1923-1932, 2010.

CHF, Congestive heart failure; *GFR,* glomerular filtration rate; *NYHA,* New York Heart Association; *PCI,* percutaneous coronary intervention; *STEMI,* ST-segment–elevation myocardial infarction.

*In the National Cardiovascular Data Registry (NCDR) risk prediction model for percutaneous coronary intervention mortality, points are assigned for the different variables, and the total number of points is used to predict the risk of inpatient mortality.

between outcome measures and hospital or physician performance. However, these tenuous associations can create challenges for the accurate assessment of outcomes. For example, the definition of a periprocedural AMI (i.e., any troponin level increase versus three or five times the baseline level) and the clinical significance of increased biomarker levels in the periprocedural period are subject to debate. Standardized protocols are needed for biomarker collection during the postprocedural period and interpretation of elevated biomarker levels in patients with acute coronary syndrome.

NCDR data have shown that only 26% of medical centers measure biomarkers after elective PCI, limiting use of the peri-PCI outcome measure.[81] Clinical data standards and definitions and standards for statistical models have been developed to help ensure consistency, but important issues remain.[82]

Many PCI-related adverse events such as death or emergency CABG are uncommon, especially when assessed at the operator level because the total number of procedures annually is modest. For example, the 95% confidence interval for a 2% mortality rate for 100 PCI procedures is 0% to 7%. This is a wide range for judging whether the operator has a low or a high mortality rate. Quarter-to-quarter or year-to-year outcome measures often vary widely when measured for a single center or operator.

Another important issue is risk adjustment. Factors other than the operator and facility influence outcome comparisons. Patient acuity, demographic features, and comorbid conditions affect the outcome independent of the quality of care provided. Risk adjustment for key clinical outcomes requires accurate and detailed clinical data and a rigorous risk-adjustment methodology to describe provider outcome measurements.

The NCDR was started in 1997 to help provider groups and institutions respond to increasing requirements to document the processes and outcomes of care in the cardiac catheter laboratory. The NCDR is the most comprehensive outcomes-based data repository program in the United States, with seven hospital-based and one practice-based registry. More than 2200 hospitals nationwide participate in one or more of the NCDR registries, which collectively have amassed more than 15 million patient records.[76] Participation in some of the NCDR registries is required by several states and several payers.

Comprehensive data from the CathPCI Registry are provided to member institutions for internal quality assessment and improvement, and confidential data for individual operators are available through a secure portal. Using these data, risk-prediction models have been developed for PCI mortality and bleeding rates (Table 64-8).[83,84]

Outcome assessment often overlaps with and represents the aggregate effect of the other two components of the triad, structure and process. Improving the end product is therefore the ultimate measure of the overall success of medical care. Ideally, outcome assessment examines an isolated episode of care (i.e., single PCI procedure) and includes a longitudinal follow-up assessment of the PCI. This may include the impact of care on indirect health-related measures such as patient satisfaction with the overall care process and quantification of the cost of the care delivery, including cost-effectiveness and cost-efficiency calculations.

DEVELOPING A QUALITY CULTURE IN THE CARDIAC CATHETERIZATION LABORATORY

Organizational Culture

Amid the escalating demands for quality health care, it is important to encourage a culture of quality in the cardiac catheterization laboratory. *Organizational culture* is the term used to describe the shared beliefs, perceptions, and expectations of individuals in organizations. Organizational culture can dramatically affect efforts to implement changes in procedures or processes.

Characteristics of organizational culture have been linked to financial performance, customer and employee satisfaction, and innovation. Supportive organizational cultures underlie successful initiatives of quality improvement, contribute to high levels of nursing care, job satisfaction, and patient safety,[85,86] and help institutions adapt to rapidly changing health care demands and remain competitive. Organizational culture is central to the operation and function of health

care institutions, providing a shared vision that can guide appropriate and goal-directed social and individual behaviors.

Some aspects of organizational culture can have an opposite effect that undermines efforts for positive change. Many quality initiatives fail because of resistance to change, ingrained attitudes, lack of understanding, and poor communication. For success, the high-level leaders of an organization must focus on the mission and vision of the organization. Mission is a fundamental unit of culture, and failure to fulfill the organization's mission impedes quality improvement efforts. By focusing on the mission and embracing the role of advancing a quality culture, leaders can facilitate dissemination of quality-oriented values throughout an organization. Four levels of intervention influence organizational culture: individual, team or microsystem, organizational, and environmental.[87] In its landmark publication, *Crossing the Quality Chasm*, the IOM asserted that all interventions must address these four dimensions.[21]

Physician Champions

Key in the development of a quality culture in the cardiac catheterization laboratory is the physician champion, who is an opinion leader, an agent of change, and a person who influences colleagues and friends. He or she is a respected individual who provides expert education, promotes a cause or a product, or gives support to staff for the diffusion and implementation of clinical practice guidelines, protocols, and research evidence. Physician champions are essential to a culture of quality and change. For example, a physician champion at a local institution can promote the increased use of radial access by education of colleagues and by helping others become proficient in the procedure.

In all cases, the physician champion is perceived as a credible individual who has the ability to persuade others. He or she often influences other physicians to implement a new or revised process or guideline for quality improvement or to become physician champions themselves. The champion's role can be an invaluable tool for change within a health care organization. However, if the physician is unable or unwilling to engage in the tasks required to be effective, the role is not clearly defined, the sphere of influence is narrow, or institutional support is lacking, he or she will not be able to fulfill the expectations of the organization, and change may not be implemented or sustainable.

Tools to Assist in Quality Improvement

The SCAI developed a quality improvement toolkit (QIT).[88] The SCAI QIT identifies routine meetings that help operationalize the activity of continuous quality improvement. Topics of these institutional conferences include morbidity and mortality, peer review of random cases, and selected interesting cases. Several hospitals have developed group meetings that address specific care processes such as for STEMI. At a minimum cardiac catheterization laboratories should have peer review and morbidity and mortality conferences monthly to quarterly to ensure timely case reviews.

Operational improvements continue to translate quality initiatives into action in the cardiac catheterization laboratory. Preprocedural checklists, structured catheterization reports, and standardized data elements provide important adjuncts in the daily practice of invasive cardiology.[89] Real-time decision support tools such as electronic health records are easily integrated into the workflow. A structured time out before each procedure ensures proper patient identification, procedure confirmation, allergy assessment (including contrast and radiation thresholds), and other data collection.

PUBLIC REPORTING AND THE CARDIAC CATHETERIZATION LABORATORY

Effects of Reporting on Quality

Although the U.S. health care system is superior in many ways, it also has shortcomings, such as gaps in care, quality issues, and costs. Private sector employers and the federal government have seen an increasing portion of their revenue consumed by providing health care for employees and Medicare beneficiaries. This financial burden has pressured payers, who have pressured providers to accelerate quality improvement efforts.

Public reporting of physician, health plan, and institutional performances is used to steer patients to the best performing providers and facilities on the assumption that they provide better and more cost-effective care. Patients are becoming more engaged in this process and seek public performance reports on providers and facilities. Public release of performance data improves the quality of care through greater transparency and accountability by health care providers.[90]

Public reporting of the results of cardiovascular interventions, especially by cardiac surgeons, is not new. Beginning in the mid-1990s, New York and Pennsylvania publicly reported cardiac surgery outcomes, and the Massachusetts Data Analysis Center started a reporting program (Mass-DAC) in 2002, as did California in 2003.[2,3,91,92] After its early years of operation, the New York program reported a reduction in the risk-adjusted mortality rate from 4.17% to 2.45%, with smaller yearly improvements thereafter.[93] The Pennsylvania CABG public reporting program documented a similar trend.[94]

In evaluating public reporting programs, it is important to understand the data source and the distinction between administrative (claims) data and clinical data sources. For example, the Mass-DAC cardiac surgery reporting program uses clinical data from the Society of Thoracic Surgery database. In an important comparative study, cardiac surgery performance results based on clinical data were compared with performance results derived from administrative data during the same period. Considerable disparities were found in the results between the two data sets, which led to the conclusion that report cards using administrative data are problematic compared with those derived from audited and validated clinical data.[95] The same comparison was made within the New York cardiac surgery reporting program with similar conclusions.[96] The use of pure administrative data was inferior to clinical data in identifying outliers and assessing surgical outcomes.

At the national level, the CMS in collaboration with the Hospital Quality Alliance issues a web-based public report.[97] The following data are reported:

- Several process of care measures for patients with acute MI, congestive heart failure, and other selected medical conditions and some surgical procedures
- Outcomes of care measures, including 30-day risk-adjusted mortality and readmission rates for MI, heart failure, and pneumonia
- Patients' hospital experiences, using information collected from the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey
- The number (volume) of Medicare patients treated for certain illnesses or diagnoses
- Medicare inpatient hospital payment information

Large-scale public reporting efforts in cardiology and interventional cardiology have primarily focused on events such as AMI and congestive heart failure or on procedures such as CABG or PCI. Although some state programs report physician-level metrics, the confidence intervals around any point estimate are necessarily wide because of the small sample size for a single physician. Most public reporting has been at the facility level because greater statistical validity and larger denominators exist. Independent review of DTB time as a publicly reported measure of quality by the CMS showed that more than a fourth of patients were excluded from hospital quality reports, The exclusion of this many patients demonstrates the potential disconnect among overall process improvement, public reporting, and reimbursement for quality measures.[98]

Meaningful programs rely on clinical data sources to avoid the pitfalls of administrative data and allow a robust risk adjustment of outcomes. In 2014, the NCDR launched a voluntary program for participants to publicly report clinically based hospital-level performance measures. Although the initial data release is limited to a few metrics

TABLE 64-9 National Cardiovascular Data Registry Measures for Public Reporting

Performance Measure	Source Registry	External Data	NQF Endorsed
Aspirin at discharge	CathPCI	No	Yes
Thienopyridine at discharge	CathPCI	No	Yes
Statins at discharge	CathPCI	No	Yes
PCI in-hospital risk-adjusted mortality (patients with STEMI and patients without STEMI)	CathPCI	No	Yes
30-Day all-cause risk-adjusted mortality (patients without STEMI or cardiogenic shock and patients with STEMI or cardiogenic shock)	CathPCI	Yes (CDC)	Yes
30-Day risk-adjusted readmission for PCI	CathPCI	Yes (CMS)	Yes

CathPCI, Subregistry of the National Cardiovascular Data Registry; *CDC,* Centers for Disease Control and Prevention; *CMS,* Centers for Medicare and Medicaid Services; *NQF,* National Quality Forum; *PCI,* percutaneous coronary intervention; *STEMI,* ST-segment–elevation myocardial infarction.

from the CathPCI Registry, this will be expanded greatly over the next few years (Table 64-9). A pilot program in collaboration with CMS resulted in more than 350 hospitals' agreeing to post their 30-day readmission rates for PCI on the CMS website. More public reporting is expected in the future.

Unintended Consequences

Concern has been expressed that public reporting programs may lead to unintended consequences that could offset their benefits.[99,100] Although the early reduction in risk-adjusted mortality from CABG in the New York experience was touted as a success, another perspective subsequently emerged. Omoigui and colleagues reviewed 9442 isolated CABG operations performed from 1989 through 1993 at the Cleveland Clinic to assess referral patterns, case mix, and outcomes.[101] Patients referred to Cleveland from New York had a higher frequency of prior open heart surgery and were more likely to have New York Heart Association (NYHA) functional class III or IV heart disease compared with patients from Ohio, other states, and other countries. Their expected mortality rate was higher than for other referral cohorts. The observed 5.2% mortality rate among patients referred from New York was significantly greater than for any of the other referral sources, leading the study authors to speculate that the public reporting of outcome data in New York likely provoked the increased referral of high-risk patients out of state, explaining the reduction of CABG-related mortality rates in New York.

Schneider and Epstein surveyed cardiologists and cardiac surgeons to determine whether they were aware of the Pennsylvania Consumer Guide to Cardiac Surgery and, if so, to determine their views on its usefulness, limitations, and influence on providers.[102] Only 10% reported that the published mortality rates were "very important" in assessing the performance of a cardiothoracic surgeon. Less than 10% reported discussing the guide with more than 10% of their patients before CABG. Among cardiologists, 87% reported that the guide had minimal or no influence on their referral recommendations. When the limitations of the guide were assessed, 78% cited the absence of indicators of quality other than mortality rates, 79% cited inadequate risk-adjustment methods, and 53% cited the unreliability of data provided by hospitals and surgeons. Notably, 59% of cardiologists reported increased difficulty in finding surgeons willing to perform CABG in severely ill patients who required it, and 63% of cardiac surgeons reported that they were reluctant to operate on these patients. In a subsequent publication, awareness and use of the consumer guide was assessed among patients undergoing CABG in the prior year; only 12% of patients were aware of the guide, and less than 1% knew the rating of their surgeon.[103]

The public reporting of PCI data has a shorter history than that of cardiac surgery, but similar observations are being made. Moscucci and coworkers compared the demographics, indications, and outcomes of 11,374 patients undergoing PCI in Michigan, where no public reporting exists, with 69,048 patients from New York, where public reporting exists.[104] Patients in Michigan more frequently underwent PCIs for AMI (14.4% vs. 8.7%, $P < .0001$) and cardiogenic shock (2.56% vs. 0.38%, $P < .0001$) compared with those in New York, and they had a higher prevalence of congestive heart failure and extracardiac vascular disease. The unadjusted in-hospital mortality rate was lower in New York than in Michigan, but after adjustment for comorbidities, there was no significant difference in mortality rates between the two groups. The study authors concluded that a propensity in New York for nonintervention in higher-risk patients might be related to the fear of public reporting of high mortality rates.

