We are honored to provide readers of the Journal with this review of major scientific work in the field of Interventional Cardiology in 2009. In addition, we have included late-breaking trials presented at the American College of Cardiology, Transcatheter Cardiovascular Therapeutics, European Society of Cardiology, and American Heart Association conferences. We hope that this article will provide a broad overview of the field for general cardiologists, as well as a framework for more detailed study for those with a specific interest in interventional cardiology.

Focused Update

A focused update of American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines for ST-segment elevation myocardial infarction (STEMI) and percutaneous coronary intervention (PCI) was published in 2009 (1). Important changes in this update are summarized in Table 1. Readers are encouraged to examine this document in detail.

Acute Myocardial Infarction

Primary PCI. In a meta-analysis of 23 randomized and 32 observational studies, Huynh et al. (2) reported significant improvement in mortality, stroke, and reinfarction comparing primary PCI with thrombolysis.

PCI after thrombolysis. Although the role of facilitated PCI remains controversial, many studies suggest it is superior to thrombolysis alone. The TRANSFER-AMI (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) study enrolled 1,059 high-risk STEMI patients treated with lytics at non-PCI centers and randomized them to immediate transfer for PCI or conservative care. The group randomized to transfer for PCI had reduced ischemia at 30 days and an improved composite of death, myocardial infarction (MI), or stroke at 12 months. Similarly, the 1-year follow-up of the REACT (Rescue Angioplasty versus Conservative Management or Repeat Thrombolysis) trial found that rescue PCI after failed thrombolysis (3) improved event-free survival compared with conservative care (81.5% vs. 67.5%; p = 0.004).

Facilitated PCI. Conversely, pharmacologic facilitation is of no benefit compared with primary PCI. The FINESE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial reported that thrombolytic- or abciximab-mediated facilitation, or both, before PCI was associated with higher bleeding but no short-term clinical advantage compared with primary PCI. However, at 1 year, a trend for lower mortality was suggested in facilitated patients with anterior MI (6.5% vs. 9.9%; p = 0.093) (4) or in high-risk patients who sought treatment at a remote hospital within the first few hours from symptom onset (5).

Drug-eluting stents (DES). A meta-analysis of 13 trials randomizing 7352 patients to DES versus bare-metal stents (BMS) for acute myocardial infarction (AMI) found reduced target vessel revascularization (TVR) (relative risk: 0.44; 95% confidence interval: 0.35 to 0.55), but no increased risk of death, MI, or stent thrombosis (ST) (6). Long-term follow-up of randomized trials suggest continued safety and efficacy of DES compared with BMS (9–13). A recently reported randomized trial (n = 466) confirmed that the sirolimus-eluting stent (SES) was superior to the BMS at improving restenosis and TVR (14). An endothelial progenitor cell capture stent had similar restenosis rates but slightly higher ST compared with BMS in a small trial (15).

Thrombectomy. In 2 small randomized trials, aspiration thrombectomy during primary PCI was associated with higher rate of ST-segment resolution and myocardial blush grade of 2 or more (16,17). In a substudy of 1 trial, patients with anterior STEMI treated with thrombectomy had less microvascular obstruction and smaller infarct on cardiac MRI (16). In the other study, the thrombus aspiration group had a higher ejection fraction (EF) and less remodeling at 6 months (17).
In contrast to these findings, a randomized trial using proximal embolic protection (Proxis, St. Jude Medical, St. Paul, Minnesota) found no difference in ST-segment resolution at 60 min in patients treated with the protection device (18). However, there did seem to be a higher rate of immediate complete ST-segment resolution in the Proxis group.

Adjunctive agents. Several studies in 2009 investigated novel pharmacologic or mechanical therapies to limit myocardial injury in AMI. In patients with anterior wall STEMI of <6 h, Stone et al. (19) demonstrated that a 90-minute infusion of supersaturated oxygen into the left anterior descending coronary artery (LAD) after reperfusion significantly decreased infarct size compared with controls (18.5% vs. 25% of the left ventricle [LV]; p = 0.02). Sezer et al. (20) found that intracoronary streptokinase administered immediately after reperfusion reduced infarct size and LV volumes at 6 months. In a small randomized trial, high-dose erythropoietin administered during primary PCI (with repeat doses at 24 and 48 h) had no effect on convalescent LV EF assessed by magnetic resonance imaging (MRI) at 6 months (21). Fokkema et al. (22) randomized 448 patients to 2 doses of intracoronary adenosine (120 μg) or placebo after thrombectomy. The primary end point, residual ST-segment elevation at 60 min in patients treated with the protection device (Class I). Prasugrel should be avoided in patients with prior history of stroke or TIA (Class III). In patients pretreated with aspirin and thienopyridine (unfractionated heparin), bivalirudin may be used (Class I) and is reasonable in STEMI patients at high risk of bleeding (Class IIa).

Both high-risk (Class IIa) and low-risk (Class IIb) patients who receive fibrinolytic therapy at a non-PCI faculty should be transferred to a PCI-capable lab. It is reasonable to use DES as an alternative to BMS in STEMI patients.

Percutaneous coronary intervention (PCI) Update

In patients with chronic kidney disease, either iso-osmolar or low-osmolar contrast may be used (Class I).

Outcomes. Two studies evaluated the relationship between volume and primary PCI outcomes. Srinivas et al. (27) studied 7,321 AMI patients in the New York State PCI Registry. Risk-adjusted in-hospital mortality was highest for low-volume operators (<10/year) in low-volume hospitals (<50/year) compared with high-volume physicians in high-volume centers. In another analysis, Kumbhani et al. (28) found high-volume primary PCI centers (>70/year) had shorter door-to-balloon times, but similar in-hospital mortality to medium-volume (36 to 70/year) and low-volume (<36/year) centers.

