We are delighted to provide readers of the *Journal* with this review of major scientific work published in the field of interventional cardiology in 2011, including 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 the paper will provide a broad overview for general cardiologists, as well as a framework for more detailed study for those interested in interventional cardiology.

**Structural Heart Disease**

**Transcatheter aortic valve replacement.** The Valve Academic Research Consortium (VARC) developed standardized definitions for transcatheter aortic valve replacement (TAVR) for clinical safety, procedure-related safety, clinical efficacy, and composite endpoints (1). The PARTNER (Placement of Aortic Transcatheter Valves) trial randomly assigned 699 high operative risk patients (cohort A) with symptomatic aortic stenosis to TAVR (SAPIEN Heart Valve System, Edwards Lifesciences, Irvine, California) or aortic valve replacement (AVR) (2). The primary endpoint was all-cause mortality at 1 year (noninferiority). At 30 days, TAVR was associated with a trend toward less mortality, major bleeding, and New York Heart Association (NYHA) functional class III/IV heart failure; similar risk of stroke and permanent pacemaker (PPM); and greater risk of major vascular complications and paravalvular aortic regurgitation (PAR) \( \geq 3 \). At 1 year, TAVR had similar mortality (Fig. 1) and NYHA class III or greater heart failure; lower mean transaortic valve gradient; and more PAR \( \geq 3 \) (6.8% vs. 1.9%, \( p < 0.001 \)). The PARTNER trial included 358 patients with inoperable aortic stenosis (cohort B), randomly assigned to TAVR or standard therapy; TAVR resulted in better quality of life at 1 year (3).

In the European PARTNER (PARTNER EU) registry of 130 patients with SAPIEN valves, TAVR success was >95%; 30-day and 6-month mortality was lower for transfemoral patients than for transapical patients (4). Investigators in Germany evaluated early (\( n = 150 \)) and recent (\( n = 149 \)) transapical SAPIEN experience (5); recent experience had lower mortality at 30 days (11.3% vs. 6.0%, \( p < 0.05 \)) and 1 year (30.0% vs. 21.5%, \( p < 0.05 \)), consistent with a learning curve. The Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry reported 1-year outcomes for 1,038 inoperable patients (6); 1-year mortality was 23.9%, but was higher in transapical patients.

The German Transcatheter Aortic Valve Interventions (TAVI) registry reported outcomes in 697 patients (CoreValve [Medtronic, Minneapolis, Minnesota], \( n = 588 \); SAPIEN valve, \( n = 109 \)) (7). Technical success was achieved in 98.4%. Outcomes at 30 days included death (12.4%), stroke (2.8%), and PPM (39.3%). The FRANCE (French Aortic National CoreValve and Edwards) registry enrolled 244 patients (\( n = 166 \) SAPIEN, \( n = 78 \) CoreValve) (8). Technical success was achieved in 98.3%. Outcomes at 30 days included death (12.7%), stroke (3.6%), acute coronary occlusion (1.2%), and PPM (11.8%). The UK TAVI (United Kingdom Transcatheter Aortic Valve implantation) registry reported 2-year outcomes in 870 patients (\( n = 452 \) CoreValve, \( n = 410 \) SAPIEN valve, \( n = 8 \) unknown) (9). Compared to the SAPIEN valve, CoreValve was associated with fewer conversions to surgical AVR (0% vs. 1.5%, \( p = 0.01 \)), but more PAR \( \geq 3 \) (17.3% vs. 9.6%, \( p = 0.001 \)), repeat procedures (1.6% vs. 0%, \( p = 0.02 \)), and PPM (24.4% vs. 7.4%, \( p < 0.001 \)). The Italian CoreValve registry reported 1-year outcomes in 663 patients (10); procedural success was achieved in 98.0%. The strongest independent predictors of 30-day mortality were conversion to surgical AVR (odds ratio [OR]: 38.68), tamponade (OR: 10.9), and major vascular complications (OR: 8.47). The strongest independent predictors of 1-year mortality were stroke (OR: 5.47), PAR \( \geq 2 \) (OR: 3.79), pulmonary disease (OR: 2.7), and renal disease (OR: 2.5). This registry reported outcomes in 24 (3.6%) of 663 patients requiring immediate valve-in-valve implantation for PAR (11). Compared to single valve patients, valve-in-valve patients had more major adverse events and higher mortality at 12 months (not statistically significant). Another study evaluated 35 patients with aortic annulus diameter <20 mm treated with a 23-mm SAPIEN valve (12). Procedural success was achieved in 97.1%. There was a significant decrease in transaortic valve gradient and increase in orifice area, but 2 patients (5.9%) had severe annular/prosthesis mismatch.
THE UK CoreValve Collaborative registry reported that 81 (33.3%) of 243 patients required PPM at a mean of 4.0 days after TAVR (13). Pre-procedural atrioventricular block (OR: 16.29) and increased QRS duration (OR: 3.45) were the strongest independent predictors of PPM. Diffusion-weighted magnetic resonance imaging was performed in 60 SAPIEN patients (14). New diffusion-weighted magnetic resonance imaging defects were identified in 68%, similar for transfemoral and transapical approaches. Most events were clinically silent, multiple, and bilateral. The spectrum of stroke-related complications after surgical AVR and TAVR was the topic of a review (15). The 30-day risk of stroke was 1.5% after surgical AVR, 2% to 4% after AVR for high-risk patients, and 1.5% to 6% after TAVR. The risks are highest at time of aortic cannulation and declamping during AVR, and at the time of balloon aortic valvuloplasty (BAV), crossing the aortic valve, and valve implantation during TAVR. After TAVR, 25% of strokes occur within 24 h, 50% within 1 to 7 days, and 25% within 7 to 30 days.

