Randomized Trial of Atopaxar in the Treatment of Patients With Coronary Artery Disease: The Lessons From Antagonizing the Cellular Effect of Thrombin–Coronary Artery Disease Trial

Summary—Thrombin is a key mediator of platelet activation in acute coronary syndromes. Atopaxar is a reversible protease-activated receptor antagonist that interferes with thrombin mediated platelet effects. The phase II Lessons From Antagonizing the Cellular Effect of Thrombin–Coronary Artery Disease (LANCELOT–CAD) trial examined the safety and tolerability of prolonged therapy with atopaxar in subjects with CAD. Seven hundred and twenty subjects were randomized in a double-blind fashion to 1 of 3 dosing regimens of atopaxar (50, 100, or 200 mg daily) or matching placebo for 24 weeks and followed up for an additional 4 weeks. Overall bleeding rates tended to be higher with atopaxar compared with placebo by Clopidogrel in Unstable Angina to Prevent Recurrent Events and Thrombolysis in Myocardial Infarction criteria without a difference in major bleeding by either category. All atopaxar regimens achieved high levels of platelet inhibition with dose-dependent rapid onset and offset. Major adverse cardiac events tended to be less frequent with atopaxar, but the trial was not powered for clinical events, and statistically significant differences were not observed. Atopaxar was generally well tolerated, but QTc prolongations and liver transaminase elevations without clinical sequelae were observed with higher-dose atopaxar. Although these data are encouraging, larger-scale trials are needed to determine the clinical efficacy and safety of protease-activated receptor-1 antagonist in patients with atherosclerotic vascular disease.

Conclusions—In this dose-ranging study of patients with CAD, treatment with atopaxar resulted in platelet inhibition, more minor bleeding, and numerically but not statistically fewer ischemic events. Larger-scale trials are needed to determine whether these patterns translate into clinically meaningful effects.

Cell Therapy in Chagas Cardiomyopathy (Chagas Arm of the Multicenter Randomized Trial of Cell Therapy in Cardiopathies Study): A Multicenter Randomized Trial

Summary—Heart failure is a common cause of death in patients with chronic chagasic cardiomyopathy. Current therapies are limited and, with the exception of heart transplantation, only delay disease progression. Cell therapy using bone marrow–derived cells has been a promising (albeit inconsistent) approach to the treatment of cardiovascular diseases. Experimental evidence in animal models and feasibility studies in patients with chronic chagasic cardiomyopathy have suggested that bone marrow mononuclear cell transplantation may improve cardiac function. This study reports the results of a multicenter, double-blind, randomized, placebo-controlled trial evaluating the efficacy of bone marrow mononuclear cells on left ventricular ejection fraction in 183 patients with chronic chagasic cardiomyopathy. Although both the placebo and cell-therapy groups showed a significant increase in left ventricular ejection fraction at 6 and 12 months of follow-up, this study failed to document a significant difference in change in left ventricular ejection fraction between the 2 groups. Intracoronary injection of bone marrow mononuclear cells was not associated with adverse clinical events. We conclude that with the methods used, no additional benefit of intracoronary mononuclear cell injection was found in patients with chronic chagasic cardiomyopathy and a left ventricular ejection fraction <35%. Nonetheless, cell-based therapies may still hold promise for chronic chagasic cardiomyopathy patients. Larger clinical trials focusing on hard clinical end points, new cell types, methods of delivery, dosage schemes, and disease stages are warranted to further test the efficacy of this novel therapeutic approach.

Conclusions—Intracoronary injection of autologous BMNCs does not improve left ventricular function or quality of life in patients with chronic chagasic cardiomyopathy.

Ischemic Preconditioning for Prevention of Contrast Medium–Induced Nephropathy: Randomized Pilot RenPro Trial (Renal Protection Trial)

Summary—The prevention of contrast medium–induced acute kidney injury is a major challenge for interventional cardiologists. Several patient and procedure-associated risk factors were identified in previous studies. Only a few contrast medium–induced acute kidney injury prevention strategies exist. Ischemic preconditioning has been shown in the RenPro (Renal Protection) Trial to be an effective, safe, and economic method for prevention of contrast medium–induced acute kidney injury in high-risk patients. The broad application of this method in daily clinical settings may remarkably influence the cardiovascular outcome in high-risk patients.

