Circulation Topic Review

Circulation: Cardiovascular Interventions Editors’ Picks
Most Important Articles Published in 2012

The Editors

The following articles are being highlighted as part of Circulation's Topic Review series. This series summarizes the most important manuscripts, as selected by the editors, published in Circulation and the Circulation subspecialty journals. The studies included in this article represent Editors’ Picks for each Circulation: Cardiovascular Interventions issue published in 2012.

Bare Metal Stent Thrombosis and In-Stent Neointimal Hyperplasia

Summary: Very late stent thrombosis occurs in patients with bare metal stent implantation, although the annual incidence is much lower than that after drug-eluting stent implantation. In-stent neointimal hyperplasia with ruptured plaques and thin-cap fibroatheromas has been observed in bare metal stents. Atherosclerotic plaques harvested from patients with very late stent thrombosis and those with acute coronary syndrome unrelated to stent thrombosis were histologically indistinguishable from each other; showing foamy macrophages, cholesterol crystals, and thin fibrous cap. Disruption of neointimal hyperplasia inside the stents could be an important underlying mechanism of very late stent thrombosis beyond 3 years after bare metal stent implantation.

Conclusion: Fragments of atherosclerotic plaque were highly prevalent in patients with VLST beyond 3 years. Disruption of in-stent neointimal hyperplasia could play an important role in the pathogenesis of VLST of BMS occurring beyond 3 years after implantation.

Composition of Target Lesions by Near-Infrared Spectroscopy in Patients With Acute Coronary Syndrome Versus Stable Angina

Summary: Whereas acute coronary syndromes typically develop from rupture and thrombosis of an underlying lipid core plaque (LCP), flow-limiting lesions in patients with chronic angina are believed to be stable, typically fibrocalscific, and less lipid laden. The term chronic stable angina is a clinical designation based on symptom patterns and does not necessarily reflect underlying plaque pathophysiology. Using intracoronary near-infrared spectroscopy to characterize plaque composition, this study found that patients with acute coronary syndromes typically have target lesions composed of LCP and commonly harbor remote, nontarget LCPs. Although as expected both target and remote LCPs were more frequent in patients with acute coronary syndromes compared with those with stable angina, intriguingly, the majority of target lesions in stable patients were composed of LCP. Overall, the findings of this study support the concept that clinical symptomatic presentation does not necessarily reflect underlying plaque pathophysiology.

Conclusion: Target lesions responsible for ACS were frequently composed of LCP; in addition, LCPs often were found in remote, nontarget areas. Both target and remote LCPs were more common in patients with ACS than in those with stable angina. Approximately one half of target lesions in stable patients were also composed of LCP.

Prehospital Abciximab in ST-Segment Elevation Myocardial Infarction: Results of the Randomized, Double-Blind MISTRAL Study

Summary: Optimal timing of administration of glycoprotein IIb/IIIa inhibitors in patients with ST-segment elevation myocardial infarction treated by percutaneous coronary intervention is controversial. The FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) study investigators recorded no benefit of early versus late abciximab administration, but administration was late. However, the ON-TIME-2 (Ongoing Tirofiban in Myocardial Infarction Evaluation 2) study investigators showed that prehospital tirofiban (door-to-balloon time, 76 minutes) in patients with ST-segment elevation myocardial infarction improved ST-segment elevation resolution and Thrombolysis In Myocardial Infarction flow. This study demonstrated that early ambulance administration of abciximab in patients with ST-segment elevation myocardial infarction did not improve either ST-segment elevation resolution or Thrombolysis In Myocardial Infarction flow rate after primary percutaneous, but it tended to improve TIMI flow pre-PCI and decreased distal embolization during procedure.

Conclusion: Early ambulance administration of abciximab in STEMI did not improve either STR or TIMI flow rate after PCI. However, it tended to improve TIMI flow pre-PCI and decreased distal embolization during procedure. Larger studies are needed to confirm these results.

Periprocedural Myocardial Infarction in a Randomized Trial of Everolimus-Eluting and Paclitaxel-Eluting Coronary Stents: Frequency and Impact on Mortality According to Historic Versus Universal Definitions

Summary: The clinical significance of small infarctions manifested by low-level biomarker elevation remains controversial. There are inadequate data to establish a single consensus definition for periprocedural MI that is appropriately sensitive for detection of myocardial necrosis while maintaining specificity for potentially clinically meaningful events. The study confirms a marked difference in periprocedural MI that is appropriately sensitive for detection of myocardial necrosis during procedure. Larger studies are needed to confirm these results.