Significant annular/prosthesis mismatch can lead to severe PAR, valve embolization, and aortic injury. One study compared transthoracic echocardiography, cardiac magnetic resonance (CMR), and cardiac computed tomography for annular sizing in 202 TAVR patients (16). This study demonstrated better agreement for cardiac computed tomography and CMR than for transthoracic echocardiography, and a strong association between PAR and larger annular dimensions by computed tomography and CMR, consistent with evolving impressions that the elliptical configuration of the annulus is more reliably assessed by cardiac computed tomography than by echocardiography.

Mitrval valve repair. An important review described the evolution from edge-to-edge surgical mitral valve repair to current transcatheter mitral valve repair (17). Another review described the anatomy of the mitral valve and its relationship to the coronary sinus and coronary arteries, the percutaneous approaches to mitral annuloplasty, and the percutaneous edge-to-edge repair using the MitraClip (Abbott Vascular, Santa Clara, California) (18). Using detailed echocardiographic and clinical criteria, 279 patients with mitral regurgitation (MR) were randomly assigned 2:1 to MitraClip or conventional surgery in the landmark EVEREST-II (Endovascular Valve Edge-to-Edge Repair Study) (19). The primary efficacy endpoint was freedom from death, mitral valve surgery, and MR at 1 year. The primary safety endpoint at 30 days favored MitraClip (15% vs. 48%, p < 0.001), driven by less blood transfusion (13% vs. 45%, p < 0.001). At 1 year, there were compelling improvements in left ventricle dimensions, volumes, and ejection fraction (EF) for both (the magnitude of improvement favored surgery); quality of life was similar (but improved faster after MitraClip); and MitraClip patients had less NYHA functional class III or greater (2% vs. 13%, p = 0.002), but more MR ≥3 (19% vs. 4%, p < 0.001). Patients <70 years of age, with degenerative MR, and EF >60% fared better with surgery. Importantly, the Mitra-
Clip did not interfere with device explantation or subsequent mitral repair or replacement (20).

MitraClip was implanted in 104 patients with MR ≥3 and NYHA functional class III or greater who were ineligible for surgery (21). Device success was achieved in 92%, and resulted in MR ≥2 in 82.5%. Echocardiography demonstrated significant improvement in LV volumes, regurgitant volumes, and forward stroke volume. In the PERMIT-CARE (Percutaneous Mitral Valve Repair in Cardiac Resynchronization Therapy) registry, MitraClip was inserted in 51 patients with severe functional MR who failed cardiac resynchronization therapy (22). Technical success was achieved in 100%, and there were highly significant improvements in left ventricle dimensions, volumes, EF, NYHA functional class, and MR.

**Left atrial appendage closure.** The Watchman device (Atritech, Minneapolis, Minnesota) is designed to occlude the left atrial appendage and reduce the risk of stroke in patients with AF. Pooled data from the randomized PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF [n = 542]) and the CAP (Watchman Continued Access Protocol [n = 460]) trials demonstrated a significant relationship between operator experience and procedural success and safety (23).

**Elective Percutaneous Coronary Intervention**

The ACC/AHA/SCAI guidelines. The new American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) guidelines for percutaneous coronary intervention (PCI) provide a comprehensive review of this rapidly evolving field (24). Important new areas include ethical aspects of PCI, vascular access considerations, hybrid revascularization, revascularization before noncardiac surgery, optical coherence tomography, advanced hemodynamic support devices, no-reflow therapies, and vascular closure devices. Full review of the guideline is beyond the scope of this article. All interventional cardiologists should read the entire document.