The conclusion was confirmed in a separate retrospective study of the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock? (SHOCK) registry comparing the outcomes of patients from New York with those from other states.[105] Patients with cardiogenic shock from New York State were less likely to receive angiography, PCI, or CABG. The in-hospital mortality rate for these patients was 1.5 times higher in New York, suggesting that life-saving treatments were being withheld to avoid the reporting of adverse outcomes. Survey data from New York physicians confirmed this, with 83% of practitioners agreeing that patients who were at high risk were denied PCI because of the fear of public reporting, and 79% confirmed that their own decisions on performing PCIs on individual patients had been influenced by the fear of public reporting.[106]

Similar concerns have been raised about the public reporting of PCI data in Massachusetts.[107] This was indirectly confirmed by studying the risk profile of patients undergoing PCI at hospitals after they were identified as outliers in a public reporting program.[108] The risk profile of PCI patients at outlier institutions was significantly lower after public identification compared with nonoutlier institutions, suggesting that risk-aversive behaviors among PCI operators at outlier institutions was an unintended consequence of public reporting.

To minimize unintended consequences, some reporting efforts specifically exclude extreme-risk and salvage patients. In the Massachusetts PCI registry (Mass-DAC), a compassionate use data element was added to capture these types of cases. In addition to concerns that the risk-adjustment methods currently available are suboptimal and do not include all relevant variables, there has been a suggestion that mortality rates must be adjudicated to determine whether they were procedure related or not. After further blinded review, about 80% of the deaths at one Massachusetts hospital were determined to not be directly related to the procedure but were instead related to the natural history of disease in the patients.[107]

Payers have been focused on cost profiling of physicians, and the accuracy of their methods have been questioned.[108] Fung and colleagues conducted a systematic review of the evidence that public reporting leads to an improvement in the quality of care.[109] They concluded that there was minimal evidence about public reporting of individual provider data and practices and that a rigorous evaluation of many major public reporting systems was lacking. They found some evidence suggesting that public release of performance data stimulated quality improvement activity at the hospital level, but the overall effect of public reporting on effectiveness, safety, and patient-centered care remains uncertain.

The most compelling justification for public reporting of clinical outcomes is the public's right to know about the care that they are likely to receive from hospitals and physicians. Transparency of information should allow patients to make better-informed decisions about their health care choices, but the reporting process must be accurate and fair. Realizing the importance of public reporting, the ACC published six principles of public reporting (Table 64-10).[110] There is also growing

TABLE 64-10 2008 American College of Cardiology Foundation Principles for Public Reporting of Physician Performance Data

- The driving force behind physician performance measurement and reporting systems should be to promote quality improvement.
- Public reporting programs should be based on performance measures with scientific validity.
- Public reporting programs should be developed in partnership with physicians.
- Every effort should be made to use standardized data elements to assess and report performance and to make the submission process uniform across all public reporting programs.
- Performance reporting should occur at the appropriate level of accountability.
- All public reporting programs should include a formal process for evaluating the impact of the program on the quality and cost of health care, including an assessment of unintended consequences.

From Drozda JP Jr, Hagan EP, Mirro MJ, et al: ACCF 2008 health policy statement on principles for public reporting of physician performance data: a report of the American College of Cardiology Foundation Writing Committee to Develop Principles for Public Reporting of Physician Performance Data. *J Am Coll Cardiol* 51[20]:1993-2001, 2008.)

interest in changing reimbursement models to be based on the quality rather than the quantity of care and on development of quality measures approved by the NQF.

CONCLUSIONS

Patients, payers, and physicians have interests in measuring and understanding the quality of interventional procedures. The goal is to measure and deliver the highest quality of care to patients undergoing invasive procedures. Current efforts to achieve this goal have fallen short, and important gaps exist in the ability to provide the highest quality of care for all patients. Implementing improvements in quality care is the next challenge in interventional cardiology. This goal is achievable if physicians and other members of the interventional care delivery team strive in their daily practice to ensure that the right patient gets the right procedure performed correctly, leading to the right outcome.

REFERENCES

1. Deming WE: The W. Edwards Deming Institute website. Available at <www.deming.org> (accessed March 25, 2015).
2. New York State Department of Health: Cardiovascular disease data and statistics. Available at <http://www.nyhealth.gov/statistics/diseases/cardiovascular> (accessed March 25, 2015).
3. Pennsylvania Health Care Cost Containment Council: Cardiac surgery in Pennsylvania. Available at <http://www.phc4.org/reports/cabg> (accessed March 25, 2015).
4. McGlynn EA, Asch SM, Adams J, et al: The quality of health care delivered to adults in the United States. *N Engl J Med* 348(26): 2635–2645, 2003.
5. Dehmer GJ, Powell W: Pay for quality—what every interventional cardiologist needs to know: part I. *Catheter Cardiovasc Interv* 68(1):169–172, 2006.
6. Centers for Medicare and Medicaid Services: Bundled payments for care improvement (BPCI) initiative. Available at <http://innovation.cms.gov/initiatives/bundled-payments> (accessed March 25, 2015).
7. Levine GN, Bates ER, Blankenship JC, et al: 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 58(24):e44–e122, 2011.
8. Bashore TM, Balter S, Barac A, et al: 2012 American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions expert consensus document on cardiac catheterization laboratory standards update: a report of the American College of Cardiology Foundation Task Force on Expert Consensus documents developed in collaboration with the Society of Thoracic Surgeons and Society for Vascular Medicine. *J Am Coll Cardiol* 59(24):2221–2305, 2012.
9. Dehmer GJ, Blankenship JC, Cilingiroglu M, et al: SCAI/ACC/AHA expert consensus document: 2014 update on percutaneous coronary intervention without on-site surgical backup. *Catheter Cardiovasc Interv* 84(2):169–187, 2014.
10. Roberts J, Coale J, Redman R: A history of the Joint Commission on Accreditation of Hospitals. *JAMA* 258(7):936–940, 1987.
11. Donabedian A: Evaluating the quality of medical care. *Milbank Mem Fund Q* 44(3 Suppl):166–206, 1966.
12. Luce JM, Bindman AB, Lee PR: A brief history of health care quality assessment and improvement in the United States. *West J Med* 160(3):263–268, 1994.
13. Laffel G, Blumenthal D: The case for using industrial quality management science in health care organizations. *JAMA* 262(20):2869–2873, 1989.
14. Berwick D: Continuous improvement as an ideal in health care. *N Engl J Med* 320(1):53–56, 1989.
15. Kritchevsky S, Simmons B: Continuous quality improvement: concepts and applications for physician care. *JAMA* 266(13): 1817–1823, 1991.
16. American Board of Medical Specialties: ABMS information. Available at <www.abms.org> (accessed March 25, 2015).
17. O'Gara PT, Oetgen WJ: The American College of Cardiology's response to the American Board of Internal Medicine's maintenance of certification requirements. *J Am Coll Cardiol* 64(5): 526–527, 2014.
18. Dans P, Weiner J, Otter S: Peer review organizations: promises and potential pitfalls. *N Engl J Med* 313(18):1131–1137, 1985.
19. Rubin HR, Rogers WH, Kahn KL, et al: Watching the doctor-watchers: how well do peer review organization methods detect hospital care quality problems? *JAMA* 267(17):2349–2354, 1992.
20. Persig RM: *Zen and the art of motorcycle maintenance: an inquiry into values*, New York, 1974, William Morrow Company.
21. Committee on Quality of Health Care in America, Institute of Medicine: *Crossing the quality chasm: a new health system for the 21st century*, Washington, DC, 2001, National Academy Press.
22. Schuster MA, McGlynn EA, Brook RH: How good is the quality of health care in the United States? *Milbank Q* 76(4):517–563, 1998.
23. Lee TH: A broader concept of medical errors. *N Engl J Med* 347(24):1965–1967, 2002.
24. Patel MR: Appropriate use criteria to reduce underuse and overuse: striking the right balance. *J Am Coll Cardiol* 60(19): 1885–1887, 2012.
25. Califf RM, Peterson ED, Gibbons RJ, et al: Integrating quality into the cycle of therapeutic development. *J Am Coll Cardiol* 40(11):1895–1901, 2002.
26. Field MJ, Lohr KN, editors: *Guidelines for clinical practice: from development to use*, Washington, DC, 1992, National Academy Press.
27. Marciniak TA, Ellerbeck EF, Radford MJ, et al: Improving the quality of care for Medicare patients with acute myocardial infarction: results from the Cooperative Cardiovascular Project. *JAMA* 279(1):1351–1357, 1998.
28. Anderson JL, Heidenreich PA, Barnett PG, et al: ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. *J Am Coll Cardiol* 63:2304–2322, 2014.
29. Spertus JA, Eagle KA, Krumholtz HM, et al: American College of Cardiology and American Heart Association methodology for the selection and creation of performance measures for quantifying and quality of cardiovascular care. *J Am Coll Cardiol* 45(7):1147–1156, 2005.
30. Kiefe CI, Allison JJ, Williams OD, et al: Improving quality improvement using achievable benchmarks for physician feedback: a randomized controlled trial. *JAMA* 285(22):2871–2879, 2001.
31. Peterson ED, DeLong ER, Masoudi FA, et al: ACCF/AHA 2010 position statement on composite measures for healthcare performance assessment. *J Am Coll Cardiol* 55(16):1755–1766, 2010.
32. O'Brien SM, Shahian DM, DeLong ER, et al: Quality measurement in adult cardiac surgery: part 2—statistical considerations in composite measure scoring and provider rating. *Ann Thorac Surg* 83(4 Suppl):S13–S26, 2007.
33. Shahian DM, O'Brien SM, Normand ST, et al: Association of hospital coronary artery bypass volume with processes of care, mortality, morbidity, and the Society of Thoracic Surgeons composite quality score. *J Thorac Cardiovasc Surg* 139(2):273–282, 2010.
34. Nallamothu BK, Tommaso CL, Anderson HV, et al: ACC/AHA/SCAI/AMA-convened PCPI/NCQA 2013 performance measures for adults undergoing percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures, the Society for Cardiovascular Angiography and Interventions, the American Medical Association-Convened Physician Consortium for Performance Improvement, and the National Committee for Quality Assurance. *J Am Coll Cardiol* 63(7):722–745, 2014.
35. Patel MR, Spertus JA, Brindis RG, et al: ACCF proposed method for evaluating the appropriateness of cardiovascular imaging. *J Am Coll Cardiol* 46(8):1606–1613, 2005.
36. Fitch K, Bernstein SJ, Aguilar MD, et al: *The RAND/UCLA appropriateness method user's manual*, Arlington, VA, 2001, RAND Corporation.
37. Hendel RC, Patel MR, Allen JM, et al: Appropriate use of cardiovascular technology: 2013 ACCF appropriate use criteria methodology update: a report of the American College of Cardiology Foundation appropriate use criteria task force. *J Am Coll Cardiol* 61(12):1305–1317, 2013.
38. Anderson HV, Shaw RE, Brindis RG, et al: Relationship between procedure indications and outcomes of percutaneous coronary interventions by American College of Cardiology/American Heart Association Task Force Guidelines. *Circulation* 112(18): 2786–2791, 2005.
39. Lopes RD, Starr A, Pieper CF, et al: Warfarin use and outcomes in patients with atrial fibrillation complicating acute coronary syndromes. *Am J Med* 123(2):134–140, 2010.
40. Goldberg RJ, Spencer FA, Steg PE, et al, for the Global Registry of Acute Coronary Events Investigators: Increasing use of single and combination medical therapy in patients hospitalized for acute myocardial infarction in the 21st century. *Arch Intern Med* 167(16):1766–1773, 2007.
41. Fornasini M, Yarzebski J, Chirboga D, et al: Contemporary trends in evidence-based treatment for acute myocardial infarction. *Am J Med* 123(2):166–172, 2010.
42. Cabana MD, Rand CS, Powe NR, et al: Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 282(15):1458–1465, 1999.
43. Alpert JS: Why are we ignoring guideline recommendations? *Am J Med* 123(2):97–98, 2010.
44. Tricoci P, Allen JM, Kramer JM, et al: Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA* 301(8): 831–841, 2009.
45. Hobbs FD, Erhardt L: Acceptance of guideline recommendations and perceived implementation of coronary heart disease prevention among primary care physicians in five European countries: the Reassessing European Attitudes about Cardiovascular Treatment (REACT) survey. *Fam Pract* 19(6):596–604, 2002.
46. Hannan EL, Racz MJ, Gold J, et al: Adherence of catheterization laboratory cardiologists to American Collage of Cardiology/American Heart Association guidelines for percutaneous coronary interventions and coronary artery bypass graft surgery. What happens in actual practice? *Circulation* 121(2):267–275, 2010.
47. Center for the Evaluative Clinical Sciences: Dartmouth atlas of health care: cardiac surgery. Available at <http://www.dartmouthatlas.org/downloads/reports/Cardiac_report_2005.pdf> (accessed March 25, 2015).
48. Lucas FL, Sirovich BE, Gallagher PM, et al: Variation in cardiologists' propensity to test and treat. Is it associated with regional variation in utilization? *Circ Cardiovasc Qual Outcomes* 3(3): 253–260, 2010.
49. Mehta RH, Peterson ED, Califf RM: Performance measures have a major effect on cardiovascular outcomes: a review. *Am J Med* 120(5):398–402, 2007.
50. Bradley EH, Herrin J, Elbel B, et al: Hospital quality for acute myocardial infarction: correlation among process measures and relationship with short-term mortality. *JAMA* 296(1):72–78, 2006.