Cardiogenic shock. Lim et al. (29) evaluated the outcomes of PCI for cardiogenic shock in 45 elderly patients (≥75 years of age). Rates of stenting (86.7%) and IIb/IIIa use (68.9%) were much higher than in prior shock studies. In-hospital and 1-year survival was similar to that of younger patients (<75 years of age). These data suggest that percutaneous revascularization is reasonable in carefully selected elderly patients with shock complicating AMI. Mehta et al. (30) examined Thrombolysis In Myocardial Infarction (TIMI) flow after PCI in shock patients and found that patients with TIMI flow grade <3 had a substantially higher mortality (63% vs. 27%) than patients with TIMI flow grade 3.

Cell therapy. Very small embryonic-like stem cells have been found in peripheral blood samples of AMI patients, but not in normal volunteers (31), suggesting that these may play a role in cardiac and endothelial repair. Intracoronary infusion of bone marrow-derived stem cells was shown to improve regional myocardial function (32) and global ejection fraction (33) in prospective, randomized trials. A nonrandomized observational study also suggested improved LV function, exercise capacity, and mortality in AMI patients treated with intracoronary stem cells (34).

Acute Coronary Syndromes (ACS)

Timing of intervention. Although the efficacy of invasive management of ACS is well established, optimal timing of

<table>
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<tr>
<th>Table 1</th>
<th>2009 Focused Update on STEMI and PCI: Key Changes</th>
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<tbody>
<tr>
<td><strong>STEMI Update</strong></td>
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<tr>
<td>Usefulness of cath lab (up front) glycoprotein IIb IIIa antagonists is uncertain (Class IIb).</td>
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<tr>
<td>A loading dose of thienopyridine should be given as soon as possible and continued for 1 year (Class I), with consideration of longer duration (&gt;15 months) in patients undergoing DES placement (Class IIb).</td>
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<tr>
<td>Prasugrel should be avoided in patients with prior history of stroke or TIA (Class III).</td>
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<td><strong>PCI Update</strong></td>
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<tr>
<td>In patients with chronic kidney disease, either iso-osmolar or low-osmolar contrast may be used (Class I).</td>
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<tr>
<td>Stenting of the left main may be considered as an alternative to CABG when anatomic and clinical conditions are favorable for PCI (Class IIb).</td>
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</table>

Adapted from Kushner et al. (1). BMS = bare-metal stent(s); CABG = coronary artery bypass graft; DES = drug-eluting stent(s); PCI = percutaneous coronary intervention; STEMI = stent thrombosis elevation myocardial infarction; TIA = transient ischemic attack.
intervention and adjunctive pharmacotherapy is not settled. The year 2009 brought numerous trials in this area. Mehta et al. (35) randomized 3,031 patients with ACS to early routine invasive (<24 h from admission) versus delayed (>36 h from admission) intervention. The trial found no difference in 6-month death/MI/stroke (9.6% vs. 11.3%; p = 0.15) for early versus delayed intervention. For patients in the highest tertile of risk (GRACE [Global Registry of Acute Coronary Events] score >140), outcome was improved with early intervention (13.9% vs. 21%; p = 0.006).

A second trial, ABOARD (Angioplasty to Blunt the Rise of Troponin in ACS), evaluated the efficacy of immediate versus delayed intervention in blunting troponin increase (36). Neither peak troponin level nor death/MI occurred, and early epibatide use resulted in more bleeding and a higher need for transfusion (8.6% vs. 6.7%; p = 0.001). Taken together, these trials suggest equivalent efficacy for an immediate or delayed PCI strategy in patients with ACS, with perhaps a need for early intervention in high-risk patients.

Outcomes. Several substudies of the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial were reported. Nikolsky et al. (38) highlighted the catastrophic prognostic implications of gastrointestinal bleeding (GIB) after PCI. One-year mortality was greater (21.9% vs. 3.9%; p < 0.0001) for the 1.3% of patients who had GIB. In addition, composite ischemia and acute ST was significantly higher (5.8% vs. 2.4%; p = 0.009). Risk factors for GIB included age, smoking status, and baseline anemia. Mehran et al. (39) assessed the prognostic impact of chronic kidney disease. Patients with creatinine clearance of <60 ml/min had a significantly higher 1-year mortality (7.9% vs. 2.8%; p < 0.001) and higher rates of ischemia and GIB. Bivalirudin appeared to lessen the risk of bleeding but did not influence 1-year mortality. Lopes et al. (40) evaluated the impact of age and found that patients older than 75 years had significantly worse outcomes. These patients were more likely to be female, to have lower weight, and to have lower creatinine clearance. Major bleeding was lessened with bivalirudin in these elderly patients (1.7% vs. 3.6%; p < 0.05) compared with heparin plus glycoprotein IIb/IIIa inhibitors. Finally, Prasad et al. (41) examined the prognostic impact of periprocedural or spontaneous MI occurring after PCI. PCI-related MI occurred in 6% of patients, and during follow-up, spontaneous MI occurred in 2.6% of patients. One-year mortality was 16% after spontaneous MI, 6% after periprocedural MI, and 2.6% when no MI occurred (p < 0.0001). Although spontaneous MI did worsen prognosis independently, periprocedural MI did not do so when baseline variable differences were accounted for in linear regression analysis.