Conclusions—Remote ischemic preconditioning before contrast medium use prevents contrast medium–induced acute kidney injury.
in high-risk patients. Our findings merit a larger trial to establish the effect of remote ischemic preconditioning on clinical outcomes.3

Multisite Randomized Trial of a Single-Session Versus Multisession Literacy-Sensitive Self-Care Intervention for Patients With Heart Failure

Summary—This manuscript describes the comparative effectiveness of 2 types of a heart failure self-care training program: single-session training versus multisession training. In a diverse population across 4 clinical sites, there was no difference in rate of hospitalization or death between the interventions. However, patient literacy was an important factor in the effect of the intervention. Patients with low literacy appeared to benefit from the multisession intervention compared with the single-session intervention, but patients with higher literacy did not benefit. Although self-care training for heart failure is an important component of guideline-based care for all patients, it may be important to focus our most intensive resources via ongoing training for patients with low literacy skills.

Conclusions—Overall, an intensive multisession intervention did not change clinical outcomes compared with a single-session intervention. People with low literacy appear to benefit more from multisession interventions than people with higher literacy.4

Randomized Trial of Cutting Balloon Compared With High-Pressure Angioplasty for the Treatment of Resistant Pulmonary Artery Stenosis

Summary—Children born with congenital heart disease not uncommonly require cardiac catheterization to treat congenital and acquired malformations such as pulmonary artery stenosis, replacing or complementing surgical techniques. In this study of Cutting Balloons compared with high-pressure balloon angioplasty for resistant pulmonary artery stenosis, we have shown superior efficacy with the Cutting Balloon technology and an equivalent safety profile. This finding has important clinical application for a population with previously untreatable disease. Although few studies have evaluated the performance of devices developed for adults but used in children, in this study, we have demonstrated that some of the unique study design and execution difficulties met in the pediatric population can be overcome. We hope that future studies will continue to rigorously evaluate the performance of devices used to treat children with rare diseases relative to more common adult indications.

Conclusions—CB therapy for pulmonary artery stenosis not responsive to low-pressure balloon is more effective than HPB therapy and has an equivalent safety profile.5

Hypothermia in Comatose Survivors From Out-of-Hospital Cardiac Arrest: Pilot Trial Comparing 2 Levels of Target Temperature

Summary—Comatose survivors from an out-of-hospital cardiac arrest present very high mortality, and survivors frequently recover with severe neurological disabilities. Early studies suggest that therapeutic hypothermia may reduce cerebral damage in this setting. However, the optimal level of cooling remains controversial. With classic cooling methods, it was very difficult to maintain a stable temperature at a particular level, which is now possible with the use of devices with automatic temperature feedback control. To further investigate the optimal target temperature during hypothermia, we conducted a pilot trial comparing cooling at 32°C versus 34°C in comatose survivors of out-of-hospital cardiac arrest. The results suggest that the lower temperature level is safe and may be associated with a better outcome in patients surviving an arrest secondary to a shockable rhythm. This observation merits further investigation in a large clinical trial with different initial rhythms.

Conclusions—The findings of this pilot trial suggest that a lower cooling level may be associated with a better outcome in patients surviving out-of-hospital cardiac arrest secondary to a shockable rhythm. The benefits observed here merit further investigation in a larger trial in out-of-hospital cardiac arrest patients with different presenting rhythms.6

A Prospective, Randomized Clinical Trial of Hemodynamic Support With Impella 2.5 Versus Intra-Aortic Balloon Pump in Patients Undergoing High-Risk Percutaneous Coronary Intervention: The PROTECT II Study

Summary—Complex percutaneous coronary intervention with hemodynamic support may offer an effective therapy for high-risk patients with multivessel or unprotected left main lesions. In the PROTECT II trial we randomly assigned 452 high-risk patients undergoing percutaneous coronary intervention to hemodynamic support with intra-aortic balloon counterpulsation or a percutaneous (Impella 2.5) axial flow left ventricular assist device. Primary outcome was incidence of major adverse events at 30 days with prospectively planned follow-up to 90 days. The trial was able to enroll the most ill population of symptomatic ischemic heart disease patients ever enrolled in a percutaneous coronary intervention trial. These patients were highly symptomatic, 66% were in New York Heart Association class III or IV, 87% had a history of heart failure, 51% had diabetes mellitus, 26% had renal insufficiency, and ejection fraction was 24%. Despite these extreme risk factors, the reported 30-day mortality of 6.7% is comparable to predicted surgical models. Angiography success was high, whereas stroke/transient ischemic attack and incidence of renal failure rates were low. At 90 days follow-up, 68% of patients had improvement in symptom status with 74% of patients either class I or class II. The trial was terminated prematurely because of the data safety monitoring board’s determination of futility. At 30 days, no difference in incidence of major adverse events occurred for either intent-to-treat or per protocol analysis. Planned follow-up at 90 days reveals a strong trend of benefit for Impella-treated patients (P=0.066, intent-to-treat) and significant for patients who actually qualified (P=0.023, per protocol).