51. Chan PS, Patel MR, Klein LW, et al: Appropriateness of percutaneous coronary intervention. *JAMA* 306:53–61, 2011.
52. Ko DT, Guo H, Wijeysundera HC, et al: Cardiac Care Network (CCN) of Ontario Variations in Revascularization Practice in Ontario (VRPO) Working Group: Assessing the association of appropriateness of coronary revascularization and clinical outcomes for patients with stable coronary artery disease. *J Am Coll Cardiol* 60(19):1876–1884, 2012.
53. Colton D: Quality improvement in health care—conceptual and historical foundation. *Eval Health Prof* 23(1):7–42, 2000.
54. Hammermeister KE: Participatory continuous improvement. *Ann Thorac Surg* 58(6):1815–1821, 1994.
55. Eagle KA, Montoye CK, Riba AL, et al: American College of Cardiology's Guidelines Applied in Practice (GAP) Projects in Michigan; American College of Cardiology Foundation Guidelines Applied in Practice Steering Committee: Guideline-based standardized care is associated with substantially lower mortality in Medicare patients with acute myocardial infarction. *J Am Coll Cardiol* 46(7):1242–1248, 2005.
56. Moscucci M, Rogers EK, Montoye C, et al: Association of a continuous quality improvement initiative with practice and outcomes variations of contemporary percutaneous coronary interventions. *Circulation* 113(6):814–822, 2006.
57. Rihal CS, Kamath CC, Holmes DR, et al: Economic and clinical outcomes of a physician-led continuous quality improvement intervention in the delivery of percutaneous coronary intervention. *Am J Manag Care* 12(8):445–452, 2006.
58. Brindis RG, Dehmer GJ: Continuous quality improvement in the cardiac catheterization laboratory: are the benefits worth the cost and effort? *Circulation* 113(6):767–770, 2006.
59. Majumdar SR, McAlister FA, Furberg CD: From knowledge to practice in chronic cardiovascular disease: a long and winding road. *J Am Coll Cardiol* 43(10):1738–1742, 2004.
60. Brindis RG, Fitzgerald S, Anderson HV, et al: The American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR): building a national clinical data repository. *J Am Coll Cardiol* 37(8):2240–2245, 2001.
61. O'Connor GT, Plume SK, Olmstead EM, et al: Results of a regional prospective study to improve the in-hospital mortality associated with coronary artery bypass grafting. *JAMA* 275:841–846, 1996.
62. Berwick DM: The society for medical decision making: the right place at the right time. *Med Decis Making* 8(2):77–80, 1988.
63. Topol EJ, Block PC, Holmes DR, et al: Readiness for the scorecard era in cardiovascular medicine: implications for cost-effectiveness. *Am J Cardiol* 75(16):1170–1173, 1995.
63a. Brindis RG, Goldberg SD, Turco MA: Quality and appropriateness of care: the response to allegations and actions needed by the cardiovascular professional. *Catheter Cardiovasc Interv* 77(1):2–4, 2011.
63b. Walker AK: More doctors accused of putting unnecessary stents in patients. *The Baltimore Sun*, October 16, 2012. Available at <http://www.baltimoresun.com/health/bs-hs-more-stent-complaints-20121015-story.html> (accessed July 27, 2015).
64. Berwick DM: Peer review and quality management: are they compatible? *QRB Qual Rev Bull* 16(7):246–251, 1990.
65. Hershey N, Bontempo LC: Assessing peer review in the quest for improved medical services: part II. *Qual Assur Util Rev* 5(1):7–11, 1990.
66. Patel MR, Wolk MJ, Allen JM, et al: The privilege of self-regulation: the role of appropriate use criteria. *J Am Coll Cardiol* 57(14):9–2011, 1557.
67. Epstein A: Performance reports on quality—prototypes, problems, and prospects. *N Engl J Med* 333(1):57–61, 1995.
68. Parmley WW: Clinical peer review or competitive hatchet job? *J Am Coll Cardiol* 36(7):2347, 2000.
69. Accreditation for Cardiovascular Excellence. ACE information. Available at <www.cvexcel.org> (accessed March 25, 2015).
70. Curran WJ: Medical peer review of physician competence and performance: legal immunity and the antitrust laws. *N Engl J Med* 316(10):597–598, 1987.
71. Snelson E: Quality assurance implications of federal peer review laws. The Health Care Quality Improvement Act and the National Practitioner Data Bank. *Qual Assur Util Rev* 7(1):2–11, 1992.
72. Heupler FA, Al-Hani AJ, Dear WE, et al: Guidelines for continuous quality improvement in the cardiac catheterization laboratory. *Cathet Cardiovasc Diagn* 30(3):191–200, 1993.
73. Heupler FA, Chambers CE, Dear WE, et al: Guidelines for internal peer review in the cardiac catheterization laboratory. *Cathet Cardiovasc Diagn* 4(1):21–32, 1997.
74. Klein LW, Uretsky BF, Chambers C, et al: Quality assessment and improvement in interventional cardiology: a position statement of the Society of Cardiovascular Angiography and Interventions, part 1: standards for quality assessment and improvement in interventional cardiology. *Catheter Cardiovasc Interv* 77(7):927–935, 2011.
75. Klein LW, Ho KK, Singh M, et al: Quality assessment and improvement in interventional cardiology: a Position Statement of the Society of Cardiovascular Angiography and Interventions, part II: public reporting and risk adjustment. *Catheter Cardiovasc Interv* 78(4):493–502, 2011.
76. National Cardiovascular Data Registry: Quality improvement for institutions. Available at <http://www.NCDR.com> (accessed March 15, 2015).
77. Bradley EH, Curry LA, Webster TR, et al: Achieving rapid door-to-balloon times: how top hospitals improve complex clinical systems. *Circulation* 113(8):1079–1085, 2006.
78. Krumholz HM, Bradley EH, Nallamothu BK, et al: A campaign to improve the timeliness of primary percutaneous coronary intervention: Door-to-Balloon: an alliance for quality. *JACC Cardiovasc Interv* 1(1):97–104, 2008.
79. Bradley EH, Nallamothu BK, Herrin J, et al: National efforts to improve door-to-balloon time results from the Door-to-Balloon Alliance. *J Am Coll Cardiol* 54(25):2423–2429, 2009.
80. Patel MR, Dehmer GJ, Hirshfeld JW, et al: ACCF/SCAI/ STS/AATS/AHA/ASNC 2009 appropriateness criteria for coronary revascularization: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology. *J Am Coll Cardiol* 53(6):530–553, 2009.
81. Wang TY, McCoy LA, Messenger JC, et al: Cardiac biomarker measurement after elective percutaneous coronary interventions in older patients: insights from the National Cardiovascular Data Registry. *Am Heart J* 166(5):927–934, 2013.
82. Krumholz HM, Brindis RG, Brush JE, et al: American Heart Association; Quality of Care and Outcomes Research Interdisciplinary Writing Group; Council on Epidemiology and Prevention; Stroke Council; American College of Cardiology Foundation: Standards for statistical models used for public reporting of health outcomes: an American Heart Association Scientific Statement from the Quality of Care and Outcomes Research Interdisciplinary Writing Group: cosponsored by the Council on Epidemiology and Prevention and the Stroke Council. Endorsed by the American College of Cardiology Foundation. *Circulation* 113(3):456–462, 2006.
83. Peterson ED, Dai D, DeLong ER, et al: Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. *J Am Coll Cardiol* 55(18):1923–1932, 2010.
84. Rao SV, McCoy LA, Spertus JA, et al: An updated bleeding model to predict the risk of post-procedure bleeding among patients undergoing percutaneous coronary intervention: a report using an expanded bleeding definition from the National Cardiovascular Data Registry CathPCI Registry. *JACC Cardiovasc Interv* 6(9):897–904, 2013.
85. Aiken LH, Clarke SP, Sloane DM, et al: Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. *JAMA* 288(16):1987–1993, 2002.
86. Aiken LH, Sochalski J, Lake ET: Studying outcomes of organizational change in health services. *Med Care* 35(11 Suppl):NS6–N18, 1997.
87. Ferlie E, Shortell SM: Improving the quality of health care in the United Kingdom and the United States: a framework for change. *Milbank Q* 79(2):281–315, 2001.
88. Society for Cardiovascular Angiography and Interventions: Quality improvement toolkit. Available at <http://www.scai.org/qit/Default.aspx> (accessed March 25, 2015).
89. Sanborn TA, Tcheng JE, Anderson HV, et al: ACC/AHA/SCAI 2014 health policy statement on structured reporting for the cardiac catheterization laboratory: a report of the American College of Cardiology Clinical Quality Committee. *J Am Coll Cardiol* 63(23):2591–2623, 2014.
90. Lansky D: Improving quality through public disclosure of performance information. *Health Aff (Millwood)* 21(4):52–62, 2002.
91. Department of Health Care Policy, Massachusetts Data Analysis Center (Mass-DAC): Risk-standardized mortality rates for hospitals performing coronary artery bypass graft surgery and percutaneous coronary interventions. Available at <http://www.massdac.org/index.php/reports/> (accessed March 25, 2015).
92. Li Z, Carlile DM, Marcin JP, et al: Impact of public reporting on access to coronary artery bypass surgery: the California Outcomes Reporting Program. *Ann Thorac Surg* 89(4):1131–1138, 2010.
93. Hannan EL, Kumar D, Racz M, et al: New York State's cardiac surgery reporting system: four years later. *Ann Thorac Surg* 58(6):1852–1857, 1994.
94. Bentley JM, Nash DB: How Pennsylvania hospitals have responded to publicly released reports on coronary artery bypass graft surgery. *Jt Comm J Qual Improv* 24(1):40–49, 1998.
95. Shahian DM, Silverstein T, Lovett AF, et al: Comparison of clinical and administrative data sources for hospital coronary artery bypass graft surgery report cards. *Circulation* 115(12):1518–1527, 2007.
96. Hannan EL, Racz MJ, Jollis JG, et al: Using Medicare claims data to assess provider quality for CABG surgery: does it work well enough? *Health Serv Res* 31(6):659–678, 1997.
97. Centers for Medicare and Medicaid Services: Hospital quality initiatives: hospital compare. Available at <http://www.hospitalcompare.hhs.gov> (accessed March 25, 2015).
98. McCabe JM, Kennedy KF, Eisenhauer AC, et al: Reporting trends and outcomes in ST-segment-elevation myocardial infarction national hospital quality assessment programs. *Circulation* 129(2):194–202, 2014.
99. Werner RM, Asch DA: The unintended consequences of publicly reporting quality information. *JAMA* 293(10):1239–1244, 2005.
100. Marshall MN, Shekelle PG, Leatherman S, et al: The public release of performance data: what do we expect to gain? A review of the evidence. *JAMA* 283(14):1866–1874, 2000.
101. Omoigui NA, Miller DP, Brown KJ, et al: Outmigration for coronary bypass surgery in an era of public dissemination of clinical outcomes. *Circulation* 93(1):27–33, 1996.
102. Schneider EC, Epstein AM: Influence of cardiac-surgery performance reports on referral practices and access to care. A survey of cardiovascular specialists. *N Engl J Med* 335(4):251–256, 1996.
103. Schneider EC, Epstein AM: Use of public performance reports: a survey of patients undergoing cardiac surgery. *JAMA* 279(20):1638–1642, 1998.
104. Moscucci M, Eagle KA, Share D, et al: Public reporting and case selection for percutaneous coronary interventions: an analysis from two large multicenter percutaneous coronary intervention databases. *J Am Coll Cardiol* 45(11):1759–1765, 2005.
105. Apolito RA, Greenberg MA, Menegus MA, et al: Impact of the New York State Cardiac Surgery and Percutaneous Coronary Intervention Reporting System on the management of patients with acute myocardial infarction complicated by cardiogenic shock. *Am Heart J* 155(2):267–273, 2008.
106. Narins CR, Dozier AM, Ling FS, et al: The influence of public reporting of outcome data on medical decision making by physicians. *Arch Intern Med* 165(1):83–87, 2005.
107. Resnic FS, Welt FG: The public health hazards of risk avoidance associated with public reporting of risk-adjusted outcomes in coronary intervention. *J Am Coll Cardiol* 53(10):825–830, 2009.
108. McCabe JM, Joynt KE, Welt FG, et al: Impact of public reporting and outlier status identification on percutaneous coronary intervention case selection in Massachusetts. *JACC Cardiovasc Interv* 6(6):625–630, 2013.
109. Adams JL, Mehrotra A, Thomas JW, et al: Physician cost profiling—reliability and risk of misclassification. *N Engl J Med* 362(11):1014–1021, 2010.
110. Fung CH, Lim Y-W, Mattke S, et al: Systematic review: evidence that publishing patient care performance data improves quality of care. *Ann Intern Med* 148(2):111–123, 2008.

