

## Circulation's Editors' Picks Most Important Articles Published Each Week, Part I

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 the Editors' Picks for each *Circulation* issue published during the first six months of 2012. (*Circulation*. 2013;127:e248-e256.)

### Supervised Exercise Versus Primary Stenting for Claudication Resulting From Aortoiliac Peripheral Artery Disease: Six-Month Outcomes From the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) Study

**Summary:** Claudication is the most common ischemic symptom of peripheral artery disease (PAD), affecting approximately 30% of these patients and limiting pain-free walking in over 2 million Americans. There are 3 treatments available to improve these symptoms, including claudication pharmacotherapy (cilostazol), supervised exercise, and endovascular revascularization, but little data comparing their relative efficacy, harm, and cost-effectiveness. There has been a marked rise in use of invasive (percutaneous) angioplasty and stenting, while PAD exercise programs remain mostly unavailable. The Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) study is an NHLBI-sponsored comparative effectiveness clinical investigation that randomly assigned 111 patients with aortoiliac PAD (the optimal anatomic site for stenting) to receive 1 of 3 treatments: optimal medical care (OMC, using home exercise and cilostazol), OMC plus supervised exercise (SE), or OMC plus stent revascularization (ST). At 6 months of follow-up (the primary end point), the improvement in peak walking time was greatest for SE, intermediate for ST, and least with OMC (mean change versus baseline 5.8±4.6, 3.7±4.9, and 1.2±2.6 minutes, respectively;  $P = 0.02$  for ST versus OMC; and  $P = 0.04$  for SE versus ST). Disease-specific quality of life improved with both SE and ST compared with OMC, but the improvement was greater with ST than SE. This study demonstrates that supervised exercise treatment results in superior treadmill walking performance than stent placement for patients with aortoiliac PAD. The longer-term impact of SE and ST on functional status and health economic outcomes in individuals with aortoiliac PAD will be assessed at 18 months.

**Conclusions:** SE results in superior treadmill walking performance than ST, even for those with aortoiliac peripheral artery disease. The contrast between better walking performance for SE and better patient-reported quality of life for ST warrants further study.<sup>1</sup>

### Determinants and Consequences of Renal Function Variations With Aldosterone Blocker Therapy in Heart Failure Patients After Myocardial Infarction: Insights From the

### Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study

**Summary:** In patients with left ventricular systolic dysfunction with or at high risk of heart failure in the postinfarction setting, adding eplerenone to standard care improves outcome even if these patients exhibit moderate reductions in estimated glomerular filtration rate, despite causing a slightly greater early reduction in estimated glomerular filtration rate compared with placebo. An early decline in estimated glomerular filtration rate by >20% was associated with worse cardiovascular outcomes independently of baseline estimated glomerular filtration rate and of the use of eplerenone, which nevertheless retained its prognostic benefits even under such circumstances. Eplerenone did not alter the usual long-term decline in renal function that occurs in this elderly population.

**Conclusions:** In patients with heart failure after acute myocardial infarction and receiving standard medical care, an early decline in eGFR is not uncommon and is associated with poor long-term outcome. Eplerenone induced a moderately more frequent early decline in eGFR, which did not affect its clinical benefit on cardiovascular outcomes.<sup>2</sup>

### Short-Term Outcomes of Acute Myocardial Infarction in Patients With Acute Kidney Injury: A Report From the National Cardiovascular Data Registry

**Summary:** Acute kidney injury (AKI) is a risk factor for long-term adverse outcomes, including acute myocardial infarction and death. We sought to explore the relationship between severity of AKI and in-hospital outcomes in the setting of acute myocardial infarction using the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry—Get With the Guidelines (GWTG), a nationwide sample of myocardial infarction patients admitted to 383 hospitals in the United States. AKI was defined using absolute changes in serum creatinine (SCr; peak SCr minus admission SCr) and categorized as no AKI (SCr change, <0.3 mg/dL), mild AKI (SCr change, 0.3–<0.5 mg/dL), moderate AKI (SCr change, 0.5–<1.0 mg/dL), and severe AKI (SCr change, ≥1.0 mg/dL). Overall, in-hospital mortality rates for those with mild, moderate, and severe AKI were 6.6%, 14.2%, and 31.8% compared with 2.1% without AKI and demonstrated similar increases in subgroups with or without prior chronic kidney disease, in-hospital shock, or coronary artery bypass graft surgery. In multivariable regression, the adjusted odds ratios for in-hospital death were 2.4 (95% confidence interval, 2.0–2.7), 4.5 (95% confidence interval, 3.9–5.1), and 12.6 (95% confidence interval, 11.1–14.3) for mild, moderate, and severe AKI compared with those without AKI. Although

patients with AKI were less likely to undergo early invasive care or to receive antiplatelet therapies, rates of major bleeding ranged from 8.4% (no AKI) to 32.7% (severe AKI). AKI is common, occurring in 16% of acute myocardial infarction patients. Furthermore, it is strongly associated with mortality and bleeding, underscoring the importance of efforts to identify risk factors and to prevent AKI in acute myocardial infarction care.