Conclusions—The 30-day incidence of major adverse events was not different for patients with IABP or Impella 2.5 hemodynamic support. However, trends for improved outcomes were observed for Impella 2.5–supported patients at 90 days.7

A Randomized and Clinical Effectiveness Trial Comparing Two Pharmacogenetic Algorithms and Standard Care for Individualizing Warfarin Dosing (CoumaGen-II)

Summary—Warfarin is characterized by marked variations in individual dose requirements and a narrow therapeutic window. Much of this variability is explained by common reduced-function variants in 2 genes, CYP2C9 and VKORC1. Pharmacogenetic (PG) guidance
of warfarin initiation could improve dosing efficiency and safety, but evidence from clinical trials is still meager. To increase understanding of the potential role of PG guidance in warfarin dose initiation and to build on an earlier study (CoumaGen-I), we designed a second 3-month study (CoumaGen-II) with 2 parts: (1) a blinded, randomized comparison of a modified 1-step (PG-1) with a 3-step PG algorithm (PG-2) (N=504) and (2) a clinical effectiveness comparison of PG-guided with standard dosing in a parallel (nonrandomized) control group (N=1866) within the Intermountain Healthcare system. A rapid method provided same-day CYP2C9 and VKORC1 genotyping. In the randomized comparison, PG-2 was noninferior but not superior to PG-1 for the primary end point of percentage of out-of-range international normalized ratios at 1 month and at 3 months and for percentage of time in therapeutic range at 3 months, suggesting that the simpler 1-step PG algorithm may be preferable for clinical application. However, PG guidance (combined cohort) was substantially superior to standard dosing in the parallel control group for these end points (all P<0.001). PG guidance also reduced percentage of international normalized ratios ≥4 and ≤1.5 and serious adverse events. These clinical effectiveness findings suggest that PG dosing should be considered for broader clinical application, a proposal that is being tested further in 3 major randomized trials. The simpler 1-stage PG algorithm provided equivalent results and may be preferable for clinical application.

Conclusions—These findings suggest that PG dosing should be considered for broader clinical application, a proposal that is being tested further in 3 major randomized trials. The simpler 1-step PG algorithm provided equivalent results and may be preferable for clinical application.

**Left Ventricular Lead Position and Clinical Outcome in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) Trial**

**Summary**—Although cardiac resynchronization therapy is an accepted therapeutic modality for patients with heart failure and conduction disturbances, a significant proportion of patients remain nonresponsive to this treatment. An important determinant of successful cardiac resynchronization therapy for heart failure is the position of the left ventricular (LV) pacing lead. The aim of this study was to analyze the impact of the LV lead position on outcome in patients randomized to cardiac resynchronization therapy—defibrillation in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) study. The LV lead position was assessed in 799 patients by means of coronary venograms and chest x-rays recorded at the time of device implantation. The LV lead location was classified along the short axis into an anterior, lateral, or posterior position and along the long axis into a basal, midventricular, or apical region. The results demonstrate that LV lead location along the short axis (ie, anterior, lateral, or posterior walls) does not influence the primary end points of heart failure hospitalization and all-cause mortality. A midventricular (lateral, anterior, or posterior) position was found in 506 (63%), a basal position in 183 (23%), and an apical position in 110 (14%) patients. The apical lead location compared with leads located in the nonapical position (basal or midventricular region) was associated with a significantly increased risk for heart failure and death (hazard ratio=1.72; 95% confidence interval, 1.09–2.71; P=0.019) after adjustment for the clinical covariates. LV leads positioned in the apical region were associated with an unfavorable outcome, suggesting that this lead location should be avoided in cardiac resynchronization therapy.

**Conclusions**—LV leads positioned in the apical region were associated with an unfavorable outcome, suggesting that this lead location should be avoided in cardiac resynchronization therapy.