Volume and Outcome

65

JAMES G. JOLLIS

KEY POINTS

- A relationship between experience and outcome for higher-risk procedures has been repeatedly demonstrated over the past 3 decades.
- In the case of percutaneous coronary intervention (PCI), the minimum volume thresholds involve low numbers of fewer than four cases per week for hospitals and one case per week for physicians.
- The volume standards affect relatively few patients (4% of all patients undergo PCI at low-volume hospitals, and 7% are treated by low-volume physicians) but relatively larger numbers of operators (27% of hospitals and 50% of physicians perform fewer than 200 and 50 cases per year respectively).
- In considering the evidence, studies must be viewed according to representation by low-volume providers, event rates, and regression techniques.
- Supporting evidence and concern for patients compel the medical community to foster experienced interventional operators and facilities to the extent possible.

A series of studies over 30 years has repeatedly identified a relationship between increased procedural volume and lower mortality, particularly for higher-risk procedures or patients.[1-16] The finding of better outcomes with increased experience seems rather obvious, and in isolation, it should not engender much controversy. When the volume–outcome relationship is applied to health policy in a manner that suggests patients should avoid low-volume hospitals or physicians, passionate debate ensues. Fueled by intense policy interests, manuscripts that support or refute volume standards continue to be published in the medical and health services research literature. This chapter examines the volume–outcome relationship for coronary interventions in depth according to the strength of the evidence and the underlying reasons why study conclusions may vary despite consistency of the relationship. Based on this review, a practical framework for public policy is proposed.

To provide some perspective on the issue, one must first understand that the proposed volume thresholds represent very low numbers and affect relatively few patients. The relationship between worse outcome and low volume is most apparent among very low-volume operators. In the case of interventional cardiologists, an overall percutaneous coronary intervention (PCI) volume of 50 cases per year requires performance of one procedure per week, and a primary PCI volume of 12 cases per year involves treatment of one ST-segment elevation myocardial infarction (STEMI) case per month. A hospital must perform 4 cases per week to reach a threshold of 200 elective PCI cases, and 3 cases per month to reach a primary PCI threshold of 36 cases. With such low thresholds, low-volume providers treat relatively few patients.

A reasonable gauge of the relative proportion of patients treated in low-volume institutions can be obtained from the National Inpatient Sample (NIS), a nationally representative cohort of patients of all ages treated at 20% of United States hospitals.[1] Data from the Cath Registry (American College of Cardiology) and the NIS indicate that only 4% of patients undergoing PCI are treated in hospitals with volumes lower than 200 cases per year; yet the low-volume institutions treating these relatively few patients represent 26% of hospitals (Fig. 65-1).[17] Similarly, physician volumes from the New York State Coronary Angioplasty Reporting System can be extrapolated to indicate that 7% of patients are treated by physicians who perform fewer than 75 cases per year, and these operators represent 30% of all physicians performing PCI. Recent declines in national procedural volume suggest that fewer than half of interventional cardiologists perform more than 50 cases of PCI per year.[16]

EVIDENCE FOR A VOLUME–OUTCOME RELATIONSHIP

The origins of the volume–outcome relationship date back to 1979, when Luft, Bunker, and Enthoven of Stanford University identified higher mortality at lower-volume hospitals for a number of surgical procedures, including open heart and vascular surgery.[2] Among 12 surgeries, the relationship was most evident for the higher-risk procedures, and their initial data identified a threshold of approximately 200 surgical procedures per year, above which procedural mortality decreased by 25% to 41%. In their initial work, the authors suggested that the observed relationships support the regionalization of higher-risk procedures. Since the initial work, the volume–outcome relationship has repeatedly been demonstrated for a number of procedures and conditions.[12] Examining more than 3 million Medicare patients hospitalized at 4679 hospitals between 2004 and 2006 for acute myocardial infarction (MI), congestive heart failure, or pneumonia, Ross and colleagues found that those treated at lower-volume hospitals had significantly higher 30-day mortality rates. For acute MI, the upper volume threshold was 610 cases per year, beyond which significant differences in mortality were no longer observed.[12]

Volume standards for PCI were first introduced in the 1988 American College of Cardiology/American Heart Association guidelines.[18] Lacking empirical evidence regarding coronary angioplasty volume, the task force selected the physician threshold volume of 50 cases per year based on the logic that one must golf about once per week to remain proficient, and such an experiential relationship can likely be extended to coronary interventions. The publication of this standard unleashed a flood of concerns from approximately half of cardiologists performing angioplasty at the time who did not meet the one-case-per-week standard. Providers opposed to volume standards were concerned about restrictions to practice in the absence of empirical evidence of a volume–outcome relationship for PCI. They were also concerned that such standards may unfairly restrict low-volume physicians with good outcomes and that annual volume standards do not take into account aggregate experience over a number of years.

Empirical evidence supporting a volume–outcome relationship for PCI began to emerge in the 1990s. In a study of Medicare procedures, Jollis and colleagues found that in-hospital mortality increased from 2.5% for high-volume hospitals to 3.9% for low-volume hospitals.[3] Among the 217,836 patients studied, the relationship between volume and outcome appeared to be J-shaped, with the highest mortality rate for hospital volumes performing fewer than 100 Medicare procedures per year (Fig. 65-2). Because Medicare primarily involves patients older than 65 years of age, a Medicare case volume of 100 represents an overall hospital volume of roughly 200 cases per year.

For 19,594 patients undergoing elective PCI in 48 hospitals in the Society for Cardiac Angiography and Interventions registry, Kimmel

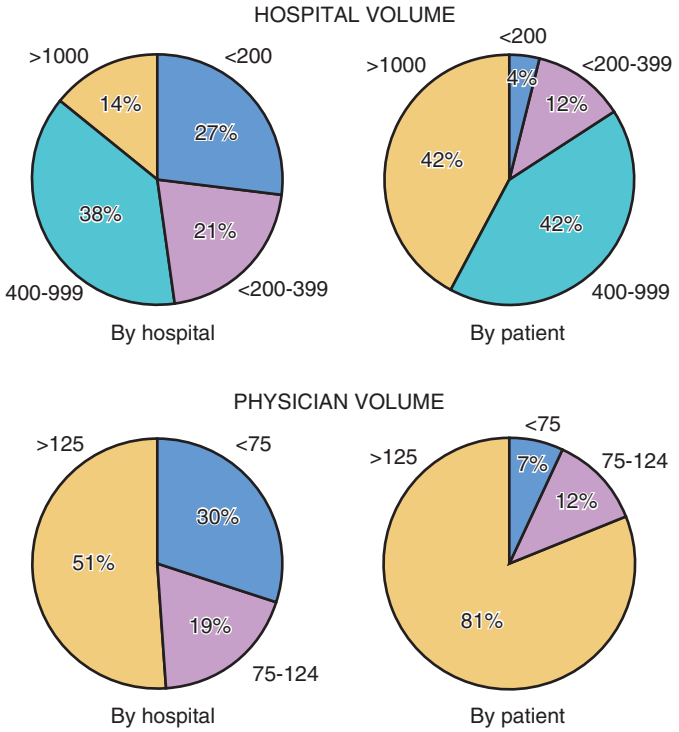


FIGURE 65-1 Distribution of hospital and physician percutaneous coronary intervention cases by hospitals, physicians, and patients. (Adapted from Epstein AJ, Rathore SS, Volpp KG, et al: Hospital percutaneous coronary intervention volume and patient mortality, 1998 to 2000: does the evidence support current procedure volume minimums? *J Am Coll Cardiol* 43:1755-1762, 2014; and Hannan EL, Wu C, Wallford G, et al: Volume-outcome relationships for percutaneous coronary interventions in the stent era. *Circulation* 112:1171-1179, 2005.)

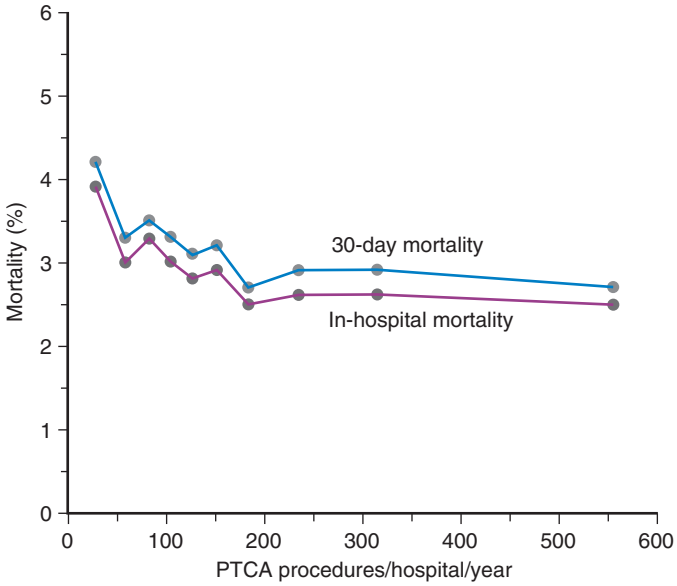


FIGURE 65-2 Mortality for Medicare beneficiaries according to hospital volume. *PTCA,* Percutaneous transluminal coronary angioplasty. (Data from Jollis JG, Peterson ED, DeLong ER, et al: The relation between the volume of coronary angioplasty procedures at hospitals treating Medicare beneficiaries and short-term mortality. *N Engl J Med* 331:1625-1629, 1994.)

and associates found significantly higher rates for mortality, emergency bypass, and major complications among patients treated at hospitals with volumes lower than 400 cases per year.[4] In the New York State Coronary Angioplasty Reporting System, Hannan and colleagues identified significantly higher risk-adjusted mortality for patients treated at hospitals with annual volumes lower than 600 cases.[5] After the widespread adoption of coronary stents, repeated analyses of Medicare data by McGrath and colleagues[6] continued to identify higher mortality at low-volume hospitals. Evidence for a relationship between physician volume and outcome also emerged, with both Jollis[7] and Hannan[5] identifying higher in-hospital mortality for physician volumes of less than 75 cases per year. With this substantial compelling evidence, the 1993 PCI guidelines revised upward the minimum volume standards to 75 cases per year for physicians and 200 cases per year for hospitals to maintain competency.[19] The relationship continues to be observed in contemporary data, including the NIS from 2005 to 2010, the German Drug Eluting Stent Registry, and the RIVAL (Radial Versus Femoral Access for Coronary Intervention) trial.[14]

Most recently, there has been a 20% decline in the number of PCI procedures performed annually in the United States with corresponding declines in hospital and physician PCI volumes.[20] In the NIS between 2005 and 2009, median operator volume fell from 53 to 33 cases per year, and median hospital volume fell from 1024 to 693 per year.[16] In reformulating the clinical competency guidelines, the writing committee indicated that most interventional cardiologists in the United States were not achieving the previously recommended threshold of 75 PCIs annually.[21] To remain relevant, the 2013 update lowered the volume standard for physicians to "a minimum of 50 coronary interventional procedures per year (averaged over a 2-year period) to maintain competency."[21]

Since the original evidence was incorporated into updated guidelines, the volume–outcome relationship has undergone regular reexamination. With improved technology and lower event rates, the question remains whether this relationship should continue to guide policy regarding hospital and operator volumes. In order to understand empirical evidence concerning the volume–outcome relationship, one must keep in perspective three basic concepts of observational research: frequency of the end point, representativeness of the sample, and regression analysis techniques. Considering more recent evidence in light of these concepts, the volume–outcome relationship continues to be observed in higher-risk populations and in samples with an adequate representation of low-volume providers.

The first consideration when evaluating empirical evidence is whether the study involves an adequate number of end points to observe a volume–outcome relationship. The relationship is most apparent in high-risk patients, who are more likely to experience complications and death. In the first study of volume and outcome for coronary interventions, the greatest differences in mortality by volume were seen in the subset of patients with acute MI. Mortality rates for low-, medium-, and high-volume hospitals were 8.1%, 7.1%, and 6.4%, respectively, compared with 1.3%, 1.2%, and 1.0% mortality, respectively, for patients without MI treated at low-, medium-, and high-volume hospitals.[3] This finding follows clinical intuition that experience is likely to be most important when one is managing complications and high-risk situations.