**Conclusion:** AKI is common and associated with mortality and bleeding, underscoring the importance of efforts to identify risk factors and to prevent AKI in acute myocardial infarction care.<sup>3</sup>

## Very Late Stent Thrombosis and Late Target Lesion Revascularization After Sirolimus-Eluting Stent Implantation: Five-Year Outcome of the j-Cypher Registry

**Summary:** There is a scarcity of long-term data from large-scale drug-eluting stent registries with a large enough sample size to evaluate low-frequency events such as stent thrombosis (ST). Five-year outcomes were evaluated in 12 812 consecutive patients undergoing sirolimus-eluting stent implantation in the j-Cypher registry. Cumulative incidence of definite ST was low (30 day, 0.3%; 1 year, 0.6%; and 5 years, 1.6%). However, late and very late ST continued to occur without attenuation up to 5 years after sirolimus-eluting stent implantation (0.26%/y). Cumulative incidence of target lesion revascularization within the first year was low (7.3%). However, late target lesion revascularization beyond 1 year also continued to occur without attenuation up to 5 years (2.2%/y). Independent risk factors of ST were completely different according to the timing of ST onset, suggesting the presence of different pathophysiological mechanisms of ST according to the timing of ST onset: acute coronary syndrome and target of proximal left anterior descending coronary artery for early ST; side-branch stenting, diabetes mellitus, and end-stage renal disease with or without hemodialysis for late ST; and current smoking and total stent length >28 mm for very late ST. Independent risk factors of late target lesion revascularization beyond 1 year were generally similar to those risk factors identified for early target lesion revascularization. Late adverse events such as very late ST and late target lesion revascularization are continuous hazards, lasting at least up to 5 years after implantation of the first-generation drug-eluting stents (sirolimus-eluting stents), which should be the targets for developing improved coronary stents.

**Conclusion:** Late adverse events such as very late ST and late target lesion revascularization are continuous hazards, lasting at least up to 5 years after implantation of the first-generation drug-eluting stents (sirolimus-eluting stents), which should be the targets for developing improved coronary stents.<sup>4</sup>

## Risk of Malignant Arrhythmias in Initially Symptomatic Patients With Wolff-Parkinson-White Syndrome: Results of a Prospective Long-Term Electrophysiological Follow-Up Study

**Summary:** Wolff-Parkinson-White syndrome decreases quality of life because of the lifetime risk of developing malignant arrhythmias and/or of dying suddenly. Specific risk factors to prevent sudden death are not yet established because no systematic long-term follow-up studies in large cohorts of patients looking at predictors of sudden death are currently available. This study presents follow-up data of 369 (23±12.5 years) untreated patients with Wolff-Parkinson-White syndrome and a first episode of supraventricular

tachycardia. The results demonstrated that at 5 years most patients (>90%) did not experience recurrent arrhythmia (168 patients) or had benign recurrences (172 patients). In contrast, a malignant presentation developed in 29 patients (7%) and hemodynamic collapse or cardiac arrest resulting from ventricular fibrillation occurred in 4 patients (1.4%), confirming that, in symptomatic patients with Wolff-Parkinson-White syndrome, the risk of malignant arrhythmia and/or sudden death is low. Multivariable predictors of malignant arrhythmias were only short accessory-pathway effective refractory period (<0.001) and atrial fibrillation after atrioventricular reentrant tachycardia (<0.001). These findings provide strong evidence that electrophysiological testing is useful for identifying initially symptomatic Wolff-Parkinson-White patients at higher risk in whom catheter ablation should be performed contextually with electrophysiological testing. Liberal indications for catheter ablation may be recommended for patients at lower risk, who represent the vast majority of symptomatic patients. Our experience for the first time demonstrates that, in initially symptomatic patients with Wolff-Parkinson-White syndrome, predictors of malignant arrhythmias are the same as for asymptomatic patients.

**Conclusions:** Symptomatic patients with Wolff-Parkinson-White syndrome generally have a good outcome, and predictors of malignant arrhythmias are similar to those reported for asymptomatic patients with ventricular preexcitation.<sup>5</sup>

## Cardiac Complications in Patients With Community-Acquired Pneumonia: Incidence, Timing, Risk Factors, and Association With Short-Term Mortality

**Summary:** Community-acquired pneumonia (CAP) is a common infection and a leading cause of morbidity and mortality that tends to occur in patients at high cardiovascular risk (ie, the elderly, smokers, diabetics, patients with chronic cardiac conditions). Community-acquired pneumonia can trigger acute cardiac complications. This study analyzed a prospective cohort of 2287 patients with community-acquired pneumonia in whom the 30-day incidence of cardiac complications was investigated. New or worsening heart failure, new or worsening arrhythmias, and myocardial infarction occurred in 20.8%, 11%, and 3% of inpatients and in 1.4%, 1%, and 0.1% of outpatients, respectively. Several patients had more than one of these conditions. Overall, cardiac complications (1 or more of the cardiac events above) were diagnosed in 27% and 2% of inpatients and outpatients, respectively. A majority of cardiac complications in both groups (89% inpatients and 75% outpatients) were diagnosed within the first week, more than half of them in the first 24 hours. Risk factors for cardiac complications included older age, nursing home residence, preexisting cardiovascular disease, and pneumonia severity. The occurrence of cardiac complications was associated with an adjusted 60% increase in risk of death at 30 days. Clinicians must recognize the burden of cardiac complications in patients with community-acquired pneumonia and exercise appropriate clinical alertness for their timely recognition. Rates of influenza and pneumococcal vaccination in groups of high cardiac risk need to be optimized. Further research to test risk stratification, prevention, and treatment strategies for incident cardiac complications in patients with community-acquired pneumonia may reduce the burden of death associated with this infection.