Elective PCI

Revascularization criteria. Early in 2009, an important document summarizing appropriateness criteria for coronary revascularization was published (42). In brief, these criteria were developed by scoring 180 prototypical clinical scenarios on a scale of 1 to 9 as inappropriate (1 through 3), uncertain (4 through 6), or appropriate (7 through 9). Key components of the criteria include patient clinical status, level of medical therapy, stress testing findings, and coronary anatomic features. Although these criteria were developed to assist clinicians, health care facilities, payors, and patients, it is important to emphasize that they are not intended to be a substitute for clinical judgment and experience. Nonetheless, the criteria are likely to be studied closely by payors, especially in the current economic climate. Readers are encouraged to review the article in detail.

Medical therapy. The BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) (43) trial provided further debate in the interventional community, but overall adds to the body of evidence that medical therapy is an excellent initial strategy in patients with stable coronary disease. A total of 2,368 patients with type 2 diabetes were randomized to intensive medical therapy or revascularization (PCI or coronary artery bypass graft surgery [CABG]) with medical therapy. At the 5-year follow-up, there was no difference in the rate of death or the composite of death/MI/stroke. Of note, however, 42% of patients in the medical therapy arm crossed over to revascularization. Additionally, patients in the revascularization arm who underwent CABG had fewer adverse events at follow-up compared with medically treated patients, driven largely by a reduced incidence of MI. A meta-analysis by Trikalinos et al. (44) reaffirmed prior observations that PCI does not impact the rate of death or MI in patients with stable disease.

LAD disease. Thiele et al. (45) presented results of a randomized trial of SES versus minimally invasive coronary artery bypass surgery for isolated proximal LAD disease. At 12 months, TVR was higher for the SES group, but overall, MACE was identical in each group (7.7%).

Multivessel disease. Results of the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial were published in 2009. One thousand ninety-five patients with 3-vessel or left main disease were randomized to CABG (n = 549) or multivessel PCI with the Taxus DES (n = 546) (46). At 1 year, there was a higher incidence of MACE (death, MI, stroke, repeat revascularization) in the PCI group compared with the CABG group (17.8% vs. 12.4%; p = 0.002). This was driven largely by a higher need for TVR in the PCI group, however, there was a lower risk of stroke (0.6% vs. 2.2%; p = 0.003). The difference in MACE was greatest in patients with more complex coronary disease (SYNTAX score, ≥33).

In an observational study of 3,720 patients with multivessel disease, patients treated with DES had a higher 3-year
rate of TVR, death, and MI (47). In contrast, Hlatky et al. (48) found no difference in long-term survival in a meta-analysis of 7,812 patients treated with PCI (37% BMS; 63% percutaneous transluminal coronary angioplasty) versus CABG; however, in patients with diabetes, mortality was lower in the CAGB group.

**Left main disease.** There is a growing body of evidence to support PCI for unprotected left main coronary artery disease. Several observational studies provided long-term outcome data with BMS and DES (49–52) (Table 2). In aggregate, DES seemed to reduce risk of TVR and MACE. Among patients with distal bifurcation disease, 2 observational studies demonstrated higher rates of adverse events when side-branch stenting was performed compared with main vessel stenting alone (51,52). Two studies (1 nonrandomized, 1 randomized) compared SES with paclitaxel-eluting stents (PES) and found similar outcomes between stent types (53,54). Park et al. (55) studied the role of intravascular ultrasound guidance in unprotected left main coronary artery stenting. In a propensity-matched analysis, patients receiving a DES had significantly lower 3-year mortality with intravascular ultrasound guidance versus angiography alone (4.7% vs. 16.0%; p = 0.048). For patients with DES restenosis, Sheibani et al. (56) found that most cases can be treated favorably with PCI. Palmerini et al. (57) studied the timing of cardiac events after unprotected left main coronary artery stenting (73% DES). In patients receiving dual antiplatelet therapy, the highest risk of events was in the first 6 months after PCI, especially among patients who initially had ACS. After clopidogrel discontinuation, the highest risk period was the first 90 days after stopping therapy.

**Fractional flow reserve guidance.** The FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) study was an important highlight of the year (58). One thousand five patients with multivessel disease undergoing PCI were randomized to stenting guided by angiography alone or guided by fractional flow reserve (FFR) measurements (stent indicated if FFR ≤0.8). Fewer stents were used in the FFR group (1.9 vs. 2.7; p < 0.001). Importantly, the primary end point (death, MI, and TVR at 1 year) was significantly lower in the FFR group (13.2% vs. 18.3%; p = 0.02) compared with the angiography group, strongly supporting routine use of FFR in multivessel intervention.

**High-risk PCI.** There are few data regarding the optimal management of high-risk patients undergoing PCI. The BCIS (Balloon Pump-Assisted Coronary Intervention Study) (the first randomized trial in this patient group) randomized 301 high-risk patients (EF ≤30%; jeopardy score ≥8) to elective versus provisional intra-aortic balloon pump (59). Twelve percent of patients required bailout intra-aortic balloon pump. There was no significant difference in MACE in either group at 30 days. This important study suggests that many patients with LV dysfunction can be treated safely without routine hemodynamic support, but did not specifically address what support strategy to use in very–high-risk patients in whom periprocedural circulatory support is considered essential. In other studies, use of the Impella 2.5 device (Abiomed, Danvers, Massachusetts) was found to be safe and feasible in high-risk patients (60,61).

**Bifurcations.** Recent studies have demonstrated that a single main vessel stent strategy is the preferred technique in coronary bifurcations. In the CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) study, 350 patients were randomized to elective crush stenting versus stenting of the main vessel only with provisional side-branch T-stenting (62). At 6 months, the incidence of angiographic restenosis (main branch and side branch) and MACE was similar in the 2 groups. In a meta-analysis of 6 trials comparing single- or double-stent strategies, a higher incidence of periprocedural MI was observed with double stenting (63).