Studies of patients with acute MI that include the universe of low-volume operators continue to provide persuasive evidence of a volume–outcome relationship. Srinivas and colleagues examined in-hospital mortality for 7321 patients undergoing primary PCI in New York State at 41 hospitals (volume range, 1 to 172 primary PCIs per year) by 266 physicians (volume range, 1 to 55 primary PCIs per year).[8] Risk-adjusted mortality was substantially lower for higher-volume hospitals at a volume threshold of 50 primary PCI cases per year (≤50, 5.4%; >50, 3.4%; odds ratio [OR], 0.58; 95% confidence interval [CI], 0.38 to 0.88)) and for physicians at 20 cases per year (≤20, 4.2%; >20, 2.9%; OR, 0.63; 95% CI, 0.44 to 0.91) (Fig. 65-3). When the risk-adjusted mortality rates were stratified by hospital and physician volume, the highest rate, 7.9% ($P = .01$), was seen for patients treated

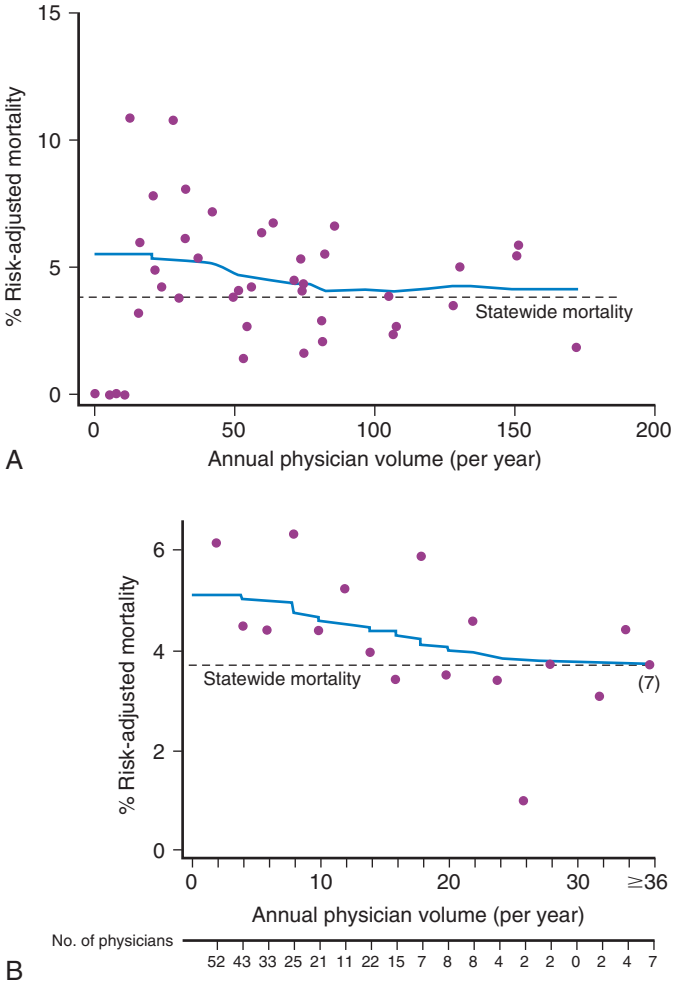


FIGURE 65-3 Volume–outcome relationships for hospitals **(A)** and physicians **(B)** performing primary percutaneous coronary interventions in New York state. (Adapted from Srinivas VS, Hailpern SM, Koss E, et al: Effect of physician volume on the relationship between hospital volume and mortality during primary angioplasty. *J Am Coll Cardiol* 53:574-579, 2009.)

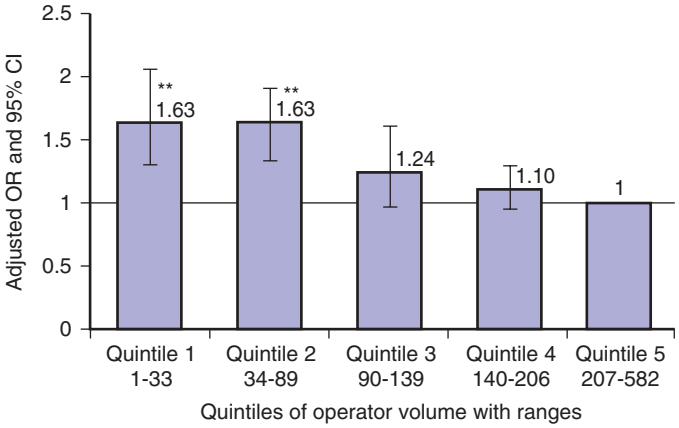


FIGURE 65-4 Adjusted odds ratios (OR) for major adverse cardiovascular events with generalized estimating equations clustering modeling. **, $P < .0001$; *CI*, confidence interval. (Adapted from Moscucci M, Share D, Smith D, et al: Relationship between operator volume and adverse outcome in contemporary percutaneous coronary intervention practice: an analysis of a quality-controlled multicenter percutaneous coronary intervention clinical database. *J Am Coll Cardiol* 46:625-632, 2005.)

by low-volume physicians (<20 primary PCIs per year) practicing in low-volume hospitals (<50 primary PCIs per year); and conversely, the lowest rate, 2.8%, was seen among patients treated by high-volume physicians (>20 primary PCIs per year) at high-volume hospitals (>50 primary PCIs per year). The stratified analyses showing an interaction between physician and hospital volume suggest that both physician and staff experience contribute to better outcomes.

When adverse outcomes decline, the volume–outcome relationship is mitigated. After the introduction of coronary stents, abrupt coronary artery closure leading to a need for urgent bypass surgery markedly decreased, from 3.8% to 1.9% in Medicare patients.[3,7] Repeated analyses by McGrath and colleagues[6] found that the inverse relationship between volume and need for surgery was no longer apparent after the adoption of coronary stents. By combining end points, the ability of an observational study to observe a volume–outcome relationship was increased. Moscucci and colleagues examined the composite end point of death, bypass surgery, stroke or transient ischemic attack, MI, and repeat PCI for 18,504 patients treated at 14 Michigan hospitals participating in a quality improvement initiative.[9] Whereas individual complications were more common for low-volume physicians, the relationships did not reach statistical significance until the outcomes were combined as a composite end point (Fig. 65-4).

To understand empirical evidence, a second important consideration is whether the study population includes a representative sample of low-volume operators. Studies that include the universe of low-volume operators according to mandatory registries or hospital claims, such as the New York Coronary Angioplasty Reporting System or the NIS, consistently identify volume–outcome relationships, whereas those that rely on voluntary participation by hospitals focused on quality improvement are less likely to include a sample of low-volume providers sufficient to characterize the volume relationship. The most representative cohort of patients with PCI is reported in the NIS, which includes discharge records for a random sample of acute care hospitals approximating a 20% stratified sample of U. S. community hospitals.[22] The NIS includes all payers and therefore includes patients younger than 65 years of age. Examining 2,243,209 procedures performed between 2005 and 2010, Badheka, Patel, and colleagues[16] found a stepwise increase in in-hospital mortality ($P < .001$) and complications ($P < .001$) according to annual physician volume quartiles (>99 cases per year, 0.6% and 5.2%, respectively; 47 to 98 cases, 0.9% and 6.0%; 17 to 46 cases, 1.2% and 7.2%; 1 to 16 cases, 1.7% and 10.1%).

Careful consideration of regression models represents a third important element of volume–outcome studies. Regression analyses simply examine the mathematical relationship between two variables according to a set of data points. As regression techniques become more complex, their presentation in manuscripts must be abbreviated to meet editorial requirements. Thus elaborate regression procedures have evolved into "black box" approaches to balancing comparisons. Without detailed presentations, readers are unable to assess whether regression techniques have overcome critical obstacles that limit their ability to reliably identify relationships of interest—namely, confounding, multicollinearity, unmeasured risk, and model fit. Even the most sophisticated modeling techniques are limited by sample size and the potential for type II errors, incorrectly accepting the null hypothesis of no difference when a significant difference exists. Mortality differences by volume apparent in unadjusted data may lose their statistical significance in regression models as statistical thresholds are raised to satisfy probability assumptions.

For example, Kumbhani and colleagues examined primary PCI volume and outcome for 29,513 patients directly admitted to 116 hospitals participating in the Get With the Guidelines (GWTG) registry.[23] When the data were stratified by annual hospital primary PCI volume, there was a trend toward higher mortality for lower-volume institutions (<36 procedures, 3.9%; 36 to 70 procedures, 3.2%; and >70 procedures, 3.0%). These differences were present despite the exclusion

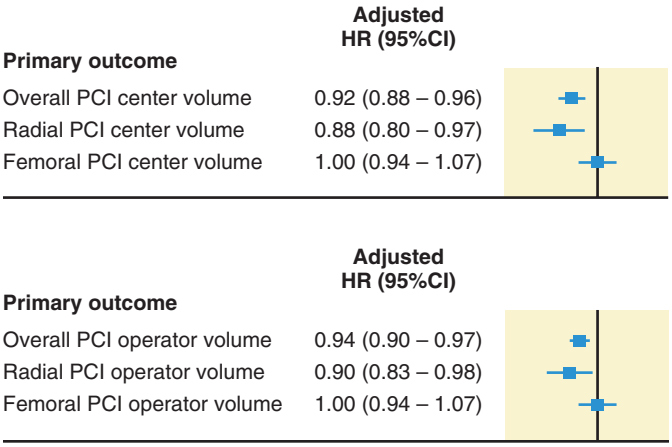


FIGURE 65-5 Adjusted rate of death, myocardial infarction, stroke, or major bleeding (primary outcome) according to center and operator volume in the RIVAL trial. *CI,* Confidence interval; *HR,* hazard ratio; *PCI,* percutaneous coronary intervention. (Data from Jolly SS, Cairns J, Yusuf S, et al; RIVAL Investigators: procedural volume and outcomes with radial or femoral access for coronary angiography and intervention. *J Am Coll Cardiol* 63:954-963, 2014.)

of patients treated in hospitals that submitted fewer than 30 patients and irrespective of the select nature of GWTG hospitals. After adjustment in regression models, the mortality difference did not reach statistical significance (low volume vs. high volume adjusted odds ratio, 1.3; $P = .15$). The study used generalized estimating equations, a technique that has become widespread over the past decade. This conservative approach accounts for the lack of independence of patients treated within the same hospital but requires larger samples or absolute differences to identify statistically significant findings compared with regression analyses that ignore within-hospital clustering. Generalized estimating equations raise the threshold for statistical significance, increasing the likelihood of a type II error.

In viewing negative findings from regression-adjusted analyses such as the Kumbhani study, one must not confuse the "absence of proof" for "proof of absence." The RIVAL trial examined volume and outcome among 7021 patients treated in 158 hospitals using proportional hazards regression models. The study adjusted for 14 demographic, clinical, and anticoagulation characteristics but did not account for the lack of independence of patients treated in the same hospital. With relatively fewer patients, the study identified significantly lower rates of the primary end point of death, MI, stroke, or major bleeding among hospitals and operators with higher overall volumes and among providers with higher radial access volumes (Fig. 65-5).[14]

PUBLIC POLICY IMPLICATIONS

As mentioned earlier, those who argue against volume standards cite concerns about restricting high-quality, low-volume providers. Participation in national registries has been put forth as an alternative to minimal procedural volumes because quality can be measured and assured. Another advantage of this approach is that low-volume providers are encouraged to avoid high-risk patients, those patients for whom the volume–outcome relationship is most apparent. On the other hand, registries lack statistical power to reliably identify quality low-volume providers due to insufficient sample size. Low-volume hospitals and physicians have worse outcomes on average, and policies that broadly apply volume standards should avert procedural complications and deaths.

Although national guidelines have incorporated volume standards, most decisions regarding physician and hospital practice occur at the local or state level irrespective of these guidelines.[21,24] Interventional cardiologists are granted privileges at the hospital level, and hospitals have a significant incentive to encourage all physicians to perform procedures in their facilities regardless of volume standards. The ability of hospitals to open and operate interventional cardiology programs is regulated by states, and standards vary widely. In many regions of the country, low-volume PCI programs are common and increasing in number despite national standards and empirical evidence. Coronary intervention represents a profitable activity from a hospital perspective, and hospitals have successfully lobbied many state governments to allow for an expansion of low-volume facilities.

With national declines in cardiac intervention, the need for continued expansion of PCI facilities is further called into question.[25] The necessity of additional hospitals and operators varies according to the elective or urgent nature of the procedure. Elective PCI procedures are relatively low risk and less subject to the volume–outcome relationship. However, the very nature of elective procedures allows for diversion of patients to higher-volume facilities, obviating the need for more PCI facilities.

Whether volume standards should be strictly applied for primary PCI procedures represents a more challenging and uncertain policy question. The time-dependent relationship between device deployment and survival, coupled with extraordinarily long "first hospital door-to-device" times for patients requiring hospital transfer for acute intervention, favors a broadening of the availability of primary PCI.[26,27] Particularly for rural hospital emergency departments for which transport times to PCI facilities are longer than 30 to 40 minutes, a case can be made for expanding PCI facilities to rural areas. High-risk patients, including those with acute MI, have the worst outcomes with low-volume providers, however, and a better strategy may involve reperfusion with fibrinolysis at the rural hospital, followed by transfer to a regional PCI facility.

CONCLUSIONS

The relationship between lower volume and worse outcomes has been established by sizeable and compelling empirical evidence over the past 30 years. This association is most apparent among high-risk patients and procedures. The strength of supporting evidence varies as a function of representation by low-volume providers, sample size, number of outcomes of interest, and regression techniques. Although procedural volume represents only one facet of quality cardiovascular care, the supporting evidence and concern for patients compel the medical community to foster experienced interventional operators and facilities to the extent possible.

REFERENCES

1. Epstein AJ, Rathore SS, Volpp KG, Krumholz HM: Hospital percutaneous coronary intervention volume and patient mortality, 1998 to 2000. *J Am Coll Cardiol* 43:1755–1762, 2004.
2. Luft HS, Bunker JP, Enthoven AC: Should operations be regionalized? The empirical relation between surgical volume and mortality. *N Engl J Med* 301:1364–1369, 1979.
3. Jollis JG, Peterson ED, DeLong ER, et al: The relation between the volume of coronary angioplasty procedures at hospitals treating Medicare beneficiaries and short-term mortality. *N Engl J Med* 331:1625–1629, 1994.
4. Kimmel SE, Berlin JA, Laskey WK: The relationship between coronary angioplasty procedure volume and major complications. *JAMA* 274:1137–1142, 1995.
5. Hannan EL, Racz M, Ryan TJ, et al: Coronary angioplasty volume outcome relationships for hospitals and cardiologists. *JAMA* 279:892–898, 1997.
6. McGrath PD, Wennberg DE, Malenka DJ, et al: Operator volume and outcomes in 12,988 percutaneous coronary interventions. *J Am Coll Cardiol* 31:570–576, 1998.
7. Jollis JG, Peterson ED, Nelson CL, et al: Relationship between physician and hospital coronary angioplasty volume and outcome in elderly patients. *Circulation* 95:2485–2491, 1997.
8. Srinivas VS, Hailpern SM, Koss E, et al: Effect of physician volume on the relationship between hospital volume and mortality during primary angioplasty. *J Am Coll Cardiol* 53:574–579, 2009.
9. Moscucci M, Share D, Smith D, et al: Relationship between operator volume and adverse outcome in contemporary percutaneous coronary intervention practice: an analysis of a quality-controlled multicenter percutaneous coronary intervention clinical database. *J Am Coll Cardiol* 46:625–632, 2005.
10. Hannan EL, Wu C, Walford G, et al: Volume-outcome relationships for percutaneous coronary interventions in the stent era. *Circulation* 112:1171–1179, 2005.
11. Vakili BA, Kaplan R, Brown DL: Volume-outcome relation for physicians and hospitals performing angioplasty for acute myocardial infarction in New York State. *Circulation* 104:2171–2176, 2001.