**Appropriateness.** There has been increasing attention regarding appropriateness of PCI procedures. An analysis of 500,154 PCI in the National Cardiovascular Data Registry (NCDR) showed that 98.6% of PCI for acute indications (ST-segment elevation myocardial infarction [STEMI], non–ST-segment elevation myocardial infarction [NSTEMI], unstable angina with high-risk features) were classified as appropriate (25). For nonacute indications,
50.4% were classified as appropriate, 38.0% as uncertain, and 11.6% as inappropriate. There was substantial hospital variation in the proportion of inappropriate PCI for nonacute procedures. These data emphasize the importance of careful case selection and clinical documentation, especially in patients with stable ischemic heart disease.

**Same-day discharge.** With continued improvements in the safety of PCI, there has been growing interest in discharging patients without overnight observation. Rao et al. (26) reported outcomes in 107,018 Medicare patients undergoing PCI, 1.25% of whom underwent same-day discharge. Compared with overnight stay patients, there was no difference in the incidence of death or rehospitalization between days 2 and 30, suggesting that same-day discharge is safe for carefully selected low-risk PCI patients.

**Periprocedural myocardial infarction.** Several articles in 2011 addressed the definition and clinical impact of periprocedural myocardial necrosis. When comparing cardiac enzyme measurements with myocardial injury on CMR, creatine kinase–myocardial band allowed more accurate diagnosis of periprocedural myocardial infarction (MI), whereas troponin was oversensitive when applying the universal definition (27). Among 6,347 PCI patients, only large creatine kinase–myocardial band elevations (30 to 50 ng/ml) were associated with increased 1-year mortality (28).

**Left main disease.** Several publications assessed the safety and efficacy of unprotected left main coronary artery stenting compared to coronary artery bypass graft surgery (CABG). Park et al. (29) randomly assigned 600 patients with left main disease to CABG or a sirolimus-eluting stent (SES). Major adverse cardiac events (MACE) were similar at 1 year, but there was more ischemia-driven target vessel revascularization (TVR) in the PCI arm at 2 years. In a meta-analysis of 4 randomized trials of PCI compared with CABG for left main disease (30), PCI was associated with a nonsignificantly higher rate of 1-year MACE (14.5% vs. 11.8%, p = 0.11) driven by more TVR. Stroke was less frequent with PCI (0.1% vs. 1.7%, p = 0.013). In the new PCI guidelines, PCI of the left main has both Class IIa and Class IIb recommendations depending on associated coronary anatomy and patient characteristics (24). Among 509 drug-eluting stent (DES) patients, angiographic restenosis occurred in 17% (31); predictors of restenosis included female sex, diabetes mellitus, renal failure, more severe disease, and distal bifurcation disease.

**Multivessel disease.** In a nonrandomized comparison of 3,042 patients (DES = 1,547, CABG = 1,495), mortality was similar and revascularization was higher in DES patients at 5.6 years (32). After 3-year follow-up in the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial, stent thrombosis occurred in 4.1% of PCI-treated patients (33). There were higher rates of MI (7.1% vs. 3.3%, p = 0.005) and mortality (9.5% vs. 5.7%, p = 0.02) with PCI; however, this excess of events was confined to patients with intermediate (23 to 32) or high (≥33) SYNTAX scores (Fig. 2). Patients with a SYNTAX score ≤22 had similar outcomes at 3 years, suggesting that PCI is an acceptable alternative to CABG in patients with less complex disease. However, patients treated with CABG had greater relief from angina at 6 and 12 months (34).

**Medical therapy.** In an analysis of 467,211 patients with stable coronary artery disease in the NCDR, fewer than half received optimal medical therapy before PCI (aspirin, beta-blocker, and statin) (35).

At 3-year follow-up in the BARI-2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) trial, patients treated with initial revascularization had less angina and subsequent revascularization compared to medically treated patients (36).

**Radial access.** Two trials in 2011 compared outcomes between radial and femoral access. Jolly et al. (37) randomly assigned 7,021 patients with ACS; the primary composite endpoint of death, MI, stroke, or non–CABG-related bleeding at 30 days was similar (radial 3.7% vs. femoral 4.0%). The incidence of major vascular complications was lower with radial access. In 1,001 STEMI patients, radial access was associated with fewer adverse events at 30 days compared with femoral access (13.6% vs. 21.0%, p = 0.003) (38). In aggregate, these studies suggest that the radial approach should be the preferred strategy in primary PCI.

**Bifurcation.** Kissing balloon dilation is often used to “optimize” the side branch. In the Nordic–Baltic Bifurcation Study III (39), 477 patients with successful main vessel stenting (and side branch ≥2.25 mm) were randomly assigned to final kissing balloon post-dilation or no post-dilation. Angiographic restenosis in the side branch was less with kissing balloon dilation; however, at 6 months, there was no difference in clinical outcome between groups, suggesting that routine kissing balloon post-dilation may not be necessary. In 370 patients with bifurcation lesions, double-kissing crush technique reduced angiographic side branch restenosis at 8 months, and TVR at 12 months compared with provisional stenting (40).