Kissing balloon dilation often is used in main vessel stenting to optimize the side branch. In the Nordic–Baltic Bifurcation Study III (64), 477 patients with successful main vessel stenting (and side branch ≥2.25 mm) were

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### Table 2

**Studies of Stenting for Unprotected Left Main Coronary Disease in 2009**

<table>
<thead>
<tr>
<th>Study (First Author, Ref #)</th>
<th>n</th>
<th>Country (yrs)</th>
<th>Stent Type</th>
<th>Follow-Up (yrs)</th>
<th>Main Findings</th>
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<tr>
<td><strong>BMS vs. DES</strong></td>
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<tr>
<td>Buszman et al. (49)</td>
<td>252</td>
<td>Poland, 1997–2008</td>
<td>158 BMS, 94 DES</td>
<td>5/10</td>
<td>Survival at 5/10 yrs, 78.1% and 68.9%; lower MACE with DES vs. BMS</td>
</tr>
<tr>
<td>Kim et al. (50)</td>
<td>1,217</td>
<td>Korea, 2000–2006</td>
<td>353 BMS, 864 DES</td>
<td>3</td>
<td>DES ↓ TLR (HR: 0.40; p = 0.03); no difference death/MI</td>
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<tr>
<td><strong>DES</strong></td>
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<tr>
<td>Toyofuku et al. (51)</td>
<td>476</td>
<td>Japan, 2004–2006</td>
<td>476 SES</td>
<td>3</td>
<td>Lower rate of TVR for ostial/shaft vs. distal lesions; for distal lesions, ↓ TLR and MACE with main-branch stenting alone vs. 2-stent technique</td>
</tr>
<tr>
<td>Vaquerizo et al. (52)</td>
<td>291</td>
<td>France, 2003-2005</td>
<td>291 PES</td>
<td>2</td>
<td>MACE, 15.8%; ST, 3.8%; higher-risk ST with side-branch stenting</td>
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<tr>
<td><strong>SES vs. PES</strong></td>
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<tr>
<td>Lee et al. (53)</td>
<td>858</td>
<td>Korea, 2000–2006</td>
<td>Nonrandomized; 669 SES, 189 PES</td>
<td>3</td>
<td>No difference outcomes SES vs. PES</td>
</tr>
<tr>
<td>Mehilli et al. (54)</td>
<td>607</td>
<td>Germany, 2005-2007</td>
<td>Randomized; 305 SES, 302 PES</td>
<td>1</td>
<td>Comparable angiographic and clinical outcomes between SES and PES</td>
</tr>
</tbody>
</table>

HR = hazard ratio; MACE = major adverse cardiac event; MI = myocardial infarction; PES = paclitaxel eluting stent; SES = sirolimus-eluting stent; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.
randomized to final kissing balloon after dilatation or no post-dilation. At 6 months, there was no difference in clinical outcome between groups, suggesting that routine kissing balloon after dilatation is not necessary.

Among patients undergoing a planned 2-stent strategy, the Nordic Stent Technique Study demonstrated similar clinical outcomes between the crush and culotte techniques (using a SES); however, angiographic restenosis in the side branch was lower with culotte stenting (65).

The DIVERGE (Drug-Eluting Stent Intervention for Treating Side Branches Effectively) study evaluated the Axcess (Devax Inc., Lake Forest, California) biolimus A9-eluting in 302 patients (66). At 9 months, there was a low rate of restenosis (3.6% parent vessel; 4.3% side branch) and MACE (7.7%) with this novel self-expanding stent.

**Chronic occlusion.** Rathore et al. (67,68) reported out-Chronic occlusion. ergs in 302 patients (66). At 9 months, there was a low rate of restenosis (3.6% parent vessel; 4.3% side branch) and MACE (7.7%) with this novel self-expanding stent.

**DES healing.** An angiographic study of 1,197 patients receiving DES found that acquired aneurysms were rare, but occurred more frequently when a DES was implanted during AMI (74). Similarly, Gonzalo et al. (75) reported that primary PCI patients had higher frequency of stent malapposition and uncovered struts assessed by optical coherence tomography 6 months after DES, compared with elective DES patients. The type of stent also influences healing with angiographic incidence of less neointimal coverage and more thrombus with PES compared with SES (76), and more restenosis but better endothelial function with BMS and zotarolimus-eluting stent (ZES) compared with SES (77).

**DES thrombosis.** DES fracture is rarely reported in clinical series, but an autopsy study reported fracture in 51 (29%) of 177 stented lesions (78). Predictors of stent fracture included longer, overlapping stents and use of SES.

Late ST after DES continues to be of interest to cardiologists. A literature review of 161 ST cases found that 88% were not taking dual antiplatelet therapy (79). If both aspirin and clopidogrel were stopped, the median time to ST was 7 days; whereas if the aspirin was continued, ST occurred 122 days after clopidogrel was stopped. Likewise, Kimura et al. (80) reported in a registry of 10,000 SES-treated patients that discontinuation of both aspirin and clopidogrel greatly increased ST, but if aspirin was continued, thrombosis was so low that there was no apparent benefit of long-term clopidogrel. However, in a 7,500-patient Taxus registry, Lasala et al. (81) found that discontinuation of thienopyridine was associated with very late (>1 year) stent thrombosis. Similarly, a Dutch registry (82) of 437 patients with ST found a strong correlation between late ST and discontinuing clopidogrel at 6 months (hazard ratio: 5.9; 95% confidence interval: 1.7 to 19.8). This registry also reported high rates of death, MI, and recurrent ST, with poor outcomes occurring more frequently in patients with low EF, diabetes, complex lesions, long stent length, TIMI flow grade <3, and implantation of additional stents for treatment of the ST (83). Other studies have shown that lack of pretreatment thienopyridine (84) or clopidogrel hyporesponsiveness (85) contribute to the risk of DES thrombosis.