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2-year mortality supports other studies in low risk patients with otherwise successful procedures.

Conclusion: There was a marked difference in periprocedural MI rates according to protocol or universal/ARC MI definitions. No association was present between periprocedural MI and mortality up to 2 years by either definition.4

Incidence and Outcome of Surgical Procedures After Coronary Bare-Metal and Drug-Eluting Stent Implantation: A Report From the CREDO-Kyoto PCI/CABG Registry Cohort-2

Summary: Surgical procedures after coronary drug-eluting stent implantation, early surgery in particular, carry significant risk for perioperative stent-related ischemic as well as bleeding complications. Surgical procedures were commonly performed after coronary stent implantation in the real clinical practice in Japan (22% at 3 years). Incidences of ischemic and bleeding complications after surgical procedures were acceptably low, with no differences regardless of bare-metal stents and drug-eluting stents use. Perioperative administration of dual-antiplatelet therapy was not associated with lower risk for ischemic events.

Conclusion: Surgical procedures were commonly performed after coronary stent implantation, and the risk of ischemic and bleeding complications in surgical procedures was low. In patients selected to receive DES or BMS, there were no differences in outcomes. Perioperative administration of dual-APT was not associated with lower risk for ischemic events.5

Platelet Function Measurement–Based Strategy to Reduce Bleeding and Waiting Time in Clopidogrel-Treated Patients Undergoing Coronal Artery Bypass Graft Surgery: The Timing Based on Platelet Function Strategy to Reduce Clopidogrel-Associated Bleeding Related to CABG (TARGET-CABG) Study

Summary: The antiplatelet effect of clopidogrel is highly variable and is negligible in up to 30% of patients; 10% to 15% of patients with acute coronary syndrome require coronary artery bypass graft surgery (CABG). The recent literature yields heterogeneous results with increased as well as similar bleeding events in patients on clopidogrel therapy clopidogrel before CABG. In patients on dual antiplatelet therapy needing CABG, targeted waiting based on preoperative platelet function monitoring shortens the recommended preoperative waiting period and results in similar bleeding as compared with clopidogrel-naive patients.

Conclusion: A strategy based on preoperative platelet function testing to determine the timing of CABG in clopidogrel-treated patients was associated with the same amount of bleeding observed in clopidogrel-naive patients and ≈50% shorter waiting time than recommended in the current guidelines.6

A Randomized, Double-Blind, Active-Controlled Phase 2 Trial to Evaluate a Novel Selective and Reversible Intravenous and Oral P2Y12 Inhibitor Elinogrel Versus Clopidogrel in Patients Undergoing Nonurgent Percutaneous Coronary Intervention: The INNOVATE-PCI Trial

Summary: Dual antiplatelet agents with aspirin and a P2Y12 inhibitor such as clopidogrel or prasugrel are cornerstone therapy in the setting of PCI in stable patients, as well as those with acute coronary syndrome. Clopidogrel is limited by significant interpatient variability while prasugrel is associated with an increase risk of bleeding. Elinogrel is a novel IV and oral competitive and reversible P2Y12 inhibitor. In this randomized, double-blind, dose-ranging phase 2b trial, elinogrel was found to have acceptable safety and tolerability compared with clopidogrel in the setting of nonurgent PCI.

Conclusion: In patients undergoing nonurgent percutaneous coronary intervention and in comparison with clopidogrel, intravenous and oral elinogrel therapy did not significantly increase thrombolysis in myocardial infarction major or minor bleeding, although bleeding requiring medical attention was more common. The significance of these findings will need to be more definitively determined in future Phase 3 studies.7

Stent Thrombosis With Everolimus-Eluting Stents: Meta-Analysis of Comparative Randomized Controlled Trials

Summary: DES have significantly reduced the risk of restenosis and ischemia-driven target vessel revascularization. There is concern about the ongoing propensity of first-generation DES for late and very late stent thrombosis. Whether more recently developed DES improve safety is unknown. This analysis provides evidence that the second-generation EES, which uses a different platform and polymer compared with first- and other second-generation DES, is associated with significantly lower rates of early, late, and 2-year definite stent thrombosis compared with pooled PES, SES, and the Resolute ZES. These findings may have practical implications in the care of patients undergoing percutaneous coronary intervention.