**Vein graft.** The safety and efficacy of DES in saphenous vein graft disease has been unclear. Mehilli et al. (41) randomly assigned 610 patients with de novo saphenous vein graft lesions to DES (SES or paclitaxel-eluting stent [PES]) or bare-metal stent (BMS) (41). At 1 year, the primary endpoint (death, MI, TLR [target lesion revascularization]) was lower after DES (15% vs. 22%, p = 0.02), driven primarily by a reduction in TLR.

**Stent thrombosis.** Stent thrombosis is an uncommon but potentially devastating complication of PCI. Three genes involved in clopidogrel metabolism and platelet receptor function were associated with stent thrombosis (CYP2C19, ABCB1, and ITGB3) (42). Peri-stent contrast staining after SES implantation was associated with subsequent TLR and very late stent thrombosis (43). At 2 years, definite or probable stent thrombosis occurred in 4.4% patients after primary PCI, but there was no difference between DES and BMS (44).
Intravascular ultrasound. Intravascular ultrasound (IVUS) is often performed to further characterize the severity of angiographically intermediate left main stenosis. In a prospective evaluation of 354 patients, a minimum lumen area $\geq 6$ mm$^2$ was shown to be a safe cutoff for deferring revascularization (45).

Contrast-induced nephropathy. N-acetylcysteine is frequently used to prevent contrast-induced nephropathy (CIN); however, no benefit was found in a randomized trial of 2,308 high-risk patients (46). In 450 STEMI patients, early hydration with pre- and post-procedure bicarbonate infusion was superior to either post-procedure isotonic saline, and no hydration (incidence of CIN: 12% vs. 22.7% vs. 27.3%, respectively; p for trend = 0.001) (47). Adequate volume expansion ($\geq 960$ ml) appeared to correlate with less CIN. In a trial comparing RenalGuard (PLC Medical Systems, Franklin, Massachusetts) to bicarbonate infusion and N-acetylcysteine in 294 high-risk patients with estimated glomerular filtration rate $\leq 30$, CIN (increase of $\geq 0.3$ mg/dl at 48 h) was less frequent with RenalGuard (11% vs. 20.5%) (48).

**Drug-Eluting Stents**

DES thrombosis. In a 478-patient registry of DES stent thrombosis, the majority of cases occurred after 1 year, and presented with MI (67% STEMI, 22% NSTEMI) (49). Nearly 30% of patients were taking dual-antiplatelet therapy (DAPT) at the time stent thrombosis occurred. By historical analysis in 127 patients who died $>1$ month after DES, localized strut hypersensitivity was seen with SES, whereas malapposition secondary to excessive fibrin deposition was seen with PES (50).

Second generation DES. Compared to first generation DES, second generation DES (everolimus-eluting stent [EES]; zotarolimus-eluting stent [ZES]) reduce restenosis, but are more deliverable and have less stent thrombosis.

Numerous studies evaluating EES were published or presented in 2011. In 1,800 patients randomly assigned to an EES or PES, the 2-year incidence of MI, TVR, and stent thrombosis was significantly lower with the EES (51). Similar findings were reported by Stone et al. (52). Two studies demonstrated similar angiographic late loss with EES and SES (53,54). In the RESET (Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent) trial, 3,200 patients were randomly assigned to EES or SES; TLR at 1 year was similar (55). A propensity-matched analysis reported less stent thrombosis with EES (56).

In a 5-year trial comparing ZES and SES, early angiographic lumen loss was higher with ZES, but clinical outcomes at 5 years favored ZES (MACE 14.0% vs. 22.2%, p = 0.05) (57). Several studies evaluated the newer Resolute-ZES (Medtronic, Minneapolis, Minnesota), which was designed to provide a longer duration of drug release. In 1,402 patients, target lesion failure was 4.7% and stent thrombosis was 0.1% at 12 months (58).

In a randomized trial comparing 2 second generation DES (Resolute ZES vs. Xience EES), the safety and efficacy of the 2 platforms were similar at 2 years in simple and complex lesion subsets (59,60).

New polymers and coatings. In a randomized study of 2,603 patients comparing biodegradable polymer DES with permanent polymer DES (SES or EES), similar clinical outcomes were observed at 3 years (61). Another trial reported similar MACE rates at 4 years between a biodegradable polymer biolimus-eluting stent and a durable polymer SES; however, there was less risk of very late stent thrombosis with the biolimus-eluting stent (62).

In a first-in-human study with the Combo dual therapy stent (biodegradable polymer with sirolimus on abluminal surface; anti–CD-34 antibody layer on the luminal side), angiographic late loss at 9 months was 0.39 mm (noninferior to Taxus Liberté PES) (63). Promising results were also reported with bioabsorbable polymer and everolimus applied only on the abluminal surface (64).