12. Ross JS, Normand SLT, Wang Y, et al: Hospital volume and 30-day mortality for three common medical conditions. *N Engl J Med* 362:1110–1118, 2010.
13. Akin I, Hochadel M, Schneider S, et al; DES.DE Study group: Volume-outcomes relationship in the era of modern coronary intervention: results from the prospective multicenter German DES.DE Registry. *Catheter Cardiovasc Interv* 82:E788–E797, 2013.
14. Jolly SS, Cairns J, Yusuf S, et al; RIVAL Investigators: Procedural volume and outcomes with radial or femoral access for coronary angiography and intervention. *J Am Coll Cardiol* 63:954–963, 2014.
15. Strom JB, Wimmer NJ, Wasfy JH, et al: Association between operator procedure volume and patient outcomes in percutaneous coronary intervention: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 7(4):560–566, 2014.
16. Badheka AO, Patel NJ, Grover PM, et al: Impact of annual operator volume on percutaneous coronary intervention outcomes: a United States experience from 2,243,209 procedures. *Circulation* 130(16):1392–1406, 2014.
17. Dehmer GJ, Weaver WD, Roe MT, et al: A contemporary view of diagnostic cardiac catheterization and percutaneous coronary intervention in the United States: a report from the CathPCI Registry of the National Cardiovascular Data Registry 2010 through June 2011. *J Am Coll Cardiol* 60:2017–2031, 2012.
18. Ryan TJ, Faxon DP, Gunnar RM, et al: Guidelines for percutaneous transluminal coronary angioplasty: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures. *Circulation* 78:486–502, 1988.
19. Ryan TJ, Bauman WB, Kennedy JW, et al: Guidelines for percutaneous transluminal coronary angioplasty: a report of the American Heart Association/American College of Cardiology Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Percutaneous Transluminal Coronary Angioplasty). *Circulation* 88:2987–3007, 1993.
20. Riley RF, Don CW, Powell W, et al: Trends in coronary revascularization in the United States from 2001 to 2009: recent declines in percutaneous coronary intervention volumes. *Circ Cardiovasc Qual Outcomes* 4:193–197, 2011.
21. Harold JG, Bass TA, Bashore TM, et al: ACCF/AHA/SCAI 2013 update of the clinical competence statement on coronary artery interventional procedures: a report of the American College of Cardiology Foundation/American Heart to Update the 2007 Clinical Competence Statement on Cardiac Interventional Procedures). *Circulation* 128:436–472, 2013.
22. Overview of the National (Nationwide) Inpatient Sample (NIS). Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. Available at <http://www.hcup-us.ahrq.gov/nisoverview.jsp>, Accessed March 14, 2015.
23. Kumbhani DJ, Cannon CP, Fonarow GC, et al: Association of hospital primary angioplasty volume in ST-segment elevation myocardial infarction with quality and outcomes. *JAMA* 302: 2207–2213, 2009.
24. Smith SC, Jr, Feldman TE, Hirshfeld JW, Jr, et al: ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol* 47:1–121, 2006.
25. Lloyd-Jones D, Adams RJ, Brown TM, et al; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee: Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation* 121:e46–e215, 2010.
26. Boersma E; The Primary Coronary Angioplasty vs. Thrombolysis (PCAT)-2 Trialists' Collaborative Group: Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J* 27:779–788, 2006.
27. Jollis JG, Roettig ML, Aluko AO, et al: Implementation of a statewide system for coronary reperfusion for ST-segment elevation myocardial infarction. *JAMA* 298:2371–2380, 2007.

66 Interventional Heart Failure

WILLIAM T. ABRAHAM

KEY POINTS

- Despite current guideline-directed drug and electrophysiologic device therapies, many heart failure patients remain highly symptomatic, and outcomes remain poor. New therapies are needed to improve patients' clinical status and outcomes.
- Several causes of heart failure are amenable to interventional device-based therapies, an observation that led to emergence of the field of interventional heart failure.
- Interventional heart failure targets include primary or secondary valve disease, left ventricular dilation or pathophysiologic remodeling, elevated left atrial and pulmonary artery pressures, and reduced cardiac output.
- Interventions include transcatheter aortic valve replacement (TAVR), percutaneous mitral valve repair, percutaneous or hybrid ventricular partitioning or restoration, interatrial shunt devices, and implantable hemodynamic monitors.
- With the exception of TAVR, percutaneous mitral valve repair (e.g., MitraClip system), and pulmonary artery pressure monitoring (e.g., CardioMEMS system), most devices remain under investigation for use in heart failure patients.
- Severe aortic stenosis is a potentially reversible cause of heart failure. TAVR improves symptoms and prolongs survival of patients with heart failure and severe aortic stenosis at high surgical risk.
- Functional mitral regurgitation contributes to the vicious cycle of progressive heart failure, and preliminary findings for several percutaneous approaches to mitral valve repair are encouraging.
- Pathologic left ventricular remodeling after anterior myocardial infarction leads to progressive heart failure. Percutaneous or hybrid ventricular partitioning or reconstruction devices restore a more normal elliptical left ventricular geometry while reducing ventricular volume, reducing end-diastolic pressure, and improving symptoms and outcomes.
- Elevated left atrial and pulmonary artery pressures increase the risk of heart failure, and interatrial shunt devices can lower left atrial pressure and improve hemodynamics in systolic and diastolic heart failure patients.
- Implantable hemodynamic monitors can guide changes in pharmacologic therapies to accomplish reductions in left atrial and pulmonary artery pressures, reducing the incidence of heart failure hospitalizations.
- Convergence between the fields of interventional cardiology and heart failure is needed to guide the application of therapies for these patients.

Heart failure is a growing public health problem. An estimated 5.1 million Americans have heart failure, and 825,000 new cases are diagnosed each year in the United States.[1] By the year 2030, the U.S. prevalence of heart failure is expected to exceed 8 million people.[2] Beyond these numbers, heart failure imposes an enormous burden on patients, caregivers, and the health care system.

New approaches are needed to improve the clinical status and outcomes of heart failure patients. Despite current drug and electrophysiologic device therapies, many patients have moderate to severe symptoms, a poor quality of life, and substantial limitations in exercise capacity. They are also at considerable risk for heart failure–related morbidity (e.g., hospitalization) and mortality.[3] Heart failure is the primary diagnosis in more than 1 million hospital admissions annually in the United States.[1] It is also associated with the highest rate of hospital readmissions compared with all other medical and surgical causes of hospitalization.[4] In 2012, due in large measure to the high rates of hospitalization and rehospitalization, the U.S. total economic burden from heart failure was estimated at $31 billion.[1]

Convergence of the fields of heart failure and interventional cardiology has produced a discipline called *interventional heart failure*. Although the term may be applied to virtually any invasive procedure performed in heart failure patients (e.g., diagnostic coronary angiography, percutaneous coronary intervention, invasive assessment of hemodynamics), it is more commonly reserved for the application of invasive therapeutic procedures intended to improve the clinical status and outcomes of heart failure patients.

Interventions usually target primary or secondary valve disease, left ventricular dilation or pathophysiologic remodeling, elevated left atrial and pulmonary artery pressures, or reduced cardiac output to improve cardiac structure, function, and hemodynamics. Myocardial ischemia is excluded from this list of interventional heart failure targets because coronary revascularization has not proved a beneficial heart failure therapy,[5] although it may be useful for the treatment of symptomatic angina in heart failure patients.[3]

Interventional heart failure procedures and devices include transcatheter aortic valve replacement (TAVR), percutaneous mitral valve repair (i.e., MitraClip percutaneous therapy), percutaneous or hybrid ventricular partitioning or restoration, interatrial shunt devices, and implantable hemodynamic monitors. With the exception of TAVR, MitraClip, and pulmonary artery pressure monitoring with the CardioMEMS heart failure system, most interventional heart failure devices remain under investigation in heart failure patients.

At least one form of neuromodulation (i.e., renal denervation) may be considered an interventional heart failure procedure when applied to the treatment of these patients, but it is not discussed in this chapter. Other forms of neuromodulation, including baroreflex activation therapy,[6,7] vagal nerve stimulation,[8,9] spinal cord stimulation,[10] and phrenic nerve stimulation,[11,12] involve the implantation of pulse stimulators and stimulation leads, and they are considered to be surgical or electrophysiologic interventions.

TRANSCATHETER AORTIC VALVE REPLACEMENT

Heart failure in patients with aortic stenosis carries a grave prognosis. If the aortic valve is not replaced, patients with heart failure due to aortic stenosis have a 2-year mortality rate of 50%.[13] In the setting of aortic stenosis, heart failure results from left ventricular hypertrophy with diastolic dysfunction or left ventricular dilation with systolic dysfunction, or both. Because heart failure results from the excess afterload caused by aortic stenosis, aortic valve replacement often leads to symptom improvement and a good outcome, especially when the preoperative gradient across the aortic valve is high or a good contractile reserve has been demonstrated when the gradient is low.[14]

Aortic valve replacement is recommended in patients with severe aortic stenosis and symptomatic heart failure with an aortic velocity of 4.0 m/sec or greater or a mean pressure gradient of 40 mm Hg or higher.[15] In patients with low-flow or low-gradient severe aortic

stenosis with a left ventricular ejection fraction (LVEF) less than 50% and not meeting one of these criteria, a low-dose dobutamine stress study should be performed. If the study shows an aortic velocity of 4.0 m/sec or greater or a mean pressure gradient of 40 mm Hg or higher with a valve area 1.0 cm^2 or less at any dobutamine dose, aortic valve replacement is recommended.[15] Surgical aortic valve replacement is recommended in patients who meet an indication for aortic valve replacement who are at low or intermediate surgical risk. Surgical aortic valve replacement in patients with a reduced LVEF significantly improves or normalizes the LVEF and improves survival.[16,17]

An alternative to surgical aortic valve replacement in patients at high or prohibitive surgical risk is TAVR.[18] The Placement of Aortic Transcatheter Valves (PARTNER) trial compared TAVR with standard therapy in high-risk patients with severe aortic stenosis and cardiac symptoms, including a cohort of patients who were not considered to be suitable candidates for surgery (i.e., Cohort B). In the PARTNER trial, TAVR was compared with medical therapy without surgical aortic valve replacement.[19,20] A total of 358 patients with severe aortic stenosis were randomized at 21 centers. At 1 year, there was a statistically significant 45% reduction in death from any cause for patients treated with TAVR compared with medically treated patients.[19] The rate of a composite end point of death from any cause or repeat hospitalization was reduced by 54% with TAVR compared with standard therapy. These benefits were sustained at 2 years.[20]

Of the patients randomized in Cohort B, 93% exhibited New York Heart Association (NYHA) class III or IV symptoms at baseline, compatible with an advanced degree of heart failure. TAVR significantly improved the NYHA class ranking compared with ongoing medical therapy alone. Data from PARTNER Cohort A (i.e., TAVR versus surgical aortic valve replacement) demonstrated significant improvement in LVEF with TAVR (from 35.7 ± 8.5% to 48.6 ± 11.3%, $P < .0001$), which was comparable to that seen with surgical aortic valve replacement.[21]

TAVR is a reasonable option for the treatment of symptomatic heart failure in patients with inoperable severe aortic stenosis. The Edwards Sapien and Medtronic CoreValve are two TAVR devices with U.S. Food and Drug Administration (FDA) approval. Numerous alternative TAVR devices are under investigation.

PERCUTANEOUS MITRAL VALVE REPAIR

Functional mitral regurgitation is common in patients with ischemic and nonischemic dilated cardiomyopathy. Some degree of functional mitral regurgitation usually exists in these patients, and 50% of heart failure patients with an LVEF of less than or equal to 35% exhibit moderate or severe functional mitral regurgitation.[22,23]

The cause of functional mitral regurgitation in dilated cardiomyopathy is complex but usually is related to increased left ventricular sphericity and apical and posterior displacement of papillary muscles.[24,25] The severity of functional mitral regurgitation in heart failure is an independent predictor of poor outcome. For example, severe functional mitral regurgitation is associated with a twofold increase in the mortality rate for patients with ischemic and nonischemic cardiomyopathy.[26]

After functional mitral regurgitation ensues in the setting of heart failure, it contributes to a vicious cycle of progressive left ventricular dilation or dysfunction and worsening of the functional mitral regurgitation (Fig. 66-1). Several heart failure therapies can break this vicious cycle and reduce the severity of functional mitral regurgitation by promoting reverse remodeling of the left ventricle. Examples include evidence-based beta-blockers and cardiac resynchronization.[27,28] These therapies significantly reduce left ventricular volumes, improve the left ventricular sphericity index (i.e., restore the normal elliptical geometry of the left ventricle), increase the LVEF, and reduce functional mitral regurgitation. They also significantly reduce morbidity and mortality rates for heart failure patients.