**Late outcomes.** Several studies with up to 5 years of follow-up report lower TVR with first-generation DES compared with BMS with similar rates of death and MI (86–90). However, consistent with some of the randomized trial data, 1 large national registry suggested that PES had an increased risk of ST and MI compared to SES or BMS (91).

Second-generation DES may have a better long-term safety profile compared with PES or SES. The SPIRIT III (Clinical Evaluation of the Xience V Everolimus-Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions) trial found improved event-free survival at 2 years with trends for reduced ST comparing Xience V (Abbott Vascular, Santa Clara, California) EES with Taxus (Boston Scientific, Natick, Massachusetts) PES (92). The larger (n = 3,687) SPIRIT IV trial confirmed that Xience was superior to
Taxus Express with significant improvement in event-free survival and ST (93). Moreover, the COMPARE (Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice) trial (n = 1,800) found significant reductions in TVR, MI, and ST with Xience compared with the new Taxus Liberté (94). Finally, the ZEST (Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent versus Sirolimus-Eluting Stent and Paclitaxel-Eluting Stent for Coronary Lesions) trial randomized 2,640 patients to ZES, SES, or Taxus Liberté (Boston Scientific) and found that Cypher SES was superior to both ZES and PES at reducing TVR and stent thrombosis (95).

Clinical and anatomic subsets. A small randomized trial reported lower rates of restenosis when SVG lesions were treated with PES compared with BMS (96). In another small randomized trial, a strategy of PES implantation for moderate vein graft lesions seemed to improve outcome compared with medical therapy (97). A registry of SES in chronic total occlusions showed safety and reduced restenosis (compared with historical controls with BMS) (98). Two large registries demonstrated that off-label use of DES had similar safety compared with BMS, yet was associated with lower TVR (99,100). A Taxus registry suggested similar angiographic and clinical outcomes between diabetics and nondiabetics (101). Among diabetics, ZES seems to be inferior to other DES (102,103). However, ZES may perform well in bifurcation lesions, given that side-branch occlusion (and periprocedural MI) occurred less frequently with ZES compared with PES (104).

The best management of DES restenosis is uncertain. ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Restenosis: Drug-Eluting Stents for In-Stent Restenosis) randomized 450 patients with SES restenosis to receive PCI with additional SES versus PES (105). They found repeat restenosis (19.0% vs. 20.6%) and clinical events were similar, suggesting no advantage in choosing a different stent for treatment of DES restenosis.

New Stents and Balloons

Drug-coated balloons. It is unknown whether adverse events after DES placement are the result of the drug, polymer, or stent itself. New technologies on the horizon include drug-eluting balloons, polymer-free stents, and bioabsorbable polymer and stents. Unverdorben et al. (106) randomized 131 patients with in-stent restenosis to treatment with a paclitaxel-eluting balloon (PEB) versus PES. A significant reduction in late loss was observed in the PEB group with a trend for reduced restenosis, TVR, and MACE compared with PES. Similarly, Herdeg et al. (107) reported that local delivery of fluid paclitaxel after BMS placement reduced neointimal proliferation and MACE compared with BMS alone. Conversely, Hamm (108) randomized 637 patients to PEB and BMS versus Cypher DES and found that the PEB and BMS combination resulted in significant increases in stent thrombosis, MI, restenosis, and TVR.

New drugs, polymers, and stents. A DES using the anti-inflammatory agent pimecrolimus was found to be inferior to BMS (109), PES (110), or dual elution of both drugs. Conversely, a biolimus-eluting stent with bioresorbable polymer was superior to PES at reducing late loss and restenosis (111). In a randomized trial of 1007 patients, Byrne et al. (112) found the ZES (Endeavor, Medtronic) stent was inferior (more late loss, restenosis, and TVR) to either SES or a novel dual-DES (polymer-free rapamycin and probucol-eluting stent). A Chinese registry (113) reported satisfactory results using an SES with biodegradable polymer; however, late loss was higher (0.21 ± 0.35 mm) than previously reported for the durable polymer SES.

Polymer-free rapamycin stents had improved neointimal coverage at 3 months (114), compared with durable polymer. Byrne et al. (115) randomized 2,603 patients to a rapamycin-eluting stent with biodegradable polymer to durable polymer stents (Cypher and Xience) and found similar angiographic and clinical outcomes. Therefore, to date, it seems that biodegradable polymers do not offer an advantage.

Other studies evaluated novel stent coatings designed to address the limitations of current stent platforms. Promising first-in-man results were seen with a nanothermic-microporous hydroxyapatite surface coating impregnated with a polymer-free low-dose of sirolimus (116), as well as a nanothermic polyezene-F–coated stent (117).

Bioabsorbable stents have been evaluated in small series and seem to have less scaffolding effect and decreased lumen size at 6 months; however, the long-term effects are favorable (118,119).