In contrast, a trial of an endothelial progenitor cell capturing stent was terminated early due excess TVF at 1 year in the cell capturing stent group compared with a DES (65).

Polymer-free DES. Polymer residue has been implicated as a potential etiology for late adverse events after DES. In a randomized trial of 3,002 patients, the polymer-free rapamycin and probucol-eluting stent was noninferior to a ZES (Endeavor Resolute) at 12 months (66). The Cre8 polymer-free SES had less late loss compared with PES (67).

DES restenosis. The optimal treatment strategy for DES restenosis has not been well defined, but 2 studies suggested that a paclitaxel-eluting balloon is a promising option. In 50 patients with in-stent restenosis randomly allocated to paclitaxel-eluting balloon versus conventional balloon angioplasty, there was less late loss (0.18 ± 0.45 mm vs. $0.72 \pm 0.55$ mm, $p = 0.001$) and lower TLR (4.3% vs. 41.7%, $p = 0.003$) after paclitaxel-eluting balloon (68). Another trial also reported less late loss and restenosis after paclitaxel-eluting balloon (69). Compared with focal in-stent restenosis, diffuse in-stent restenosis was associated with more TLR (70).

Bioresorbable scaffold. At 12 months, a second generation biodegradable EES had no change in scaffold area, late loss of 0.27 ± 0.32 mm, and 96.69% strut coverage by optical coherence tomography (71). Implantation of a 3.0-mm biodegradable scaffold in smaller vessels appears to be safe (72). These findings represent an exciting step forward in the field of biodegradable vascular scaffolds.

**Acute Myocardial Infarction**

PCI after thrombolysis. Thiele et al. (73) randomly assigned 162 patients with long transfer times to pre-hospital tenecteplase before PCI or to primary PCI alone (all patients <3 h acute myocardial infarction [AMI] onset). Although the facilitated PCI group had better TIMI (Thrombolysis In Myocardial Infarction) flow grade in the
infarct-related artery, there was a trend toward larger infarct size and more microvascular obstruction. A meta-analysis of routine versus ischemia-guided PCI after initial fibrinolysis reported that 30-day death, reinfarction, and ischemia were lower after routine PCI (7.3% vs. 13.5%, p < 0.0001) driven by less reinfarction and ischemia (74).

**Transfer.** Several studies focused on optimizing the care of STEMI patients who initially present to a hospital without PCI. Wang et al. (75) reported that the median door-in to door-out time was 68 min in a cohort of 14,821 STEMI patients (75). Only 11% patients had a door-in to door-out time <30 min (which has been established as a new clinical performance measure). In 107,028 STEMI patients (<12 h) treated with on-site fibrinolysis or transfer for primary PCI, clinical outcomes were best when PCI-related delay was <60 min (76). Importantly, there was no mortality advantage for PCI if the delay to PCI exceeded 120 min. Door-to-balloon times <90 min can be achieved in a rural setting with implementation of protocols for rapid triage and transfer of STEMI patients (77).

**Drug-eluting stents.** Although DES improve short-term outcomes in STEMI patients compared to BMS, it is unclear whether these benefits are sustained. In the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial, PES resulted in a 40% reduction in ischemia-driven TLR at 3 years (78). Although 1 study reported less TLR with SES at 4 years, (79), another reported no difference in clinical outcomes at 5 years with a PES (80). Of note, stent thrombosis was similar between DES and BMS in all 3 studies.

Very late stent thrombosis (>1 year) may occur as late as 11 years after primary PCI, and the frequency of very late stent thrombosis is higher with DES (81). In 118 STEMI patients, optical coherence tomography at 1 year demonstrated less neointimal hyperplasia, and more malapposition and uncovered stent struts after PES compared with BMS (82).

**Multivessel disease.** Two studies evaluated culprit only PCI, multivessel PCI in the same setting, or staged PCI for STEMI patients with multivessel disease (83,84). Both reported higher mortality with multivessel PCI in the same setting, and the best outcomes were observed after staged procedures.

**Bleeding.** In-hospital major bleeding is an important predictor of short-term mortality and clinical outcomes after primary PCI. In 3,345 patients in the HORIZONS AMI trial, patients with major in-hospital bleeding had higher mortality (24.6% vs. 5.4%, p < 0.0001) and more MACE (40.3% vs. 20.5%, p < 0.0001) at 3 years (85). Compared to continuing unfractionated heparin plus a glycoprotein (GP) IIb/IIIa receptor inhibitor, patients who were switched to bivalirudin had less bleeding and improved late survival (86).