**Collagenase Total Occlusion-1 (CTO-1) Trial: A Phase I, Dose-Escalation, Safety Study**

**Summary**—Chronic total occlusions (CTO) are common and have been identified in ≥20% to 30% of all coronary angiograms. The majority of patients are treated medically, with <10% of patients undergoing percutaneous coronary interventions. The reluctance to attempt percutaneous coronary intervention in symptomatic patients is due in part to a lower success rate (<70% to 85%, depending on operator expertise and case selection) and prolonged procedure times. The Collagenase Total Occlusion-1 (CTO-1) trial is the first human coronary CTO experience of injecting collagenase into CTO, followed by a percutaneous coronary intervention attempt the next day. The study is based on extensive preclinical work showing that locally injected collagenase produced by Clostridium histolyticum directly into experimental CTO softens the collagen within the occlusive plaque and facilitates guide wire crossing. In the phase I, dose-escalation CTO-1 Trial, increasing doses of collagenase were successfully injected into CTO with a microcatheter. The main finding of the CTO-1 Trial is that collagenase delivery is feasible and safe, with no untoward clinical effects related to collagenase or the delivery technique. In this first-in-humans experience, the 75% success rate for guide wire crossing after collagenase treatment in 20 previously failed cases was encouraging, particularly because crossings were achieved with soft-tip guide wires in 75% of the successful cases. The CTO-1 Trial offers an innovative, biologically based approach that may improve percutaneous coronary intervention results in difficult-to-treat coronary chronic occlusions. Future studies are needed to determine the utility of this new therapeutic approach.

**Conclusions**—Local delivery of collagenase into coronary chronic total occlusion is feasible and safe with encouraging guide wire crossing results in previously failed cases. Larger clinical trials are required to determine efficacy.

**Stroke After Carotid Stenting and Endarterectomy in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)**

**Summary**—Stroke is a feared complication of carotid endarterectomy (CEA) and carotid stenting (CAS). The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) and European trials have shown that CAS is associated with a greater risk of stroke than CEA. CREST also showed that CEA was associated with a greater risk of myocardial infarction (MI) than CAS. The greater risk of MI numerically balanced the greater risk of stroke, so that the composite primary outcome (periprocedural stroke, MI, or death and ipsilateral stroke at up to 4 years) was similar for CEA and CAS. This result has invited criticism because of the differing directions of stroke and MI within the composite outcome. To understand further, we examined the strokes that occurred as a complication of the procedure. Stroke was still more common after CAS, but overall the risk of severe stroke was <1% and was similar for CEA and CAS. The delayed timing of some major strokes, particularly intracerebral hemorrhage that occurred a few days postoperatively, makes it plausible that these postoperative strokes are preventable, perhaps with careful attention to blood pressure control. Minor stroke occurred most commonly on
the same day as CAS, which suggests that the technical aspects of the procedure could be improved to minimize stroke as a complication. Previously, we reported that MI, including biomarker-only MI, was associated with an increased risk in long-term mortality. Here we report that stroke, including minor stroke, was also associated with an increased risk in long-term mortality. Carotid intervention with CEA or CAS is safe. Periprocedural stroke incurred significant morbidity and mortality.

Conclusions—Stroke, particularly severe stroke, was uncommon after carotid intervention in CREST, but stroke was associated with significant morbidity and was independently associated with a nearly 3-fold increased future mortality. The delayed timing of major and hemorrhagic stroke after revascularization suggests that these strokes may be preventable.11

Treatment of Unexplained Syncope: A Multicenter, Randomized Trial of Cardiac Pacing Guided by Adenosine 5′-Triphosphate Testing

Summary—Syncope commonly occurs in the general population, especially in the elderly; its origin remains unexplained in up to 40% of patients. Permanent cardiac pacing represents an effective therapy in patients with syncope of unknown origin that results from neurally mediated cardio-inhibition. The ATP test was introduced in 1986 as a convenient and safe tool to identify patients with syncope of unknown origin with neurally mediated cardiac inhibition. This patient-blinded, multicenter, randomized trial demonstrated that, in patients with syncope of unknown origin and a positive ATP test with no other precluding possible indications, cardiac pacing is an effective therapy, leading to a significant reduction of syncope recurrences. Although only some patients with syncope of unknown origin have a positive ATP test, this quick and safe procedure should be considered part of the armamentarium of syncope diagnosis.