Pharmacotherapy

Clopidogrel. Because clopidogrel does not have antiplatelet effect until it is converted by hepatic cytochrome P-450, its antiplatelet effect can be quite variable. There may be genetic predisposition to reduced clopidogrel responsiveness and higher MACE in patients with cytochrome P-450 polymorphisms (120–122). Moreover, drugs that affect cytochrome P-450 (particularly the proton pump inhibitor omeprazole) have been shown to reduce clopidogrel effectiveness and increase ischemic complications (123,124). Despite a Food and Drug Administration (FDA) advisory suggesting caution, other studies reported that the combined use of clopidogrel and omeprazole is safe (125,126) and provide reassurance. However, numerous investigators have shown a higher risk of ST in patients with clopidogrel hyporesponsiveness (85), and these patients may benefit from more potent antiplatelet agents such as a glycoprotein IIb/IIIa inhibitor (127,128).

Higher-dose clopidogrel also may improve clinical outcomes. In STEMI patients undergoing primary PCI, pretreatment with 600 mg clopidogrel was associated
with a reduced rate of ST, MI, and death compared with a 300-mg dose (129). The CURRENT OASIS-7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions) trial randomized 17,000 ACS patients undergoing PCI to double dosing (600 mg load and 150 mg/day for 7 days followed by 75 mg/day) versus conventional dosing (130). The double-dose group had significant reductions in death, MI, and stroke and a 42% decrease in ST (Fig. 1). At our institution, we have used 600-mg loading doses for several years, but based on this study, we are now giving 150 mg clopidogrel for the first 7 days in all ACS and STEMI patients.

Although concern still exists regarding pretreatment with clopidogrel in ACS patients who ultimately may require CABG, the ACUITY trial reported a significant reduction in ischemic events in patients who received clopidogrel before CABG (131).

**Prasugrel.** Results of the 3,534 STEMI patients within the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38) trial were published in 2009 (132). Patients were randomized to receive prasugrel (60 mg loading, 10 mg maintenance) or clopidogrel (300 mg loading, 75 mg daily). Only 27% patients received medication before PCI. At 30 days, patients treated with prasugrel had a significantly lower incidence of the primary end point, death/MI/stroke (6.5% vs. 9.5%; p = 0.0017), and ST (1.2% vs. 2.4%; p = 0.0084), without an increased risk of major bleeding. Further studies are needed to determine if prasugrel is beneficial compared to patients receiving higher clopidogrel dosing for STEMI. In a separate analysis from the trial, prasugrel was beneficial in ACS patients regardless of whether a glycoprotein IIb/IIIa inhibitor was used (133). Additionally, prasugrel was found to reduce both periprocedural and spontaneous MI (134).

**Ticagrelor.** Ticagrelor is an oral reversible ADP inhibitor that has more rapid and consistent platelet inhibition than clopidogrel. The PLATO (Platelet Inhibition and Patient Outcomes) trial randomized 18,624 ACS patients to receive ticagrelor or clopidogrel (135). The overall trial demonstrated a significant reduction in death/MI/stroke at 12 months with ticagrelor, without an increase in major bleeding. Results of 2 planned substudies also were presented (136,137). In patients with STEMI (n = 8,430) and ACS patients with a planned invasive strategy (n = 13,408), ticagrelor was associated with significant reductions in death, MI, and ST. This represents an important step forward in oral antiplatelet therapy, and based on these results, ticagrelor likely will become the standard of care for ACS patients.

**Cangrelor.** Intravenous cangrelor, a rapid-acting, reversible adenosine diphosphate (ADP) receptor antagonist, was evaluated in 2 large randomized trials (138,139). In one trial, clopidogrel 600 mg was given before PCI, and in the other trial, clopidogrel 600 mg was given after PCI. In both studies, cangrelor failed to improve the incidence of death/MI/ischemia-driven TVR at 48 h, but there was a lower incidence of ST in patients who were not pretreated with clopidogrel (138).

**Cilostazol.** Addition of cilostazol to aspirin and clopidogrel results in greater ADP-induced platelet inhibition compared with dual antiplatelet therapy alone. In a randomized trial, Jeong et al. (140) demonstrated that patients with a suboptimal response to dual antiplatelet therapy have
greater platelet inhibition when cilostazol is added compared with aspirin plus clopidogrel 150 mg daily. Triple antiplatelet therapy also seemed to improve clinical outcomes in a nonrandomized study of STEMI patients treated with a DES (141).

Glycoprotein (GP) IIb/IIIa inhibitors. A wealth of information exists regarding the benefits of abciximab during primary PCI; however, these studies were conducted before the widespread use of clopidogrel and the cost constraints of our current health care system. Two meta-analyses comparing results of small molecule GP IIb/IIIa inhibitors with abciximab during primary PCI (142,143) did not demonstrate any difference in angiographic or clinical outcomes. The necessity of GP IIb/IIIa may be in question, with more randomized trials showing lack of benefit of pre-catheterization administration before (144–147). In patients who receive GP IIb/IIIa agents, it may be possible to reduce bleeding complications and cost by reducing the infusion duration to 2 h (148).

PAR-1. Oral SCH 530 548, an oral platelet protease-activated receptor-1 antagonist, was developed to prevent thrombin-mediated platelet activation. In a trial of 1,030 patients undergoing cardiac catheterization, the agent was found to be safe and did not increase risk of TIMI bleeding, even when administered with aspirin and clopidogrel (149).

Bivalirudin. Mehran et al. (150) published 1-year results of the HORIZONS AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial. Patients treated with bivalirudin had significantly improved outcomes at 1 year compared with those treated with heparin plus GP IIb/IIIa inhibitor: net adverse clinical events (15.6% vs. 18.3%; p = 0.022), major bleeding (5.8% vs. 9.2%; p < 0.001), and mortality (3.5% vs. 4.8%; p = 0.037).