**Adjunctive therapies.** Previous studies suggested that intra-aortic balloon pump counterpulsation before reperfusion reduces myocardial injury. In 337 nonshock anterior MI patients randomly assigned to intra-aortic balloon pump before PCI versus primary PCI alone, there was no difference in infarct size at 3 to 5 days by CMR (87). Intravenous erythropoietin given within 4 h of successful primary PCI did not reduce infarct size, but was associated with more clinical events (88).

**Cell therapy.** Several studies investigated intracoronary infusion of mononuclear cells to improve ventricular function after STEMI. Administration of bone marrow or peripheral mononuclear cells 3 to 8 days after large AMI did not improve left ventricular volumes or infarct size at 4 months (89). In a small randomized trial (n = 101), myocardial viability improved after infusion of bone marrow mononuclear cells 7 to 10 days after AMI (90). Late administration of bone marrow mononuclear cells (2 to 3 weeks post-MI) to 87 patients with EF ≤45%, did not improve global or regional left ventricle function or volumes at 6 months (91).

**Acute Coronary Syndromes**

A focused update of the ACCF/AHA guidelines for management of patients with unstable angina and NSTEMI presented new recommendations for: 1) antiplatelet therapy including upstream use of GP IIb/IIIa inhibitor in high-risk patients, use of prasugrel, maintenance dose and duration of thienopyridines after PCI, and use of platelet function testing and genotyping; 2) invasive versus conservative management strategies; and 3) management of patients with diabetes and chronic kidney disease (92).

Application of the SYNTAX score in patients with acute coronary syndrome (ACS) undergoing PCI is recommended as patients in the highest tertile of SYNTAX score had higher mortality, MI, and TVR (93).

**Pharmacotherapy**

**Clopidogrel.** DUAL-ANTIPLATELET THERAPY. Several studies addressed the optimal duration of DAPT. In 1,443 DES patients, there was no difference in TVF (death, MI, TVR) for 6 months versus 12 months of DAPT (94). Likewise, there was no difference in the composite of death, MI, and stroke at 2 years in another study of 2,013 patients, but there was significantly more bleeding after prolonged DAPT (6 vs. 24 months) (95). A series of larger DAPT trials are currently ongoing.

**LOADING DOSE.** Compared with a 300 mg loading dose in STEMI patients, the 600 mg loading dose was associated with smaller infarct size (96).

**MAINTENANCE DOSE.** Several studies suggested a direct relationship between on-treatment platelet reactivity and clinical outcomes (97,98). In a crossover study, clopidogrel 150 mg per day was shown to improve platelet inhibition compared with clopidogrel 75 mg per day (99). Whether a higher dosing strategy is beneficial in patients with suboptimal platelet inhibition has been in question. Price et al. (100) randomly assigned 2,214 patients with high residual
platelet reactivity (platelet reactivity units ≥230) on clopidogrel to high-dose (150 mg daily) versus standard-dose clopidogrel for 6 months (100). High-dose clopidogrel caused a 22% reduction in platelet reactivity but did not reduce clinical events.

**GENOTYPE TESTING.** The CYP2C19 polymorphisms have been shown to impact the antiplatelet effect of clopidogrel and may impact clinical outcomes. A point-of-care assay was used to assess CYP2C19*2 carrier status (carriers received prasugrel; noncarriers received clopidogrel) and guide antiplatelet therapy (101). With this strategy, there was a marked reduction in the proportion of CYP2C19*2 carriers with high on-treatment platelet reactivity (0% on prasugrel vs. 30.4% on clopidogrel, \( p = 0.009 \)), suggesting that genotype testing may play a role in determining the optimal antiplatelet regimen after PCI.

**Prasugrel.** Seventy-six (25.2%) of 301 ACS patients who were given a loading dose of prasugrel had suboptimal platelet inhibition (measured within 6 to 12 h using the vasodilator-stimulated phosphoprotein index), which was associated with an increased risk of adverse events at 1 month (102). Prasugrel resulted in greater platelet inhibition than high-dose clopidogrel (600 mg loading dose, 150 mg maintenance) in diabetic patients (103), as well as greater platelet inhibition than standard maintenance dose clopidogrel in patients with high on-clopidogrel platelet reactivity (104).

**Ticagrelor.** In the PLATO (Platelet Inhibition and Patient Outcomes) trial, ticagrelor reduced the risk of death, MI, and stroke compared with clopidogrel in ACS patients, but less benefit was observed in North America. This geographic difference may have been due to higher doses of aspirin in North America (105). Low-dose aspirin is currently recommended for patients receiving ticagrelor.

**Cilostazol.** Cilostazol is a selective phosphodiesterase-3 inhibitor with antplatelet and antiproliferative properties. After implantation of a long ZES (>30 mm), addition of cilostazol to aspirin and clopidogrel resulted in less late loss and restenosis at 8 months (106). In 960 DES patients, triple therapy resulted in greater platelet inhibition, but there was no difference in the composite of death, nonfatal MI, ischemic stroke, or TLR at 6 months (107).