Conclusions—This study suggests that, in elderly patients with syncope of unknown origin and positive ATP tests, active dual-chamber pacing reduces syncope recurrence risk by 75% (95% confidence interval, 44–88).12

Randomized Clinical Trial of Aspirin and Simvastatin for Pulmonary Arterial Hypertension: ASA-STAT

Summary—Pulmonary arterial hypertension (PAH) is a progressive disease that causes exercise limitation, heart failure, and death. Aspirin and simvastatin have powerful effects on atherosclerosis, but have not been studied in PAH. We performed a randomized, double-blind, placebo-controlled 2×2 factorial clinical trial of aspirin and simvastatin in patients with PAH receiving background therapy at 4 centers. Sixty-five subjects were randomized when the trial was terminated by the Data Safety and Monitoring Board after an interim analysis showed futility in reaching the primary end point for simvastatin. After adjustment for baseline 6-minute walk distance, there was no significant difference in the 6-minute walk distance at 6 months between those given aspirin (n=32) or placebo (n=33); placebo-corrected difference −0.5 m [95% confidence interval −28.4 to 27.4 m], P=0.97) or between those given simvastatin (n=32) or placebo (n=33; placebo-corrected difference −27.6 m [95% confidence interval −59.6 to 4.3 m], P=0.09). This trial did not show any clinical benefit with the use of aspirin or simvastatin in patients with PAH. Traditional indications for these drugs should guide their use in patients with PAH.

Conclusions—Neither aspirin nor simvastatin had a significant effect on the 6-minute walk distance, although patients randomized to simvastatin tended to have a lower 6-minute walk distance at 6 months. These results do not support the routine treatment of patients with PAH with these medications.13

Renal Sympathetic Denervation for Treatment of Drug-Resistant Hypertension: One-Year Results From the Symplicity HTN-2 Randomized, Controlled Trial

Summary—Patients with uncontrolled hypertension are at significant risk for cardiovascular events, and a subset of these patients who do not respond to aggressive pharmacological treatment (23 antihypertensive drugs including a diuretic) are considered to have treatment-resistant hypertension. It has been shown that activation of the sympathetic nervous system is involved in the pathogenesis and maintenance of hypertension. Renal denervation with the Symplicity catheter is a minimally invasive procedure based on the premise that interruption of renal afferent and efferent nerves with resultant decreased sympathetic outflow to the kidneys will reduce renal release and sodium retention, increase renal blood flow, and lower blood pressure. The Symplicity HTN-2 trial demonstrates that radiofrequency ablation of renal nerves can significantly lower blood pressure in patients with systolic blood pressures >160 mmHg with no loss of treatment effect through 1 year and thus may provide a safe and effective adjunctive therapy for treatment-resistant hypertensive patients.

Conclusions—Control patients who crossed over to renal denervation with the Symplicity system had a significant drop in blood pressure similar to that observed in patients receiving immediate denervation. Renal denervation provides safe and sustained reduction of blood pressure to 1 year.14

Chronic Inhibition of cGMP Phosphodiesterase 5A Improves Diabetic Cardiomyopathy: A Randomized, Controlled Clinical Trial Using MRI With Myocardial Tagging

Summary—Type 2 diabetes mellitus is associated with cardiac remodeling that may occur independently of ischemic heart disease, hypertension, or macrovascular complications. Cardiac magnetic resonance can be used to measure diabetic cardiomyopathy, for which there is currently no specific treatment. In vitro studies have shown that phosphodiesterase 5 overexpression reduces cGMP levels and exacerbates remodeling. Inhibiting cGMP hydrolysis in stimulated cardiomyocytes can prevent hypertrophy. We studied the effects of 3-month daily sildenafil treatment (a phosphodiesterase 5A inhibitor) on cardiac remodeling in a cohort of asymptomatic, middle-aged men with type 2 diabetes mellitus. Cardiac MRI revealed that diabetic cardiomyopathy in these patients produced an uncoupling in left ventricular contraction between longitudinal strain, which is reduced, and cardiac axial rotation, which is increased. We found that long-term sildenafil treatment restored coupling by reducing torsion and improving strain. It also reduced the ratio of left ventricular mass to end-diastolic volume that is increased in the presence of concentric hypertrophy. These data suggest that phosphodiesterase 5 inhibition could work as an anti-remodeling drug by acting directly on cardiac tissue, independently of other secondary vascular, endothelial, or metabolic effects. Our findings also have an impact on the clinical monitoring of patients.
Insulin Receptor Substrate 1 Gene Variation Modifies Insulin Resistance Response to Weight-Loss Diets in a 2-Year Randomized Trial: The Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) Trial