Targeting functional mitral regurgitation to break the vicious cycle of progressive heart failure and worsening functional mitral regurgitation (see Fig. 66-1) may also improve patients' clinical status and outcomes. Evidence to support this idea is lacking, and carefully conducted, prospective, randomized, controlled trials that address this issue are needed.

In the absence of definitive evidence, heart failure guidelines offer only a very weak recommendation (i.e., class IIb) for valve surgery for severe functional mitral regurgitation.[3] Many heart failure specialists do not refer these patients for surgical valve repair with ongoing pharmacologic therapy and if indicated cardiac resynchronization therapy, constituting the mainstay of treatment for functional mitral regurgitation in heart failure. Physicians are reluctant to refer heart failure patients with severe functional mitral regurgitation for surgical valve repair because of a lack of proof of efficacy and concerns about surgical morbidity and mortality.

Catheter-based alternatives to surgical mitral valve repair have been developed. A percutaneous approach to mitral valve repair using the MitraClip system is approved for the treatment of degenerative mitral regurgitation (Fig. 66-2). The device is intended for the percutaneous reduction of significant symptomatic mitral regurgitation (≥3+) due to a primary abnormality of the mitral apparatus (i.e., degenerative mitral regurgitation) in patients who are at prohibitive surgical risk for mitral valve surgery.

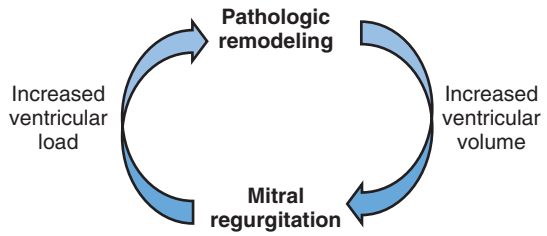


FIGURE 66-1 Pathologic left ventricular remodeling leads to increased left ventricular volume with an increase in left ventricular sphericity and apical and posterior displacement of the papillary muscles, resulting in functional mitral regurgitation. Functional mitral regurgitation increases the left ventricular load, resulting in additional left ventricular dilation and dysfunction.

FIGURE 66-2 The MitraClip system approach is derived from the edge-to-edge surgical procedure for mitral valve repair. The MitraClip system replaces suturing with a clip to join the free edges of the opposing leaflets at the site of regurgitation. (Courtesy Abbott Vascular, Santa Clara, CA.)

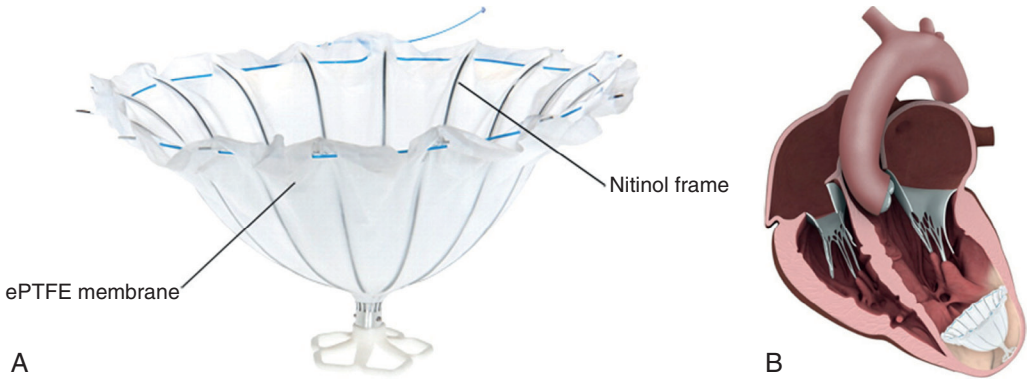


FIGURE 66-3 **A,** The Parachute device is constructed of an expanded polytetrafluoroethylene (ePTFE) membrane stretched over a conical nitinol frame. **B,** The device is deployed in the damaged apex of the left ventricle, where it reduces wall stress in the upper chamber by changing left ventricular geometry and reducing volume. (Courtesy CardioKinetix, Menlo Park, CA.)

The feasibility of the percutaneous approach using the MitraClip system was demonstrated in the first Endovascular Valve Edge-to-Edge Repair Study (EVEREST I). This was followed by EVEREST II, a randomized, controlled trial that enrolled patients who had an indication for and could undergo mitral valve surgery.[29] The trial enrolled patients with degenerative (73%) and functional (27%) mitral regurgitation. The study demonstrated the superior safety of the MitraClip device compared with mitral valve surgery, although the degree of mitral regurgitation reduction was somewhat less in the MitraClip group.

Despite the difference favoring surgery, reduction in left ventricular size was demonstrated in the MitraClip and surgery groups, and similar improvements were seen in both groups for NYHA class ranking and quality of life scores. Shorter intensive care unit time, shorter overall hospital length of stay, and a lower requirement for nursing or rehabilitation care after hospitalization were seen with MitraClip compared with mitral valve surgery.

Given the modest size of the EVEREST II trial (i.e., 60 device roll-in patients, 184 patients randomized to the device, and 95 control subjects) and the relatively low percentage of functional mitral regurgitation patients enrolled, the study was not considered to be a definitive test of percutaneous mitral valve repair in functional mitral regurgitation. EVEREST II selected patients with functional mitral regurgitation who could be randomized to surgical valve repair or replacement rather than treated with standard optimal medical treatment.[3] The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial was initiated to address these issues.

COAPT is a prospective, randomized, parallel-controlled, multicenter clinical evaluation of the MitraClip device for the treatment of clinically significant functional mitral regurgitation in symptomatic heart failure patients who are treated with the standard of care and who have been determined by the center's local heart team as inappropriate candidates for mitral valve surgery because of high surgical risk status or because surgical valve repair is not considered the standard of care by the center for these patients. The goal of the ongoing COAPT study is to evaluate the safety and effectiveness of the MitraClip system for the treatment of functional mitral regurgitation in patients with symptomatic heart failure. It is adequately powered to assess the primary end point of hospitalization for recurrent heart failure. The results should inform future decisions about the management of functional mitral regurgitation in heart failure.

PERCUTANEOUS OR HYBRID VENTRICULAR PARTITIONING OR RESTORATION

The effects of reducing ventricular volume and improving ventricular geometry through surgical ventricular restoration on ischemic heart failure have been reviewed elsewhere.[30] The Reconstructive Endoventricular Surgery Returning Torsion Original Radius Elliptical Shape to the Left Ventricle (RESTORE), an international registry of 1198 heart failure patients after anterior myocardial infarction, suggested that surgical ventricular restoration improved ventricular function and could be effective therapy in the treatment of ischemic cardiomyopathy.[31] However, the randomized, controlled Surgical Therapies for Ischemic Congestive Heart Failure (STICH) trial failed to confirm these results.[32]

The reasons for the failure of the STICH trial are uncertain, but the nature and risks of the surgical procedure itself and the technique used for ventricular reconstruction may have limited its effectiveness. The study authors postulate that "the lack of benefit seen with surgical ventricular reconstruction is that benefits anticipated from surgical reduction of left ventricular volume (i.e., reduced wall stress and improvement in systolic function) are counterbalanced by a reduction in diastolic distensibility."[32]

Minimally invasive percutaneous or hybrid approaches to ventricular restoration have been developed. A catheter-based approach using the Parachute device shows promise for the treatment of heart failure in patients with remote anterior myocardial infarction.[33] The Parachute device is constructed of an expanded polytetrafluoroethylene (ePTFE) membrane stretched over a nitinol conical frame (Fig. 66-3). It is deployed into the apex of the left ventricle to partition off damaged myocardium. The device reduces wall stress in the upper chamber by changing the left ventricular geometry and reducing volume. The compliant Parachute replaces stiff or rigid scar and provides an outward force with the anchors to aid in diastolic filling. It improves diastolic compliance, which reduces end-diastolic filling pressures.

The safety, feasibility, and preliminary clinical efficacy of the Parachute device were demonstrated in a small observational study, the Percutaneous Ventricular Restoration in Chronic Heart Failure Patients (PARACHUTE) trial.[34] Subsequent findings have suggested improved clinical outcomes for patients implanted with the Parachute device.[35] A multicenter, randomized, controlled trial (PARACHUTE IV) is evaluating the possibility of percutaneous ventricular restoration using the Parachute device.[36] The study is randomly assigning 478 patients with NYHA class III or IV ischemic heart failure, akinetic or dyskinetic left ventricular wall abnormality, and an LVEF between 15% and 35% to optimal medical therapy (i.e., control group) or optimal medical therapy plus implantation of the Parachute device. The primary end point is death or rehospitalization for worsening heart failure.

A minimally invasive approach to left ventricular reconstruction using the Revivent system (Bioventrix, San Ramon, CA) is being investigated.[37,38] Preliminary data support its safety and efficacy. It is implanted surgically, but the system may ultimately allow a hybrid approach involving the interventional cardiologist and cardiac surgeon.

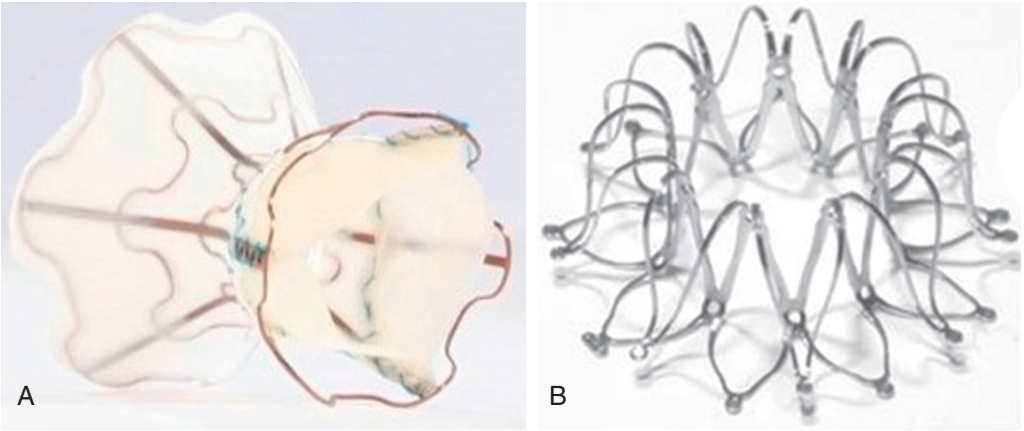


FIGURE 66-4 **A,** Unidirectional (valved) left-to-right interatrial shunt device. **B,** Open left-to-right interatrial shunt device. (**A,** Courtesy V-Wave Medical, Hod HaSharon, Israel; **B,** Courtesy DC Devices, Tewksbury, MA.)

INTERATRIAL SHUNT DEVICES

Elevated intracardiac and pulmonary artery pressures are associated with poorer outcomes for patients with chronic heart failure, regardless of ejection fractions.[39,40] Excursions of left atrial pressure into an elevated range are a strong predictor of adverse clinical events.[40] Chronically lowering these pressures reduces the risk of heart failure related hospitalizations.[40,41]

Although lowering intracardiac and pulmonary artery pressures may be successfully accomplished in some patients with pharmacologic therapies, some patients are refractory to these therapies or poorly tolerate them. Pharmacologic therapies also may not fully address the dynamic increase in left atrial pressure during heart failure exacerbations or during exercise.[42]

A small interatrial shunt may reduce left atrial pressure and limit left atrial pressure increases during exercise and heart failure exacerbations. Evidence in support of this notion comes from patients with mitral valve stenosis and coexisting atrial septal defect. They have fewer symptoms than mitral valve stenosis patients with an intact septum.[43] Conversely, closure of an atrial septal defect in patients with left ventricular failure may worsen heart failure symptoms.[44]

Two devices for the creation of an interatrial shunt are being investigated for the treatment of heart failure (Fig. 66-4), and the early clinical experience has been good.[45,46] Both devices have been safely implanted in heart failure patients. The use of a unidirectional left-to-right interatrial shunt device in a patient with NYHA class III heart failure and an LVEF of 35% produced a pulmonary artery to systemic (ascending aorta) blood flow ratio (Q_P/Q_S) of 1.17 and resulted in improvement in the NYHA class, quality of life score, exercise capacity, echocardiographic parameters, hemodynamics, and N-terminal pro-B-type natriuretic peptide levels at 3 months.[45] A few additional patients implanted with this device have shown similar improvements (unpublished observations). Similarly, the use of an open interatrial shunt device in 11 patients with heart failure with a preserved ejection fraction improved hemodynamics and functional class.[46] Further studies are evaluating these findings.

IMPLANTABLE HEMODYNAMIC MONITORS

Another approach to chronically lowering left atrial and pulmonary artery pressures is the use of an implantable hemodynamic monitor to guide changes in pharmacologic therapy. The CardioMEMS heart failure system was approved by the FDA on the basis of the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial.[47,48] The pulmonary artery pressure sensor consists of a coil and a pressure-sensitive capacitor encased in a capsule. It is implanted into a branch of the pulmonary artery using a specialized delivery system during a right heart catheterization. It has no battery and is powered by a radiofrequency signal from outside of the body. Pressure data are transmitted wirelessly to a secure website, where physicians and nurses can view discrete data or pressure trends graphed longitudinally over time.