**Conclusions:** Incident cardiac complications are common in patients with community-acquired pneumonia and are associated with increased short-term mortality. Older age, nursing home residence, preexisting cardiovascular disease, and pneumonia severity are associated with their occurrence. Further studies are required to test risk

stratification and prevention and treatment strategies for cardiac complications in this population.<sup>6</sup>

## Metabolic Syndrome in Adolescence: Can It Be Predicted From Natal and Parental Profile? The Prediction of Metabolic Syndrome in Adolescence (PREMA) Study

**Summary:** The prevalence of metabolic syndrome in adolescence has gradually increased to approximately 10% in the United States and Western Europe. Because it is strongly associated with adult metabolic syndrome, subclinical atherosclerosis, and type 2 diabetes mellitus, the early detection of children at high risk may have potential clinical impact. After assessment of an overall urban population of 2361 white children and adolescents over a 10-year period, the present study showed that birth measurements and family history can be helpful for the practicing clinician in classifying children according to risk of metabolic syndrome in adolescence. The coexistence of low birth weight (<10th percentile) and small birth head circumference (<10th percentile) together with parental (in at least 1 parent) overweight or obesity was found to predict metabolic syndrome in adolescence with a sensitivity of 91% and a specificity of 98%. Thus, the coexistence of low birth weight, small head circumference, and parental history of overweight or obesity may be helpful in targeting children at risk for developing metabolic syndrome in adolescence who may benefit especially from early institution of heart-healthy behaviors.

**Conclusions:** The coexistence of low birth weight, small head circumference, and parental history of overweight or obesity may be useful for detection of children at risk of developing MetS in adolescence.<sup>7</sup>

## Association of Proton Pump Inhibitor Use on Cardiovascular Outcomes With Clopidogrel and Ticagrelor: Insights From the Platelet Inhibition and Patient Outcomes Trial

**Summary:** The clinical significance of the interaction between clopidogrel and proton pump inhibitors (PPIs) remains unclear. We examined the relationship between prior PPI use and 1-year cardiovascular events in patients with acute coronary syndrome randomized to clopidogrel or ticagrelor in a prespecified, nonrandomized subgroup analysis of the Platelet Inhibition and Patient Outcomes (PLATO) trial. The use of a PPI was independently associated with a higher rate of cardiovascular events in patients with acute coronary syndrome receiving clopidogrel; however, a similar association was observed between cardiovascular events and PPI use during ticagrelor treatment and with other non-PPI gastrointestinal treatment. Therefore, in the PLATO trial, the association between PPI use and adverse events may be due to confounding, with PPI use more of a marker for, than a cause of, higher rates of cardiovascular events. With recognition of the inherent limitations of nonrandomized comparisons, our findings do not support the need to avoid concomitant PPI use with clopidogrel or ticagrelor.

**Conclusions:** The use of a PPI was independently associated with a higher rate of cardiovascular events in patients with acute coronary syndrome receiving clopidogrel. However, a similar association was observed between cardiovascular events and PPI use during ticagrelor treatment and with other non-PPI gastrointestinal treatment. Therefore, in the PLATO trial, the association between PPI use and adverse events may be due to confounding, with PPI use more of a marker for, than a cause of, higher rates of cardiovascular events.<sup>8</sup>

## Cost-Effectiveness of Transcatheter Aortic Valve Replacement Compared With Standard Care Among Inoperable Patients With Severe Aortic Stenosis: Results From the Placement of Aortic Transcatheter Valves (PARTNER) Trial (Cohort B)

**Summary:** In patients deemed ineligible for cardiac surgery, the Placement of Aortic Transcatheter Valves (PARTNER) trial recently demonstrated a 20% absolute survival difference at 12 months when transcatheter aortic valve replacement (TAVR) was compared with standard nonsurgical therapy. The costs and cost effectiveness of this clinical strategy, which would typically be applied to elderly patients, have not been evaluated previously. Empirical data regarding survival, quality of life, medical resource use, and hospital costs were collected during the PARTNER trial and used to project life expectancy, quality-adjusted life expectancy, and lifetime medical care costs. Average costs for the initial TAVR procedure and hospital stay were \$42 806 and \$78 542, respectively, but follow-up costs through 12 months were approximately \$24 000 lower per patient with TAVR because of higher rates of cardiovascular hospitalization with standard therapy. We projected that over a patient's lifetime, TAVR would increase life expectancy by 1.9 years (1.6 years after application of a standard 3% discount rate to future costs and benefits) at a discounted lifetime incremental cost of \$79 837. The incremental cost-effectiveness ratio for TAVR was thus estimated at \$50 200 per year of life gained, or \$61 889 per quality-adjusted life-year gained, values generally considered acceptable within the context of the US healthcare system. These estimates were only slightly altered when assumptions about future costs and survival were varied within plausible ranges.

**Conclusions:** For patients with severe aortic stenosis who are not candidates for surgery, TAVR increases life expectancy at an incremental cost per life-year gained well within accepted values for commonly used cardiovascular technologies.<sup>9</sup>

## Prognostic Values of Clockwise and Counterclockwise Rotation for Cardiovascular Mortality in Japanese Subjects: A 24-Year Follow-Up of the National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged, 1980 to 2004 (NIPPON DATA80)

**Summary:** The transitional zone is related to the direction of the QRS axis in the horizontal plane. Although clockwise rotation and counterclockwise rotation are distinct findings on ECG, their clinical values have not been well studied, and their prognostic significance has been studied rarely. In this study, we assessed the independent prognostic values of clockwise rotation and counterclockwise rotation for mortality due to cardiovascular disease and its subtypes in a large cohort of participants obtained from randomly selected health districts in Japan. We found a significant positive association of clockwise rotation and a significant inverse association of counterclockwise rotation with cardiovascular disease mortality in men and in men and women combined, independent of confounding factors including other ECG changes. Although the mechanisms for these associations are not clear at present, in clinical practice, we may need to pay attention to these ECG changes that have been ignored for more than a century.