Enoxaparin. In a follow-up report from the STEEPLE (Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients, an International Randomized Evaluation) trial, 1-year survival was similar in patients who received either enoxaparin or unfractionated heparin during initial elective PCI (151).

Statins. Statin pretreatment seems to reduce periprocedural myocardial injury during PCI. In 668 statin-naïve patients, a single dose of atorvastatin 80 mg given the day before PCI significantly reduced the incidence of MI compared with no statin (9.5% vs. 15.8%; p = 0.014) (152). In another trial, Di Sciascio et al. (153) demonstrated that an atorvastatin reload (80 mg 12 h before PCI; 40 mg periprocedural) also improves results in patients receiving chronic statin therapy, with a significant reduction in periprocedural MI (13% vs. 24%; p = 0.017) and MACE (3.7% vs. 9.4%; p = 0.037). In ACS patients, intensive statin (atorvastatin 80 mg) therapy reduced recurrent events at 30 days compared with moderate-dose statin (pravastatin 40 mg) therapy (154).

Pioglitazone. In a small randomized trial of 97 diabetic patients receiving BMS, pioglitazone was associated with a trend toward a lower in-stent neointimal volume by intravascular ultrasound at 6 months (155).

Contrast Nephropathy

Prevention. Both short- and long-term prognosis after PCI is markedly impaired if contrast-induced nephropathy (CIN) develops. Jabara et al. (156) point out that the rate of CIN can vary from 3.3% to 10.2% in the same patient population depending on the definition. Currently, the most frequently used definition of CIN is an absolute 0.5 mg/dl increase in creatinine or a 25% increase over baseline. In a meta-analysis, Brown et al. (157) conclude that hydration with combination N-acetylcysteine (NAC) and sodium bicarbonate is the most effective treatment tested in large populations. Spargias et al. (158) randomized 208 patients with baseline creatinine of more than 1.4 mg/dl to placebo or infusion of iloprost at 1 ng/kg/min for 4 h. CIN occurred in 22% of control and 8% of treated patients (p = 0.005). This finding must be replicated in larger trials.

Contrast agents. Controversy still exists regarding whether contrast media type influence the development of CIN. Mehran et al. (159) found that with a background of 70% use of NAC, no difference in incidence of CIN occurred when an ionic, low-osmolar agent (ioxaglate) was compared with a nonionic agent (iodixanol). In another randomized trial of 324 patients, there was no difference between iodixanol and iomeprol (160). A meta-analysis of 16 trials found that iodixanol was not associated with lower rates of CIN compared with low-osmolar agents (161). This entire question remains clouded in uncertainty. No acceptable animal model exists. Most trials are small and underpowered. Each trial has differences in hydration strategies; each had different background NAC and bicarbonate use. Most trials that do not specifically test contrast do not standardize the contrast agent used. Today, optimal preprocedure hydration, NAC pretreatment, and judicious use of total contrast volume remains the backbone of preventative efforts to decrease CIN.

Peripheral Vascular Disease

Renal sympathetic denervation. In a landmark article, Krum et al. (162) presented the results of a study using radiofrequency catheter-based renal sympathetic denervation in 50 patients with resistant hypertension (systolic blood pressure ≥160 mm Hg with 3 or more medications). At the 1-year follow-up, there was a substantial and sustained improvement in blood pressure (approximately 27/13 mm Hg) with no evidence of deterioration in renal function. A prospective, randomized trial currently is underway to evaluate this exciting technology further.

Renal artery stenting. In a large randomized trial, 806 patients with atherosclerotic renal artery stenosis were assigned to undergo renal revascularization plus medical therapy or to receive medical therapy alone (163). During the 5-year follow-up, there was no significant difference.
between the groups in renal function (the primary end point, measured by the reciprocal of the serum creatinine level), blood pressure, or renal events. These results undoubtedly will impact the use of renal revascularization therapy.

**Carotid disease.** Gray et al. (164) studied 30-day clinical outcomes among 6,320 high surgical risk patients undergoing carotid artery stenting (CAS) in 2 recent prospective, multicenter registries. In patients younger than 80 years of age, the incidence of death or stroke was 5.3% for symptomatic patients and 2.9% for asymptomatic patients. These results demonstrate that CAS outcomes continue to improve and now meet American Heart Association standards for carotid endarterectomy in both symptomatic (<6%) and asymptomatic (<3%) lesions.

The role for CAS in patients older than 80 years has been questioned. Among 142 elderly patients, Chiam et al. found a more than 85% survival at 2 years, suggesting that CAS is a reasonable strategy in carefully selected patients (165).

**Superficial femoral artery disease.** In a meta-analysis of 10 trials comparing stenting versus angioplasty for symptomatic SFA disease, there was a higher immediate success rate with stenting, but no difference in restenosis or repeat revascularization at follow-up (166).

**Structural Heart Disease**

**Aortic valve.** Transcatheter aortic valve implantation (TAVI) for treatment of calcific aortic stenosis has generated enormous scientific and public interest. The year 2009 brought much more published information concerning the 2 currently available valves (Edwards-Sapien, Edwards, Irvine, California; CoreValve device, Medtronic, Minneapolis, Minnesota). Clavel et al. (167) carefully analyzed the hemodynamic results of 50 patients with successful Edwards valve implants compared with a matched control group of 50 patients with surgically implanted bioprosthetic valves. Although postoperative gradients were similar, patients with small outflows (annulus <22 mm) tended to have more prosthesis–patient mismatch with surgical implants. Conversely, patients with larger annulus sizes (>24 mm) tended to have a higher incidence of paravalvular leak with percutaneous aortic valve implantation (PAVI). These data suggest that with currently available valve sizes, hemodynamics is superior with PAVI in smaller annulus dimensions and superior with surgical implants in larger annulus sizes.