**Protease-activated receptor-1 inhibitors.** Platelet activation can also occur through the protease-activated receptor (PAR)-1 on the platelet surface. In a study of 12,944 ACS patients randomly assigned to the oral PAR-1 antagonist vorapaxar or placebo, 58% underwent PCI (108). Vorapaxar did not reduce the composite endpoint (cardiovascular death, MI, stroke, hospitalization for ischemia, or urgent revascularization) and was associated with more bleeding, including intracranial hemorrhage. Atopaxar, another PAR-1 inhibitor with a shorter half-life than vorapaxar, was studied in ACS and stable CAD patients (109,110). Atopaxar resulted in greater platelet inhibition but no difference in major bleeding. A dose-dependent transaminase elevation and relative QTc prolongation were seen with the highest dose of atopaxar.

**Glycoprotein IIb/IIIa inhibitors.** A meta-analysis of GP IIb/IIIa in elective PCI (22 studies; \( n = 10,123 \)) showed no difference in mortality, but less nonfatal MI in the GP IIb/IIIa patients (111). There has been uncertainty about the role of abciximab in patients with NSTEMI undergoing PCI. Kastrati et al. (112) randomly assigned 1721 NSTEMI patients to abciximab and unfractionated heparin versus bivalirudin. At 30 days, there was no difference in the primary endpoint, a composite of death, large MI, or urgent TVR, but there was more bleeding with abciximab (4.6% vs. 2.6%, \( p = 0.02 \)).

Previous studies suggested a possible benefit for intracoronary versus intravenous abciximab in primary PCI for STEMI, but a randomized study in 2,065 STEMI patients showed no difference in infarct size (peak creatine kinase release), ST-segment resolution, or clinical outcomes (113).

**Low-molecular-weight heparin.** In a randomized trial of intravenous enoxaparin (0.5 mg/kg with or without GP IIb/IIIa inhibitor) versus UFH in primary PCI, the primary endpoint (composite of death, complications of MI, procedural failure, and non-CABG major bleeding at 30 days) was lower with enoxaparin (28% vs. 34%, \( p = 0.06 \)) without a difference in bleeding (114).

**Factor Xa inhibitors.** Several studies evaluated the role of factor Xa inhibition in ACS, including 15,526 patients randomly assigned to twice-daily doses of 2.5 mg or 5 mg rivaroxaban or placebo (115). Approximately 60% of patients underwent PCI, and >90% received thienopyridines. Both doses of rivaroxaban reduced the risk of the primary composite endpoint (death, MI, or stroke at 30 days), and the 2.5 mg dose (but not the 5 mg dose) was associated with better survival at 13 months. However, rivaroxaban increased the risk of major bleeding (2.1% vs. 0.6%, \( p < 0.001 \)) and intracranial hemorrhage (0.6% vs. 0.2%, \( p = 0.009 \)).

Apixaban was studied in ACS patients, the majority of whom were also receiving DAPT (~44% underwent PCI), but the trial was terminated prematurely due to an increased risk of major bleeding without reduction in ischemic events (116). Finally, darexaban also resulted in a dose-related increased risk of bleeding (117).

**Statins.** Statin pre-treatment reduces periprocedural MI during elective PCI. In a meta-analysis of 13 randomized trials (3,341 PCI patients), high-dose statin before PCI resulted in a 44% reduction in periprocedural MI (creatine kinase–myocardial band >3 times upper limit of normal), and less 30-day MACE compared to low-dose statin or no statin (118).

**Proton pump inhibitors.** There is controversy about the use of proton pump inhibitors in patients requiring clopidogrel. In a French registry of 3,670 MI patients, proton pump inhibitor use was not associated with an increased risk of death or cardiovascular events at 1 year, regardless of the type of proton pump inhibitor or CYP2C19 genotype (119).
Vascular Medicine

Carotid disease. Studies of carotid artery stenting (CAS) have reported the importance of operator experience on outcomes, provided more insight into quality of life after carotid revascularization, and proposed updated guidelines for the management of carotid disease. In 3,388 asymptomatic patients in the CAPTURE 2 (Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events) registry, the combined risk of death and stroke at 30 days was 3.3% (120). There was an inverse relationship between adverse events and operator volume, and 72 CAS procedures was the threshold to achieve death/stroke <3%. In a Medicare database study of 24,701 CAS procedures, there was an inverse relationship between mortality and operator volume (121). A CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial) substudy evaluated quality of life after CAS and carotid endarterectomy (122). At 2 weeks and 30 days, CAS patients had significantly better physical function; there were no differences at 1 year. Periprocedural stroke had greater impact on quality of life than did MI or cranial nerve injury.