The CHAMPION trial randomized 550 NYHA class III heart failure patients with reduced or preserved LVEF to a treatment group for which investigators had access to daily pulmonary artery pressure measurements and used them to guide therapy or to a control group for which investigators had no access to daily pulmonary artery pressure measurements and managed patients using standard of care heart failure monitoring. During the first 6 months after randomization, there was a 28% reduction in the risk of heart failure hospitalizations for the treatment group compared with the control group ($P < .00002$). During the entire single-blinded follow-up period averaging more than 15 months, the treatment group demonstrated a significant 37% decrease in the rate of heart failure hospitalizations compared with the control group. Therapy guided by the CardioMEMS system reduced the risk of heart failure hospitalizations for systolic and diastolic heart failure patients.[48,49]

An implantable system for the direct measurement of left atrial pressure is under investigation. The system consists of an implantable sensor lead coupled to a subcutaneous antenna coil, a patient advisory module, and remote access by clinicians through a secure computer-based data management system. The sensor lead is implanted using a transvenous approach and transseptal crossing of the interatrial septum, placing the tip of the sensor system lead in the left atrium.[50,51] Observations from a pilot study in which patients served as their own controls demonstrated a significant reduction in the annualized rate of heart failure hospitalizations.[52] An ongoing large, randomized, controlled trial of this system should further define its value.

CONCLUSIONS

We are entering an era in which interventional cardiologists and heart failure specialists will work hand in hand to offer patients novel devices to improve their clinical status and outcomes. The devices can enhance cardiac structure, function, and hemodynamics. Many of these devices remain under investigation, but even if only a few succeed, the future of this new field of interventional heart failure will be bright.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al: Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation* 129:e28–e292, 2014.
2. Heidenreich PA, Albert NM, Allen LA, et al: Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 6:606–619, 2013.
3. Yancy CW, Jessup M, Bozkurt B, et al: 2013 ACCF/AHA guideline for the management of heart failure. *Circulation* 128:e240–e327, 2013.
4. Jencks SF, Williams MV, Coleman EA: Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med* 360:1418–1428, 2009.
5. Velazquez EJ, Lee KL, Deja MA, et al: Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med* 364:1607–1616, 2011.
6. Georgakopoulos D, Little WC, Abraham WT, et al: Chronic baroreflex activation: a potential therapeutic approach to heart failure with preserved ejection fraction. *J Card Fail* 17:167–178, 2011.
7. Gronda E, Seravalle G, Brambilla G, et al: Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac haemodynamics in heart failure: a proof-of-concept study. *Eur J Heart Fail* 16:977–983, 2014.
8. Premchand RK, Sharma K, Mittal S, et al: Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. *J Card Fail* 20:808–886, 2014.
9. Zannad F, De Ferrari GM, Tuinenburg AE, et al: Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the neural cardiac therapy for heart failure (NECTAR-HF) randomized controlled trial. *Eur Heart J* 36:425–433, 2014.
10. Tse HF, Turner S, Sanders P, et al: Thoracic spinal cord stimulation for heart failure as a restorative treatment (SCS HEART study): first-in-man experience. *Heart Rhythm* 12:588–595, 2015.
11. Ponikowski P, Javaheri S, Michalkiewicz D, et al: Transvenous phrenic nerve stimulation for the treatment of central sleep apnoea in heart failure. *Eur Heart J* 33:889–894, 2012.
12. Costanzo MR, Khayat R, Ponikowski P, et al: Mechanisms and clinical consequences of untreated central sleep apnea in heart failure. *J Am Coll Cardiol* 65:72–84, 2015.
13. Ross J, Jr, Braunwald E: Aortic stenosis. *Circulation* 38(Suppl):61–67, 1968.
14. Carabello BA: Evaluation and management of patients with aortic stenosis. *Circulation* 105:1746–1750, 2002.
15. Nishimura RA, Otto CM, Bonow RO, et al: AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 129:2440–2492, 2014.
16. Connolly HM, Oh JK, Schaff HV, et al: Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction: result of aortic valve replacement in 52 patients. *Circulation* 101:1940–1946, 2000.
17. Pereira JJ, Lauer MS, Bashir M, et al: Survival after aortic valve replacement for severe aortic stenosis with low transvalvular gradients and severe left ventricular dysfunction. *J Am Coll Cardiol* 39:1356–1363, 2002.
18. Agarwal S, Tuzcu EM, Krishnaswamy A, et al: Transcatheter aortic valve replacement: current perspectives and future implications. *Heart* 101:169–177, 2015.
19. Leon MB, Smith CR, Mack M, et al: Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 363:1597–1607, 2010.
20. Makkar RR1, Fontana GP, Jilaihawi H, et al: Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med* 366:1696–1704, 2012.
21. Elmariah S1, Palacios IF, McAndrew T, et al: Outcomes of transcatheter and surgical aortic valve replacement in high-risk patients with aortic stenosis and left ventricular dysfunction: results from the Placement of Aortic Transcatheter Valves (PARTNER) trial (Cohort A). *Circ Cardiovasc Interv* 6:604–614, 2013.
22. Trichon BH, O'Connor CM: Secondary mitral and tricuspid regurgitation accompanying left ventricular systolic dysfunction: is it important, and how is it treated? *Am Heart J* 144:373–376, 2002.
23. Koelling TM, Aaronson KD, Cody RJ, et al: Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. *Am Heart J* 144:524–529, 2002.
24. Kono T, Sabbah HN, Rosman H, et al: Left ventricular shape is the primary determinant of functional mitral regurgitation in heart failure. *J Am Coll Cardiol* 20:1594–1598, 1992.
25. Yiu SF, Enriquez-Sarano M, Tribouilloy C, et al: Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. *Circulation* 102:1400–1406, 2000.
26. Rossi A, Dini FL, Faggiano P, et al: Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and nonischaemic dilated cardiomyopathy. *Heart* 97:1675–1680, 2011.
27. Lowes BD, Gill EA, Abraham WT, et al: The effect of carvedilol on left ventricular mass, chamber geometry, and mitral regurgitation in chronic heart failure. *Am J Cardiol* 83:1201–1205, 1999.
28. St. John-Sutton MG, Plappert T, Abraham WT, et al: Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation* 107:1985–1990, 2003.
29. Feldman T, Foster E, Glower DG, et al: Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 364:1395–1406, 2011.
30. Shanmugam G, Ali IS: Surgical ventricular restoration: an operation to reverse remodeling: clinical application (part II). *Cur Cardiol Rev* 5:350–359, 2009.
31. Athanasuleas CL, Buckberg GD, Stanley AH, et al: Surgical ventricular restoration in the treatment of congestive heart failure due to post-infarction ventricular dilation. *J Am Coll Cardiol* 44:1439–1445, 2004.
32. Jones RH, Velazquez EJ, Michler RE, et al: Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med* 360:1705–1717, 2009.
33. Abraham WT: Could the Parachute™ ventricular partitioning device be a winner in the fight against heart failure? *Expert Rev Cardiovasc Ther* 11:263–265, 2013.
34. Mazzaferri EL, Jr, Gradinac S, Sagic D, et al: Percutaneous left ventricular partitioning in patients with chronic heart failure and a prior anterior myocardial infarction: results of the PercutAneous Ventricular RestorAtion in Chronic Heart failUre PaTiEnts Trial. *Am Heart J* 163:812–820, 2012.
35. Costa MA, Mazzaferri EL, Jr, Sievert H, Abraham WT: Percutaneous ventricular restoration using the parachute device in patients with ischemic heart failure: three-year outcomes of the PARACHUTE first-in-human study. *Circ Heart Fail* 7:752–758, 2014.
36. Costa MA, Pencina M, Nikolic S, et al: The PARACHUTE IV trial design and rationale: percutaneous ventricular restoration using the parachute device in patients with ischemic heart failure and dilated left ventricles. *Am Heart J* 165:531–536, 2013.
37. Faria R, Melica B, Pires-Morais G, et al: New less invasive ventricular reconstruction technique in the treatment of ischemic heart failure. *Rev Port Cardiol* 33:469.e1–469.e5, 2014.
38. Wechsler AS1, Sadowski J, Kapelak B, et al: Durability of epicardial ventricular restoration without ventriculotomy. *Eur J Cardiothorac Surg* 44:e189–e192, 2013.
39. Stevenson LW, Zile M, Bennett TD, et al: Chronic ambulatory intracardiac pressures and future heart failure events. *Circ Heart Fail* 3:580–587, 2010.
40. Ritzema J, Troughton R, Melton I, et al: Physician-directed patient self-management of left atrial pressure in advanced chronic heart failure. *Circulation* 121:1086–1095, 2010.
41. Abraham WT, Adamson PB, Bourge RC, et al: Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 377:658–666, 2011.
42. Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM: Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. *J Am Coll Cardiol* 56:855–863, 2010.
43. Lutembacher R: De la stenose mitrale avec communication interauriculaier. *Arch Mal Cœur* 9:237–260, 1916.
44. Ewert P, Berger F, Nagdyman N, et al: Masked left ventricular restriction in elderly patients with atrial septal defects: a contraindication for closure? *Catheter Cardiovasc Interv* 52:177–180, 2001.
45. Amat-Santos IJ, Bergeron S, Bernier M, et al: Left atrial decompression through unidirectional left-to-right interatrial shunt for the treatment of left heart failure: first-in-man experience with the V-Wave device. *EuroIntervention* 10:1127–1131, 2015.
46. Søndergaard L, Reddy V, Kaye D, et al: Transcatheter treatment of heart failure with preserved or mildly reduced ejection fraction using a novel interatrial implant to lower left atrial pressure. *Eur J Heart Fail* 16:796–801, 2014.
47. Adamson PB, Abraham WT, Aaron M, et al: CHAMPION trial rationale and design: the long-term safety and clinical efficacy of a wireless pulmonary artery pressure monitoring system. *J Card Fail* 17:3–10, 2011.
48. Abraham WT, Adamson PB, Bourge RC, et al: Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 377:658–666, 2011.
49. Adamson PB, Abraham WT, Bourge RC, et al: Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. *Circ Heart Fail* 7:935–944, 2014.
50. Ritzema J, Melton IC, Richards AM, et al: Direct left atrial pressure monitoring in ambulatory heart failure patients: initial experience with a new permanent implantable device. *Circulation* 116:2952–2959, 2007.
51. Troughton RW, Ritzema J, Eigler NL, et al: Direct left atrial pressure monitoring in severe heart failure: long-term sensor performance. *J Cardiovasc Transl Res* 4:3–13, 2011.
52. Ritzema J, Troughton R, Melton I, et al: Physician-directed patient self-management of left atrial pressure in advanced chronic heart failure. *Circulation* 121:1086–1095, 2010.

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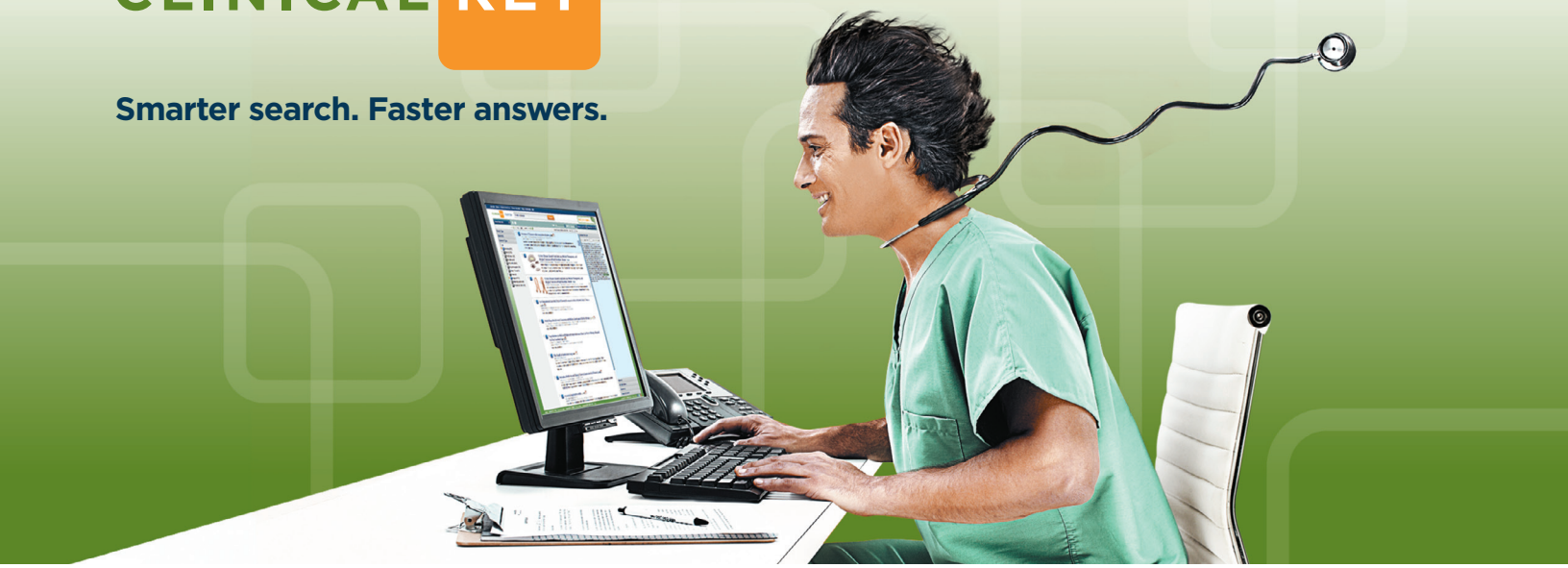

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