**Conclusions:** We found a significant positive association of clockwise rotation and a significant inverse association of counterclockwise



rotation with CVD mortality in men and in men and women combined, independent of confounding factors including other ECG changes.<sup>10</sup>

## Preoperative Serum Brain Natriuretic Peptide and Risk of Acute Kidney Injury After Cardiac Surgery

**Summary:** Cardiovascular disease and heart failure are highly prevalent among those who undergo cardiac surgery, contributing to hemodynamic stress that may be poorly characterized by clinical history. Consequently, natriuretic peptide biomarkers that better characterize this underlying physiology have become well established in the diagnosis and management of patients with heart failure. In this study, 1139 adults who underwent cardiac surgery were evaluated from 6 centers to establish whether preoperative brain natriuretic peptide (BNP) levels predict postoperative acute kidney injury (AKI; defined by Acute Kidney Injury Network definitions; at least mild AKI was a  $>0.3$ -mg/dL [ $26 \mu\text{mol/L}$ ] or 50% rise in creatinine, and severe AKI was either a doubling of creatinine or the requirement of acute renal replacement therapy). In this high-risk cohort, AKI was common (at least mild AKI,  $n = 407$  [36%]; severe AKI,  $n = 58$  [5.1%]). After adjustment for different preoperative characteristics, preoperative BNP was a strong and independent predictor of mild and severe AKI. Compared with the lowest BNP quintile, the highest quintile had significantly higher risk of at least mild AKI (risk ratio, 1.87) and severe AKI (risk ratio, 3.17). After adjustment for clinical predictors, the addition of BNP improved the area under the curve to predict at least mild AKI and severe AKI. Compared with clinical parameters alone, BNP also improved risk prediction of AKI cases into lower and higher risk. Preoperative BNP level is associated with postoperative AKI in high-risk patients undergoing cardiac surgery and may be a valuable component of future efforts to improve preoperative risk stratification among surgical candidates.

**Conclusions:** Preoperative BNP level is associated with postoperative AKI in high-risk patients undergoing cardiac surgery. If confirmed in other types of patients and surgeries, preoperative BNP may be a valuable component of future efforts to improve preoperative risk stratification and discrimination among surgical candidates.<sup>11</sup>

## Predictors of Long-Term Survival After Coronary Artery Bypass Grafting Surgery: Results From the Society of Thoracic Surgeons Adult Cardiac Surgery Database (The ASCERT Study)

**Summary:** Most survival prediction models for coronary artery bypass grafting surgery are limited to in-hospital or 30-day end points. However, particularly as short-term mortality rates decrease, it is increasingly important for providers, patients, payers, and other stakeholders to better understand the likelihood of long-term survival. We linked broadly representative, real-world clinical data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database and vital status from Medicare claims data to construct a robust, long-term coronary artery bypass grafting surgery survival prediction model. This study included 348 341 patients aged  $\geq 65$  years who underwent isolated coronary artery bypass grafting surgery between 2002 and 2007. Because of the large study cohort and clinical predictors, model performance is excellent. On the basis of the results of this study, late outcomes for patients who initially survive coronary artery bypass grafting surgery are less affected by traditional predictors of early mortality such as emergency status, shock, and reoperation. Conversely, late mortality is increasingly associated with chronic debilitating diseases such as insulin-dependent diabetes mellitus and dialysis-dependent renal failure and behaviors such as smoking. This is valuable information for shared decision making,

comparative effectiveness research, quality improvement, patient counseling, and provider profiling.

**Conclusions:** Using clinical registry data and longitudinal claims data, we developed a long-term survival prediction model for isolated coronary artery bypass grafting. This provides valuable information for shared decision making, comparative effectiveness research, quality improvement, and provider profiling.<sup>12</sup>

## Mitral Valve Prolapse With Mid-Late Systolic Mitral Regurgitation: Pitfalls of Evaluation and Clinical Outcome Compared With Holosystolic Regurgitation

**Summary:** Mitral valve prolapse (MVP) is frequent, and its outcome is highly dependent on the severity of mitral regurgitation (MR) it causes. MR of MVP is predominant and often is limited to the mid or later part of systole, but the impact of such MR timing on MR assessment, on the volume overload it causes, and on outcome is unknown. To address this issue, we prospectively quantified MR in patients with MVP and midlate systolic MR and compared them with matched patients with MVP and holosystolic MR. The study shows that midlate systolic MR can be misleading because it presents with similar jet area, velocity, and effective regurgitant orifice but has less regurgitant volume because of its shorter duration. Furthermore, midlate systolic MR causes less volume overload with smaller left ventricles and atria, lower pulmonary pressure, and less frequent flow reversal in the pulmonary veins. In regard to outcome, midlate systolic MR was benign in comparison to holosystolic MR, with much fewer cardiac events during follow-up, independently of any baseline characteristics. This event rate was independently linked to the regurgitant volume (not orifice), which is smaller in midlate systolic MR. Therefore, for clinical management and surgical referral of patients with MVP, clinicians should carefully take into account the timing and consequences of MR.