Conclusion: EES compared with a pooled group of paclitaxel-eluting stents, sirolimus-eluting stents, and zotarolimus-eluting stents is associated with a significant reduction of definite ST, an effect that appears early and increases in magnitude through at least 2 years.8

Predictors and Prognostic Value of Myocardial Injury During Transcatheter Aortic Valve Implantation

Summary: Periprocedural myocardial injury is known to be a clinically relevant complication during cardiac surgery and percutaneous coronary intervention. Transcatheter aortic valve implantation is a novel treatment of patients with symptomatic aortic valve stenosis, in which the occurrence and clinical relevance of myocardial injury has been inadequately described. This study describes the predictors and prognostic value of myocardial injury in the setting of transcatheter aortic valve implantation (TAVI) with the Medtronic-CoreValve device. Preventive measures to reduce the amount of myocardial injury could be of positive influence for clinical outcome after TAVI. Future studies with larger patient populations are needed for further examination.

Conclusion: After transcatheter aortic valve implantation, serum levels of both CK-MB and cTnT increase, reflecting the occurrence of periprocedural myocardial injury. A longer procedural duration, the absence of β-blocker use, peripheral arterial disease, and a deeper prosthesis insertion are associated with myocardial injury. Together with preprocedural hospitalization and left ventricular mass, myocardial injury is an independent predictor for 30-day mortality after TAVI.9
Should We Recommend Oral Anticoagulation Therapy in Patients With Atrial Fibrillation Undergoing Coronary Artery Stenting With a High HAS-BLED Bleeding Risk Score?

Summary: Guidelines on the management on AF recommend the assessment of bleeding risk in patients before prescribing antithrombotic therapy using the HAS-BLED score. Patients with AF with an acute coronary syndrome and/or undergoing PCI represent a high-risk population. The “net clinical benefit” of triple therapy in patients with AF undergoing coronary artery stenting with high HAS-BLED score (ie, high risk of bleeding) is unknown. Most patients with AF undergoing coronary stenting are at high risk for major bleeding (HAS-BLED score ≥3). In patients with high HAS-BLED score (≥3), the nonuse of oral anticoagulation, age, and heart failure were the only independent predictors of death in the first year. Even in these patients, oral anticoagulation improves prognosis but with an increase in major bleeding; thus, management decisions in these high-risk patients should be individualized.

Conclusion: Most patients with atrial fibrillation undergoing percutaneous coronary intervention/stenting have a high risk for major bleeding (HAS-BLED score ≥3). Even in these patients, oral anticoagulation therapy improves prognosis in these patients (reduced mortality and major adverse cardiac events) with an increase in major bleeding.10

Percutaneous Coronary Intervention Versus Optimal Medical Therapy in Stable Coronary Artery Disease: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

Summary: The optimal management of stable coronary artery disease is controversial. With evolving percutaneous coronary intervention strategies and novel medical therapies, the best evidence-based treatment strategy is unknown. In this meta-analysis of 7182 individuals, percutaneous coronary intervention, as compared with optimal medical therapy, did not reduce the risk of mortality, cardiovascular death, nonfatal myocardial infarction, or revascularization. Revascularization with percutaneous coronary intervention was associated with greater angina relief, compared with optimal medical therapy alone. It is unknown whether the above results hold true in the contemporary era of third generation drug-eluting stents and contemporary medical management. Larger studies with sufficient power are required to detect contemporary differences in treatment strategies.

Conclusion: In this most rigorous and comprehensive analysis in patients with stable coronary artery disease, PCI, as compared with optimal medical therapy, did not reduce the risk of mortality, cardiovascular death, nonfatal myocardial infarction, or revascularization. PCI, however, provided a greater angina relief compared with optimal medical therapy alone, larger studies with sufficient power are required to prove this conclusively.11

Diagnostic Accuracy of Combined Intracoronary Pressure and Flow Velocity Information During Baseline Conditions: Adenosine-Free Assessment of Functional Coronary Lesion Severity

Summary: The use of intracoronary physiology is important for guidance of percutaneous coronary intervention. FFR, CFVR, or HSR may be used for this purpose, but they rely critically on a maximal hyperemic state. The use of potent vasodilators to achieve a maximal hyperemic state can be cumbersome in daily clinical practice. The BSR, a vasodilator-free parameter, results in similar diagnostic accuracy for myocardial ischemia as compared with FFR and CFVR. When the use of potent vasodilators is cumbersome in daily clinical practice, BSR may provide a useful tool for stenosis severity assessment.