Summary—Although recent data from gene–environment interaction analyses provide support for the notion of a personalized nutrition approach, evidence from clinical trials is scarce. Genome-wide association studies have identified common genetic variants in the IRS1 locus associated with insulin resistance and hyperinsulinemia, as well as type 2 diabetes mellitus and coronary heart disease. In a 2-year randomized weight-loss trial, the Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial, we genotyped the best associated variant (single nucleotide polymorphism rs2943641) in 738 overweight adults, to examine the modifications of the IRS1 gene variation on the long-term changes in body weight, fasting insulin, and insulin resistance in response to weight-loss diets with different compositions of macronutrients. Our results indicated that participants with the IRS1 rs2943641 CC genotype might obtain more benefits in weight loss and improvement of insulin resistance than those without this genotype in response to a high-carbohydrate/low-fat diet. Our data may provide novel information for the development of effective dietary intervention strategies based on genetic background in preventing diseases related to obesity and insulin resistance, such as type 2 diabetes mellitus and cardiovascular disease.

Conclusions—Individuals with the IRS1 rs2943641 CC genotype might obtain more benefits in weight loss and improvement of insulin resistance than those without this genotype by choosing a high-carbohydrate and low-fat diet.

Apolipoprotein B Synthesis Inhibition With Mipomersen in Heterozygous Familial Hypercholesterolemia: Results of a Randomized, Double-Blind, Placebo-Controlled Trial to Assess Efficacy and Safety as Add-On Therapy in Patients With Coronary Artery Disease

Summary—Heterozygous familial hypercholesterolemia is a common genetic disorder that leads to premature coronary artery disease. Despite aggressive lipid-lowering therapy, many patients with heterozygous familial hypercholesterolemia fail to achieve optimal low-density lipoprotein cholesterol (LDL-C) goals. We evaluated mipomersen, an apolipoprotein B synthesis inhibitor, to further lower LDL-C in patients with heterozygous familial hypercholesterolemia with coronary artery disease who were already on maximally tolerated lipid-lowering therapy and had LDL-C >2.6 mmol/L (100 mg/dL). The phase 2, double-blind, placebo-controlled trial randomized 124 patients (41 placebo, 83 mipomersen) to weekly subcutaneous mipomersen 200 mg or placebo (2:1) for 26 weeks. The primary end point was percent change in LDL-C from baseline at week 28. Safety assessments included adverse events, laboratory tests, and MRI assessment of hepatic fat. Mean LDL-C decreased 28.0% with mipomersen compared with a 5.2% increase with placebo (P < 0.001), and 45.1% compared with 4.9% achieved LDL-C <2.6 mmol/L (100 mg/dL), respectively. Mipomersen significantly (P < 0.001) reduced apolipoprotein B (−26.3%) and lipoprotein(a) (−21.1%) compared with placebo. More frequent and severe injection site reactions occurred with mipomersen, and 5 mipomersen-treated patients (6%) had 2 consecutive alanine aminotransferase levels ≥3 times the upper limit of normal at least 7 days apart; none were associated with significant bilirubin increases. Hepatic fat content increased a median of 4.9% with mipomersen versus 0.4% with placebo (P < 0.001). The clinical implications of such increases in hepatic fat and transaminase elevations are unclear and must be elucidated in longer-term studies. We conclude that mipomersen is effective to further reduce apolipoprotein B–containing lipoproteins, including LDL and lipoprotein(a), in patients with heterozygous familial hypercholesterolemia with coronary artery disease on statins and other lipid-lowering therapy.

Conclusions—Mipomersen is an effective therapy to further reduce apolipoprotein B–containing lipoproteins, including LDL and lipoprotein(a), in HeFH patients with coronary artery disease on statins and other lipid-lowering therapy. The significance of hepatic fat and transaminase increases remains uncertain at this time.