**Conclusions:** MR of mitral valve prolapse that is purely midlate systolic causes more benign consequences and outcomes than holosystolic MR. Assessment may be misleading because jet area and ERO by flow convergence appear similar to those of holosystolic MR. However, shorter MR yields lower regurgitant volume, consequences, and benign outcomes. Instantaneous ERO by flow convergence should be interpreted in context, and in midlate systolic MR, regurgitant volume provides information more reflective of MR severity. Therefore, for clinical management and surgical referral, clinicians should carefully take into account the timing and consequences of MR.<sup>13</sup>

## Impact of Changes in Resuscitation Practice on Survival and Neurological Outcome After Out-of-Hospital Cardiac Arrest Resulting From Nonshockable Arrhythmias

**Summary:** Although the overall incidence of out-of-hospital cardiac arrest has not changed in recent years, reports indicate that the proportion of arrests caused by shockable rhythms is diminishing. The vast majority of out-of-hospital cardiac arrests are now attributable to nonshockable arrhythmias—asystole and pulseless electric activity—from which survival is especially poor and for which a treatment strategy that improves outcome has yet to be identified. In a number of communities, adoption of recent changes in cardiopulmonary resuscitation guidelines that prioritized the time devoted to chest compressions during resuscitation was associated with improved survival among patients with out-of-hospital cardiac arrest resulting from shockable rhythms. In this cohort investigation, we found that implementation of these

guidelines was also associated with a significant improvement in short- and long-term survival and with favorable neurological outcome, specifically among patients with nonshockable out-of-hospital cardiac arrest. After multivariable adjustment, the odds ratio of 1-year survival from nonshockable out-of-hospital cardiac arrest on implementation of these guideline changes compared with beforehand was 1.85 (95% confidence interval, 1.29–2.66). Comparably significant improvements were observed in return of spontaneous circulation, hospital admission rates, survival to hospital discharge, favorable neurological status at hospital discharge, and 1-month survival. These improvements could not be merely attributed to temporal trends within the study periods but appeared to coincide with the change in the cardiopulmonary resuscitation protocol itself. Our findings suggest that increasing the basic provision of cardiopulmonary resuscitation has the potential to improve outcomes for all victims of cardiac arrest and are of particular relevance and importance because of the changing epidemiology of the condition.

**Conclusions:** Outcomes from OHCA resulting from nonshockable rhythms, although poor by comparison with shockable rhythm presentations, improved significantly after implementation of resuscitation guideline changes, suggesting their potential to benefit all presentations of OHCA.<sup>14</sup>

## Comparative Outcomes for Patients Who Do and Do Not Undergo Percutaneous Coronary Intervention for Stable Coronary Artery Disease in New York

**Summary:** Little is known about the relative frequencies of different treatments that patients receive after being diagnosed with stable coronary artery disease and what the comparative outcomes are for routine medical treatment (RMT) versus percutaneous coronary intervention (PCI) with RMT for patients not in randomized controlled trials. Consequently, patients with stable coronary artery disease undergoing cardiac catheterization in New York State between 2003 and 2008 were followed up to determine the treatment they received. Patients receiving RMT and patients receiving PCI with RMT were propensity matched through the use of 20 factors that could have a bearing on outcomes. The resulting cohort of 933 matched pairs was used to compare mortality/myocardial infarction (MI), mortality, MI, and subsequent revascularization rates. Most of the patients (89%) underwent PCI. PCI/RMT patients had significantly lower adverse outcome rates at 4 years for mortality/MI (16.5% versus 21.2%;  $P = 0.003$ ), mortality (10.2% versus 14.5%;  $P = 0.02$ ), MI (8.0% versus 11.3%;  $P = 0.007$ ), and subsequent revascularization (24.1% versus 29.1%;  $P = 0.005$ ). Adjusted RMT/PCI hazard ratios were 1.49 (95% confidence interval, 1.16–1.93) for mortality/MI and 1.46 (95% confidence interval, 1.08–1.97) for mortality. There were no differences in treatment outcomes for patients <65 years of age or for patients with single-vessel disease. Most patients with stable coronary artery disease in New York undergoing catheterization between 2003 and 2008 received PCI, and those patients who received PCI experienced lower mortality, mortality/MI, and revascularization rates. The reasons for this finding need to be better understood, including the possible role of low medication adherence rates that have been found in other studies.

**Conclusions:** Most patients with stable coronary artery disease in New York undergoing catheterization between 2003 and 2008 received PCI. Patients who received PCI experienced lower mortality, mortality/MI, and revascularization rates. The reasons for this finding need to be better understood, including the possible role of low medication adherence rates that have been found in other studies.<sup>15</sup>

## Determinants of Residual Risk in Secondary Prevention Patients Treated With High-Versus Low-Dose Statin Therapy: The Treating to New Targets (TNT) Study

**Summary:** Cardiovascular risk among statin-treated individuals remains high and has been called residual risk, but the mechanisms underlying this residual risk are uncertain. Hence, we aimed to identify determinants of this risk above and beyond lipid-related risk factors in a secondary prevention population that achieved low low-density lipoprotein cholesterol targets. The study population comprised 9251 coronary patients with low-density lipoprotein cholesterol <130 mg/dL randomized to double-blind atorvastatin 10 or 80 mg/d in the Treating to New Targets (TNT) study who had complete on-treatment 1-year lipid data. Median follow-up was 4.9 years. The primary end point was major cardiovascular events ( $n = 729$ ): coronary death, nonfatal myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke. Multivariable determinants of increased risk were older age, increased body mass index, male sex, hypertension, diabetes mellitus, baseline apolipoprotein B and blood urea nitrogen, current smoking, prior cardiovascular disease, and calcium channel blocker use. Determinants of decreased risk were high-dose statin, aspirin use, and baseline apolipoprotein A-I. These known baseline clinical and lipid-related variables performed moderately well in discriminating future cases from noncases. On-treatment 1-year levels of lipids and apolipoproteins were not selected into the multivariable model because they were not associated with risk after baseline apolipoproteins and clinical risk factors were taken into account. In sum, residual risk among statin-allocated coronary patients was related to baseline lipid-related and nonlipid risk factors. Thus, a multifaceted secondary prevention approach targeting modifiable risk factors should be underscored as the cornerstone of optimal residual risk assessment and prevention.