Two trials evaluated proximal versus distal embolic protection devices (EPD); one randomly assigned 53 patients with lipid-rich plaque to distal EPD (Filterwire EZ, Boston Scientific, Santa Clara, California) or proximal EPD (MO.MA, Invatec, Roacadel, Italy) (123). Using transcranial Doppler, there was less embolization with proximal EPD. In the other study, 62 patients with symptomatic stenosis were randomly assigned to distal EPD (EmboShield Protection System, Abbott Vascular, Abbott Park, Illinois) or proximal EPD with MO.MA (124). Using diffusion-weighted magnetic resonance imaging, the number and volume of new cerebral ischemic lesions were significantly reduced by proximal EPD.

The 2011 American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery guidelines (125) developed the following recommendations for CAS: Class I for CAS as an alternative to carotid endarterectomy in symptomatic standard-risk patients with severe carotid stenosis; Class IIa for CAS when revascularization is needed in patients with unfavorable neck anatomy, and for EPD during CAS; and Class IIb for CAS in highly selected patients with asymptomatic severe carotid stenosis, and for CAS or carotid endarterectomy in high-risk symptomatic or asymptomatic patients (acknowledging that superiority to medical therapy has not been demonstrated). The European guidelines for extracranial carotid disease are incorporated into the peripheral arterial disease (PAD) guidelines (126). The European guidelines provide a Class IIa (rather than IIb) recommendation for CAS for symptomatic high-risk patients with severe carotid stenosis; a Class IIb recommendation (rather than I) for symptomatic standard-risk patients; and Class IIb recommendation (rather than IIa) for EPD during CAS.

Peripheral arterial disease. Studies of PAD have reported new findings regarding medical and interventional management of patients with claudication and critical limb ischemia (CLI), as well as important new guidelines from the United States and Europe. The CLEVER (Claudication: Exercise Versus Endoluminal Revascularization) study randomly allocated 111 patients with Rutherford class 1 to 3 claudication and aortoiliac PAD to optimal medical care, optimal medical care and stent, or optimal medical care and supervised exercise (127). Supervised exercise achieved the greatest increase in peak walking time, whereas stenting achieved the greatest improvement in claudication-onset time, pedometer walking, and quality of life. A single-center database identified 360 endovascular CFA interventions, including percutaneous transluminal balloon angioplasty (PTA), stents for suboptimal PTA, and excisional atherectomy (128). Outcomes at 1 year included restenosis in 27.6% and TLR in 19.9%. Stents were independent predictors of procedural success, and freedom from restenosis and TLR; profunda involvement was predictive of procedural failure, restenosis, and TLR.

The Zilver PTX randomized clinical study randomly allocated 480 patients with symptomatic femoropopliteal PAD to PTA or paclitaxel-coated Zilver PTX DES (Cook Medical, Bloomington, Indiana); 120 PTA failures underwent secondary randomization to DES or BMS (129). Compared to PTA at 1 year, DES had better event-free survival (90.4% vs. 82.6%, p = 0.004), primary patency (83.1% vs. 3.8%, p < 0.001), and clinical benefit (88.3% vs. 75.8%, p < 0.001). Compared to provisional BMS at 1 year, provisional DES had better primary patency (89.9% vs. 73.0%, p = 0.01) and clinical benefit (90.5% vs. 72.3%).

For infrapopliteal PAD, 161 patients with severe claudication or critical limb ischemia (CLI) were randomly allocated to sirolimus-eluting stent (SES) or BMS (130). The SES had better primary patency (80.6% vs. 55.6%, p = 0.004), secondary patency (91.9% vs. 71.4%, p = 0.005), and improvement in claudication (p = 0.004). In another study, 104 patients with severe claudication or CLI due to infrapopliteal PAD were treated with the In.Pact Amiphirion paclitaxel-eluting balloon (Medtronic) (131). Angiographic restenosis occurred in 27.4%, clinical improvement in 91.2%, and limb salvage in 95.6% of patients.

The 2011 ACCF/AHA focused update of the guideline for the management of patients with PAD (132) revised the 2005 guidelines; there are new recommendations for reporting ankle-brachial index, smoking cessation, DAPT, and PTA as an alternative to surgery for CLI patients. The European
Society of Cardiology guidelines on the diagnosis and treatment of PAD recommend an endovascular-first approach to TASC (Trans-Atlantic Inter-Society Consensus) type A through C lesions, if revascularization is indicated (133).

Hypertension. Intervventional therapy appears promising for refractory hypertension. In a 265-patient randomized trial, carotid baroreceptor activation with the Rhoes System (CVRx, Minneapolis, Minnesota) was safe and resulted in improved systolic blood pressure at 6 months (134). Bilateral renal sympathetic denervation (Symplicity System, Medtronic) reduced blood pressure, fasting glucose, insulin levels, and C-peptide levels in a 50-patient study at 3 months (135).

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