Conclusion: Combined pressure and flow velocity measurements during baseline conditions may provide a useful tool for functional lesion severity assessment without the need for potent vasodilators.12

First Serial Assessment at 6 Months and 2 Years of the Second Generation of Absorb Everolimus-Eluting Bioresorbable Vascular Scaffold: A Multi-Imaging Modality Study

Summary: The first generation of fully bioresorbable everolimus-eluting scaffold exhibited late recoil at 6 months, with a late lumen loss intermediate between bare-metal stent and drug-eluting stent. The second generation of everolimus-eluting bioresorbable vascular scaffold, with changes in the design platform and manufacturing process, fully remediated this mechanical deficiency, and the scaffold area was found to be unchanged at 6 months by optical coherence tomography (OCT). At 12 month follow-up, analysis by OCT and ultrasound confirmed the persistence of an unchanged scaffold area without substantial loss in lumen area, whereas vasomotion became again detectable. From 6 to 24 months, late luminal loss increased from 0.16±0.18 to 0.27±0.20 mm on quantitative coronary angiography, with an increase in neointima of 0.68±0.43 mm² on OCT and 0.17±0.26 mm² on intravascular ultrasound. Struts still recognizable on OCT at 2 years showed 99% of neointimal coverage with optical and ultrasonic signs of bioresorption accompanied by increase in mean scaffold area compared with baseline (0.54±0.19 mm² on intravascular ultrasound, \( P = 0.003 \) and 0.77±1.33 mm² on OCT, \( P = 0.016 \)). The increase in scaffold area may be a prelude to the late lumen enlargement seen with the first generation. Two-year major adverse cardiac event rate was 6.8% without any scaffold thrombosis.

Conclusion: This serial analysis of the second generation of the everolimus-eluting bioresorbable vascular scaffold confirmed, at medium term, the safety and efficacy of the new device.15

Comparison of Resolute Zotarolimus-Eluting Stents and Sirolimus-Eluting Stents in Patients With De Novo Long Coronary Artery Lesions: A Randomized LONG-DES IV Trial

Summary: Although first-generation drug-eluting stents reduced neointimal hyperplasia and restenosis, these stents were associated with delayed arterial healing and vascular inflammation. This finding provided some mechanistic insight to understand the potential propensity for late thrombosis following first-generation drug-eluting stents, especially in high-risk lesions such as long coronary segments. Resolute zotarolimus-eluting stents, in which the antiproliferative agent is released over a long period of time from a novel 3-component durable polymer onto a low-profile, thin-strut, cobalt-alloy stent, were developed to further enhance the clinical safety and efficacy of stenting. These devices have shown promising clinical and angiographic outcomes in large registry and randomized trials. To date, there have been limited data comparing Resolute zotarolimus-eluting stents with the first-generation sirolimus-eluting stents in the treatment of long coronary artery disease segments. In this prospective, randomized trial involving patients with long coronary artery lesions, Resolute zotarolimus-eluting stents were noninferior to sirolimus-eluting stents as assessed by 9-month angiographic in-segment late luminal loss. Both stent platforms were associated with comparable low rates of clinical end points at 12 months, suggesting that both stents are equally effective at 1 year in the treatment of long coronary artery lesions.
Conclusion: For patients with de novo long coronary artery disease, resolute zotarolimus-eluting stent implantation showed noninferior angiographic outcomes as compared with sirolimus-eluting stent implantation. 14

Bivalirudin Versus Heparin Plus a Glycoprotein IIb/IIIa Inhibitor in Patients With Non–ST-Segment Elevation Myocardial Infarction Undergoing Percutaneous Coronary Intervention After Clopidogrel Pretreatment: Pooled Analysis from the ACUITY and ISAR-REACT 4 Trials

Summary: Patients with non–ST-segment elevation acute coronary syndrome undergoing percutaneous coronary intervention benefited from unfractionated heparin plus abciximab. Bivalirudin, a direct thrombin inhibitor, has improved outcomes of patients with a broad spectrum of acute coronary syndromes as compared with a regimen of heparin plus a glycoprotein IIb/IIIa inhibitor. This pooled analysis of patients in the ACUITY and ISAR-REACT 4 randomized trials, who underwent a percutaneous coronary intervention after clopidogrel treatment, showed a 46% reduction of the bleeding risk with bivalirudin compared with heparin plus a glycoprotein IIb/IIIa inhibitor. The risk of ischemic complications (a composite of death, myocardial infarction, or urgent target vessel revascularization) was not affected by bivalirudin. The treatment effect of bivalirudin was consistent across various subgroups and not dependent on the type of heparins (unfractionated heparin or enoxaparin) and glycoprotein IIb/IIIa inhibitor (abciximab versus eptifibatide versus tirofiban) assigned in the control group.