**Conclusions:** Determinants of residual risk in statin-treated secondary prevention patients included lipid-related and nonlipid factors such as baseline apolipoproteins, increased body mass index, smoking, hypertension, and diabetes mellitus. A multifaceted prevention approach should be underscored to address this risk.<sup>16</sup>

## Long-Term Outcomes of Mechanical Valve Replacement in Patients With Atrial Fibrillation: Impact of the Maze Procedure

**Summary:** It has remained controversial whether the concomitant maze procedure may improve long-term clinical outcomes in chronic atrial fibrillation patients who undergo mechanical heart valve replacement. In the present study, a retrospective analysis was carried out on 569 consecutive patients with atrial fibrillation-associated valvular heart disease who underwent mechanical valve replacement. Of them, 317 patients concomitantly underwent the maze procedure and 252 underwent mechanical valve replacement alone. After adjustment for differences in baseline risk profiles between the 2 groups of patients, patients who had undergone the maze procedure were at similar risks of death (hazard ratio, 1.15; 95% confidence interval, 0.65–2.03;  $P = 0.63$ ) but were at a significantly lower risk of thromboembolic events (hazard ratio, 0.29; 95% confidence interval, 0.12–0.73;  $P = 0.008$ ) compared with those who underwent valve replacement alone at a median follow-up of 63.6 months (range, 0.2–149.9 months). The effect of superior event-free survival by the concomitant maze procedure was notable in a low-risk EuroSCORE (0–3) subgroup ( $P = 0.049$ ), but it was insignificant in a high-risk EuroSCORE ( $\geq 4$ ) subgroup ( $P = 0.65$ ). Furthermore, the combination of the maze procedure resulted in superior left ventricular ( $P < 0.001$ ) and tricuspid valvular functions ( $P < 0.001$ ) compared

with valve replacement alone on echocardiographic assessments performed at a median of 52.7 months (range, 6.0–146.8 months) after surgery. These findings suggest that the combination of the maze procedure is a reasonable option for this population, especially for those with low risks of surgery. Further prospective, randomized studies are needed to confirm the findings of this study.

**Conclusion:** Compared with valve replacement alone, the addition of the maze procedure was associated with a reduction in thromboembolic complications and improvements in hemodynamic performance in patients undergoing mechanical valve replacement, particularly in those with low risk of surgery.<sup>17</sup>

## Metabolite Profiling Identifies Pathways Associated With Metabolic Risk in Humans

**Summary:** Although metabolic risk factors are known to cluster in individuals who are prone to developing diabetes mellitus and cardiovascular disease, the underlying biological mechanisms remain poorly understood. To acquire a more detailed understanding of the biochemical pathways, we applied high-throughput metabolite profiling to samples from 1761 individuals from 2 large, well-characterized clinical cohorts. We observed that the presence of metabolic risk factors (including obesity, insulin resistance, high blood pressure, and dyslipidemia) was significantly associated with variation in select metabolites, including branched-chain amino acids, other hydrophobic amino acids, tryptophan breakdown products, and nucleotide metabolites. We observed particularly strong associations of insulin resistance traits with decreased glutamine and increased glutamate. We followed up these findings in experimental models and demonstrated that glutamine administration in mice resulted in both increased glucose tolerance and decreased blood pressure. Taken together, our clinical and experimental data highlight the glutamine-glutamate metabolic pathway as a potential target for interventions aimed at attenuating metabolic risk in humans. Furthermore, by demonstrating the feasibility and utility of biochemical profiling in large clinical samples, we anticipate that our data could serve as a resource for future studies of the human metabolome and its relevance to cardiovascular and metabolic diseases. Because metabolites represent intermediate traits that may play functional roles (either adaptive or maladaptive) in disease pathogenesis, future applications of metabolomics technology can provide additional insights into the mechanisms by which established risk factors are associated with clinically important outcomes.

**Conclusions:** Biochemical profiling identified circulating metabolites not previously associated with metabolic traits. Experimentally interrogating one of these pathways demonstrated that excess glutamine relative to glutamate, resulting from exogenous administration, is associated with reduced metabolic risk in mice.<sup>18</sup>