Himbert et al. (168) described a large French experience of 75 patients treated with the Edwards-Sapien valve (51 PAVI, 24 TAVI). In-hospital mortality was 10%, and the incidence of stroke was 4%. One-year survival was 78%. A definite learning curve exists: for the first 25 patients, the 1-year survival was 60%, compared with 93% for the last 50 patients. This fact has important implications for the current pivotal trial (PARTNER [Placement of Aortic Transcatheter Valve]) that has completed enrollment in the U.S. The large majority of patients enrolled in PARTNER were treated in centers with fewer than 25 patients, so this pivotal randomized trial (that will be definitive for U.S. FDA approval) is basically a trial of the learning curve of a new technology compared with a mature surgical approach. Webb et al. (169) similarly reported outcomes for 168 patients with the Edwards-Sapien valve in Vancouver. Again, operative mortality fell from 14% in the early experience to 8% in the later stage of investigation. In the PAVI group, mortality fell from 12% to 3%, and in the TAVI group, mortality fell from 25% to 11%. Paravalvular regurgitation was mild and stable over follow-up. At 3 years, no structural failure of the prosthetic valve occurred. Webb et al. (170) even more forcefully present the value of center and operator experience for this procedure. Here they describe their more recent experience in 25 high-risk aortic stenosis patients with aortic valve area of 0.59 ± 0.15 cm² who underwent implantation with a new-generation Edwards-Sapien valve. Successful implantation occurred in 100% and 30-day survival was 100%. Finally, Détaint et al. (171) found that moderate to severe aortic regurgitation occurred in 40% of patients treated in the early experience at their center, compared with 15% in the later stages of experience. Overall, these studies make a strong argument for centralization of this procedure.

**Mitral valve.** Feldman et al. (172) reported long-term outcomes in 107 patients treated with the Mitraclip device (Evalve, Inc., Menlo Park, California) for symptomatic mitral regurgitation resulting from functional or degenerative disease. Freedom from surgery at 3 years occurred in 76% of patients. In those patients who required surgery, 84% of patients initially eligible for valve repair were able to undergo successful valve repair rather than replacement. This study suggests that the procedure is durable in the medium term and that surgical correction is not eliminated as an option if recurrent mitral regurgitation occurs. This device is likely to receive FDA approval and will be the first commercially available device in the U.S. Sack et al. (173) and Schofer et al. (174) reported initial feasibility with novel coronary sinus mitral annuloplasty devices.

**Left atrial appendage occlusion.** Previous studies suggest that the left atrial appendage (LAA) is the source of emboli in many patients with atrial fibrillation. For this reason, percutaneous occlusion of the LAA has been studied avidly. Holmes et al. (175) describe the Watchman LAA system for embolic protection. They screened 4,998 patients with paroxysmal or chronic AF and randomized 707 warfarin-eligible patients to LAA occlusion and subsequent warfarin discontinuation or warfarin. Serious device-related events, including major bleeding, pericardial effusion, and device embolization, were more frequent in the active treatment group. The primary efficacy end point was a composite of death, stroke, and systemic embolism. LAA occlusion was noninferior to warfarin therapy. Thus, for patients who can tolerate warfarin, initial device-related complications were higher, but long-term efficacy in stroke prevention did occur. Ideally, clinicians really would like to use this device...
in patients at risk of cardiac emboli who cannot tolerate warfarin. These data are not yet available. Block et al. (176) also reported late outcomes of 64 patients treated with another LAA occlusion device. At 5 years, the annualized stroke/transient ischemic attack rate was 3.8%/year, which was less than expected.

**Patent foramen ovale (PFO).** The interventional community has been accused of the Sir Edmund Hilary approach to PFO: “Close them because they are there!” In this regard, the year 2009 brought more discipline to this field. Ford et al. (177) presented the Mayo Clinic experience with PFO closure. Between 2001 and 2006, they implanted devices in 352 patients. Indications included 225 patients with cryptogenic stroke and 118 patients with transient ischemic attack. Recurrent stroke or transient ischemic attack occurred in 0.9% of patients at 1 year and in 2.8% of patients at 4 years. Of the 8 patients with recurrent stroke, 5 had factor V Leiden deficiency, protein C deficiency, or protein S deficiency. This experience suggests excellent efficacy for secondary prevention and also provides a strong argument for screening for thrombophilic disorders in these patients. Similarly, Wahl et al. (178) present the long-term Bern experience of 620 patients with PFO closure. They found an event-free survival of 97% at the 5-year follow-up. Despite these outstanding results, definitive proof of efficacy of PFO closure for secondary prevention does not exist. For this reason, O’Gara et al. (179) make an impassioned plea in an American Heart Association/American Stroke Association/American College of Cardiology Foundation Science Advisory for clinicians to enter their patients into ongoing pivotal randomized trials.

An even more contentious indication for PFO closure is migraine prevention. Previously, the MIST trial failed in its primary end point of prevention of migraine. Vigna et al. (180) report a systematic evaluation of closure in 82 patients with migraine and definite subclinical MRI abnormalities. Among 52 patients who underwent PFO closure and 29 (control) who did not, a 50% reduction in migraine frequency occurred in 87% of the treated patients, whereas only 17% of controls demonstrated reduction in migraine frequency ($p < 0.001$). Although the study is limited by its size and nonrandomized nature, it is very provocative with respect to efficacy. More will surely follow!

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Key Words: interventional  ●  stent  ●  vascular  ●  peripheral.