Conclusion: Net adverse clinical event rates were not significantly different between bivalirudin and heparin plus a glycoprotein IIb/IIIa inhibitor (GPI) in patients with non–ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention after clopidogrel pretreatment. Although no significant difference in efficacy was seen in terms of suppression of adverse ischemic events, bivalirudin was superior to heparin plus a GPI in terms of reducing bleeding events. 15

Refined Balloon Pulmonary Angioplasty for Inoperable Patients with Chronic Thromboembolic Pulmonary Hypertension

Summary: The efficacy of balloon pulmonary angioplasty (BPA) was previously reported in a small series of inoperable patients with chronic thromboembolic pulmonary hypertension, who have a poor prognosis. However, BPA has not been widely adopted owing to relatively less improvement and higher mortality compared with surgical pulmonary endarterectomy. We have refined the procedure of BPA by using intravascular ultrasound to provide more accurate estimates of the diameters of target pulmonary arteries. We performed BPA in a staged fashion over multiple procedures to reduce the risk of pulmonary reperfusion injury while still achieving an effective therapeutic result. Although there is a learning curve in performing this procedure, our refined approach to BPA may be a treatment option for patients with inoperable chronic thromboembolic pulmonary hypertension.

Conclusion: Our refined BPA procedure improves clinical status and hemodynamics of inoperable patients with chronic thromboembolic pulmonary hypertension, with a low mortality. A refined BPA procedure could be considered as a therapeutic approach for patients with inoperable chronic thromboembolic pulmonary hypertension. 16

Repeat Revascularization After Contemporary Percutaneous Coronary Intervention: An Evaluation of Staged, Target Lesion, and Other Unplanned Revascularization Procedures During the First Year

Summary: Restenosis and target lesion revascularization (TLR) occur less frequently since the introduction of drug-eluting stents. Nonetheless, repeat revascularization remains common after contemporary percutaneous coronary intervention (PCI). It remains unclear whether these repeat events represent TLR, staging of complex PCI procedures, or progressive atherosclerosis or unrecognized ischemia at previously untreated sites. In a large multicenter registry of contemporary PCI, repeat revascularization occurred in ≈12% of patients within 1 year. One fourth of these repeat procedures were staged or planned, generally occurring within the first 1 to 2 months after PCI, and there was significant variability in multivessel disease management between hospitals. The remaining 9% of repeat procedures were unplanned, with half involving TLR and half involving nontarget revascularization, and predictors of these 2 subgroups of repeat revascularization were remarkably different. The low early hazard for stent thrombosis decreases even further after the first month. These findings suggest that future efforts should concentrate as much on identifying ischemia-producing lesions and intensifying secondary prevention therapies as on the prevention of restenosis.

Conclusion: Among unselected patients undergoing PCI in the drug-eluting stent era, the incidence of repeat revascularization at 1 year is ≈12%. Among unplanned procedures, only half are performed for TLR. To achieve further improvements in PCI outcomes, future efforts should concentrate as much on identifying ischemia-producing lesions and intensifying secondary prevention therapies as on the prevention of restenosis. 17

A Randomized, Controlled Pilot Study of Autologous CD34+ Cell Therapy for Critical Limb Ischemia

Summary: Human CD34+ cells are well known as hematopoietic stem cells used for stem-cell transplants in patients who have bone marrow ablation by chemotherapy or radiation therapy. Preclinical studies in models of myocardial or limb ischemia show that local delivery of human CD34+ cells improves perfusion and function in ischemic tissue. In a double-blind, randomized, placebo-controlled, pilot clinical trial in patients with Rutherford class 4 and 5 critical limb ischemia, direct intramuscular injection of autologous CD34+ cells was associated with reductions in the frequency of amputations. The strategy of mobilizing and collecting autologous CD34+ cells in critical limb ischemia patients was shown to be feasible and was not associated with an adverse safety signal. Further study is warranted.

Conclusion: This study provides evidence that intramuscular administration of autologous CD34+ cells was safe in this patient population. Favorable trends toward reduced reduction of cell-treated versus control subjects were observed. These findings warrant further exploration in later-phase clinical trials. 18

References