## Risk of Arrhythmia and Sudden Death in Patients With Asymptomatic Preexcitation: A Meta-Analysis

**Summary:** The incidence of sudden cardiac death (SCD) and the management of this risk in patients with asymptomatic preexcitation remain controversial. We performed a meta-analysis of 20 studies reporting on asymptomatic patients ( $n = 1869$ ) with preexcitation who did not undergo ablation (11 722 person-years of follow-up). A total of 10 SCDs were reported with 9 SCDs from studies originating from Italy. The risk of SCD is estimated at 1.25 per 1000 person-years (95% confidence interval, 0.57–2.19). The risk of supraventricular tachycardia was 16 (95% confidence interval, 10–24) events per 1000 person-years of follow-up. The risk of SCD was statistically significantly lower in the non-Italian compared with the Italian studies ( $P = 0.0044$ ). Children had a numerically higher SCD event rate ( $P = 0.07$ ) and supraventricular tachycardia event rate ( $P = 0.38$ ) compared with adults. Therefore, a

higher index of suspicion for arrhythmia is warranted, and careful follow-up with monitoring for arrhythmia in children seems prudent. When considering management options in patients with asymptomatic preexcitation, a carefully informed patient (or parent) needs to choose between the risk of SCD and the success and complication rates associated with electrophysiological study and ablation. The evolution of the clinical status from an asymptomatic state to symptoms likely portends a higher risk for SCD, and these patients should seek medical review.

**Conclusion:** The low incidence of SCD and low risk of supraventricular tachycardia argue against routine invasive management in most asymptomatic patients with the Wolff-Parkinson-White ECG pattern.<sup>19</sup>

## Prevalence of Kawasaki Disease in Young Adults With Suspected Myocardial Ischemia

**Summary:** Kawasaki disease (KD) is an acute, self-limited vasculitis of unknown origin that occurs most commonly in young children. Diagnosis depends on recognition of the clinical syndrome because no diagnostic test exists. Thus, the prevalence of individuals with missed KD is unknown. Up to 25% of patients with untreated KD and 5% of those treated with intravenous immunoglobulin will develop coronary artery aneurysms. Persistent aneurysms may remain silent until later in life when myocardial ischemia can occur. The impact of coronary aneurysms and coronary artery damage caused by KD and their prevalence among young adults presenting with symptoms of cardiac ischemia have not previously been studied. This study systematically evaluated a population of young adults undergoing coronary angiography at 4 hospitals in San Diego, CA, to estimate the prevalence of antecedent KD as a potential cause. We found that  $\approx 5\%$  of young adults who undergo coronary angiography to evaluate symptoms for myocardial ischemia may have coronary artery aneurysms with KD as the underlying cause. Thus, coronary sequelae of KD are responsible for a small but important percentage of young adults who present with myocardial ischemia. As more children with a history of KD reach adulthood, adult cardiologists are likely to see increasing numbers of patients with acute and subacute presentations of coronary sequelae of KD. Cardiologists should be aware of this special subset of patients who may benefit from medical and invasive management strategies that differ from those used to treat atherosclerotic coronary artery disease.

**Conclusions:** Coronary sequelae of KD are present in 5% of young adults evaluated by angiography for myocardial ischemia. Cardiologists should be aware of this special subset of patients who may benefit from medical and invasive management strategies that differ from the strategies used to treat atherosclerotic coronary artery disease.<sup>20</sup>

## Pacemaker Therapy in Patients With Neurally Mediated Syncope and Documented Asystole: Third International Study on Syncope of Uncertain Etiology (ISSUE-3): A Randomized Trial

**Summary:** We evaluated a treatment strategy based on early application of the implantable loop recorder in patients  $\geq 40$  years with a certain or highly likely diagnosis of neurally mediated syncope based on clinical evaluation. In our patients, therapy was delayed until documentation of a spontaneous prolonged (mean, 11 s) asystolic event was obtained by implantable loop recorder. In this highly selected population, which we estimated to be 9% of neurally mediated syncope patients referred for evaluation, cardiac-pacing therapy is effective in reducing syncopal recurrences. We found that  $\approx 1$  of 3



pacemaker patients will benefit from pacing therapy within the subsequent 2 years.

**Conclusions:** Dual-chamber permanent pacing is effective in reducing recurrence of syncope in patients  $\geq 40$  years with severe asystolic neurally mediated syncope. The observed 32% absolute and 57% relative reduction in syncope recurrence support this invasive treatment for the relatively benign neurally mediated syncope.<sup>21</sup>

## Human Genome-Wide Association and Mouse Knockout Approaches Identify Platelet Supervillin as an Inhibitor of Thrombus Formation Under Shear Stress

**Summary:** Platelets play a central role in ischemic arterial vascular disease, and antiplatelet therapies are mainstays of treatment. The findings in this study identify a novel platelet protein, supervillin, which functions to dampen the early formation of platelet thrombi under high shear stress. Although these results will not alter current management of vascular disease, there are potential clinical implications. Supervillin is an interaction hub for many proteins that regulate cell adhesion and contractility. Drug targeting of supervillin or one of its binding partners in a manner that would decrease platelet adhesion under high shear forces may have antithrombotic benefit for arterial vascular diseases such as myocardial infarction and stroke. This benefit could be especially pronounced in African Americans, who suffer disproportionately from cardiovascular disease. Conversely, drugs that knowingly or unknowingly block supervillin function in platelets could have untoward effects of promoting thrombosis. The shear dependence of the supervillin effect presents an opportunity to develop therapies that differentially affect arterial and venous thrombosis by inhibiting platelet thrombus formation under high shear settings (eg, acute coronary syndromes or percutaneous coronary intervention) without altering the normal hemostatic function of platelets in low-shear veins or microcirculation. Finally, single-nucleotide polymorphisms strongly linked to the causative supervillin variant may be useful as a biomarker for risk of thrombosis or hemorrhage.

**Conclusions:** We show for the first time that (1) platelets contain supervillin; (2) platelet thrombus formation in the PFA-100 is associated with human SVIL variants and low SVIL expression; and (3) murine platelets lacking supervillin exhibit enhanced platelet thrombus formation at high shear stress. These data are consistent with an inhibitory role for supervillin in platelet adhesion and arterial thrombosis.<sup>22</sup>

## Off-Pump Coronary Artery Bypass Surgery Is Associated With Worse Arterial and Saphenous Vein Graft Patency and Less Effective Revascularization: Results From the Veterans Affairs Randomized On/Off Bypass (ROOBY) Trial

**Summary:** The Department of Veterans Affairs Randomized On/Off Bypass (ROOBY) trial is the largest trial to date to compare angiographic outcomes in off-pump versus on-pump coronary artery bypass graft (CABG) surgery. One-year follow-up angiography was obtained in 685 off-pump and 685 on-pump patients. Angiograms were analyzed in a blinded manner by intention to treat. Grafts were classified as patent (open versus closed) and were assessed for quality with the FitzGibbon classification system. Every patient was also assessed for effective revascularization, which was defined as follows: All 3 major coronary territories with significant disease

were revascularized by a FitzGibbon A-quality graft to the major diseased artery, the graft was placed in proper position relative to native disease, and there were no new postanastomotic lesions. Effective revascularization has not been reported previously in a study of post-CABG graft patency. This study is the first randomized study of off-pump versus on-pump CABG to indicate that both graft patency and effective revascularization are clearly worse with off-pump CABG. FitzGibbon graft patency was worse for arterial, left internal mammary artery pedicle, and vein graft conduits. In addition, every coronary territory was revascularized less effectively with off-pump CABG. At the 1-year follow-up angiography,  $\approx 50\%$  of off-pump CABG patients had at least 1 coronary territory that was at risk for ischemia. Those patients with less effective revascularization had significantly more adverse cardiac events by 1 year after CABG.

**Conclusions:** Off-pump CABG resulted in significantly lower FitzGibbon A patency for arterial and saphenous vein graft conduits and less effective revascularization than on-pump CABG. At 1 year, patients with less effective revascularization had higher adverse event rates.<sup>23</sup>

## Remote Monitoring Reduces Healthcare Use and Improves Quality of Care in Heart Failure Patients With Implantable Defibrillators: The Evolution of Management Strategies of Heart Failure Patients With Implantable Defibrillators (EVOLVO) Study

**Summary:** Heart failure patients with implantable defibrillators often visit the hospital for unscheduled examinations, placing a great burden on healthcare providers. Device manufacturers offer a technology for remote defibrillator monitoring with the purpose of allowing physicians to remotely access patients' data and reducing unnecessary routine and interim visits. The Evolution of Management Strategies of Heart Failure Patients With Implantable Defibrillators (EVOLVO) study was a multicenter randomized trial designed to assess whether remote management can reduce emergency healthcare use in heart failure patients implanted with defibrillators endowed with specific diagnostic features compared with standard management consisting of scheduled in-office visits and patient response to audible alerts. Over 16 months, the rate of emergency department or urgent in-office visits for heart failure, arrhythmias, or device-related events decreased by 35% and total healthcare visits were 21% less frequent with remote monitoring. Moreover, with remote monitoring system, the time from an alert condition to review of the data was reduced from 24.8 to 1.4 days, and the change in patients' quality of life was more favorable. These findings may have important implications. Indeed, our study confirmed that remote management of heart failure patients implanted with defibrillators allows timely notification of potentially critical situations. Moreover, it has the effect of shifting healthcare visits from the emergency department to the clinic and increasing the appropriateness of in-office visits, thereby reducing costs and the burden on the healthcare system. Thus, compared with the standard follow-up through in-office visits and audible alerts, remote monitoring results in increased efficiency for healthcare providers and improved quality of care for patients.

**Conclusions:** Remote monitoring reduces emergency department/urgent in-office visits and, in general, total healthcare use in patients with ICD or defibrillators for resynchronization therapy. Compared with standard follow-up through in-office visits and audible ICD alerts, remote monitoring results in increased efficiency for healthcare providers and improved quality of care for patients.<sup>24</sup>

## The United States Registry for Fibromuscular Dysplasia: Results in the First 447 Patients

**Summary:** Fibromuscular dysplasia (FMD) is a nonatherosclerotic, noninflammatory vascular disease that primarily affects women in the prime of their life. There is an average delay of 5 years from the onset of symptoms until the diagnosis of FMD is made. FMD most commonly affects the renal, carotid, and vertebral arteries but may occur in virtually every artery of the body. Multivessel involvement is common. The most common clinical manifestations of FMD are hypertension, headaches, pulsatile tinnitus, and dizziness. However, 1 in 5 patients experience a dissection, and 17% have one or more aneurysms. A cerebrovascular event including transient ischemic attack, stroke, and/or amaurosis fugax occur in 1 of every 4 patients with FMD. The presence of a carotid bruit in a patient under 60 or an epigastric bruit in a patient with hypertension should alert the clinician to the possible diagnosis of FMD. Earlier diagnosis may prevent the consequences of poorly controlled hypertension, and allow for the identification of aneurysms and dissections and their appropriate treatment.

**Conclusions:** In this registry, FMD occurred primarily in middle-aged women, although it presents across the lifespan. Cerebrovascular FMD occurred as frequently as renal FMD. Although a significant proportion of FMD patients may present with a serious vascular event, many present with nonspecific symptoms and a subsequent delay in diagnosis.<sup>25</sup>

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