ST-Elevation Acute Coronary Syndromes in the Platelet Inhibition and Patient Outcomes (PLATO) Trial: Insights From the ECG Substudy

Summary—In a prespecified analysis of 6311 ST-elevation patients in the PLATElet inhibition and patient Outcomes (PLATO) study, we explored whether ticagrelor’s treatment effect would be amplified by the extent of baseline ECG abnormalities and associated with less residual ST change at discharge. The extent of ΣST-deviation present at the time of randomization was independently associated with 1-year vascular death and myocardial infarction. The benefit of ticagrelor versus clopidogrel was consistent irrespective of the extent of baseline ΣST-deviation and no treatment effect of ticagrelor versus clopidogrel was evident on the resolution of baseline ST-deviation at hospital discharge. As compared with clopidogrel, ticagrelor tended to provide greater benefit among those patients who achieved the greatest resolution of ST-deviation at discharge. These data suggest that the main effects of ticagrelor may not relate to the rapidity of acute reperfusion but rather prevention of recurrent vascular events known to modulate long term outcomes.

Conclusions—Ticagrelor did not modify ΣST-dev resolution at discharge nor was its benefit affected by the extent of baseline ΣST-dev. These hypothesis-generating observations suggest that the main effects of ticagrelor may not relate to the rapidity or the completeness of acute reperfusion, but rather the prevention of recurrent vascular events by more powerful platelet inhibition or other mechanisms.
Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard System in High-Risk Patients for Contrast-Induced Acute Kidney Injury

Summary—The use of the RenalGuard System to create high urine output and fluid balancing may be beneficial in preventing contrast-induced acute kidney injury (CI-AKI). Patients with an estimated glomerular filtration rate ≤30 mL·min⁻¹·1.73 m⁻² and/or a risk score ≥11 were randomly assigned to sodium bicarbonate solution and N-acetylcysteine (control group) or the RenalGuard therapy, ie, hydration with saline and N-acetylcysteine controlled by the RenalGuard System and furosemide (RenalGuard group). Contrast-induced acute kidney injury (defined as an increase of ≥0.3 mg/dl in the serum creatinine concentration at 48 hours after the procedure) occurred in 16 of 146 patients in the RenalGuard group (11%) and in 30 of 146 patients in the control group (20.5%; P = 0.025; odds ratio, 0.47; 95% confidence interval, 0.24–0.92). Serum cystatin C values (P = 0.004; F = 5.52 by ANOVA model) and the rate of in-hospital dialysis (4.1% versus 7.0%; P = 0.056) were higher in the control group. RenalGuard therapy is superior to sodium bicarbonate and N-acetylcysteine in preventing contrast-induced acute kidney injury in high-risk patients. The present study supports that concept that increasing the urine flow rate reduces the toxic effect of contrast media. The RenalGuard system is helpful in guiding the physician in achieving high urine output (≥300 mL/h) while simultaneously balancing urine output and venous fluid infusion to prevent hypovolemia.

Conclusions—RenalGuard therapy is superior to sodium bicarbonate and N-acetylcysteine in preventing contrast-induced acute kidney injury in high-risk patients.  

Influence of Mitral Regurgitation Repair on Survival in the Surgical Treatment for Ischemic Heart Failure Trial

Summary—Chronic ischemic mitral regurgitation (MR) is associated with heart failure and increased mortality. The optimal treatment strategy for ischemic MR remains controversial. European practice guidelines recommend mitral valve repair in patients with severe or even moderate ischemic MR and an ejection fraction >30% who are undergoing coronary artery bypass grafting (CABG), even though retrospective analyses using propensity score matching showed no survival benefit of adding mitral valve repair to CABG. The need to add mitral valve repair in patients with an indication for CABG becomes even less clear when left ventricular dysfunction is more severe. The Surgical Treatment for Ischemic Heart Failure (STICH) trial randomized 1212 patients with severe left ventricular dysfunction (ejection fraction <35%) and coronary artery disease amenable to CABG to intensive medical therapy alone or in association with CABG. The decision to repair the mitral valve was left to the operating surgeon. Survival in the medically treated cohort depended strongly on MR grade at baseline, with mortality hazard being increased twice in patients with moderate to severe MR compared with patients with no MR. In patients with mild MR, CABG was associated with improved survival. In patients with moderate to severe MR, adding mitral valve repair to CABG tended to improve survival compared with CABG alone or medical therapy alone. Unfortunately, the decision to repair the valve was not randomized; therefore, even though risk adjustment actually accentuated the difference of survival in favor of adding mitral valve repair, a randomized trial is required to confirm our findings.

Conclusions—A regimen of 24 months of clopidogrel therapy in patients who had received a balanced mixture of drug-eluting or bare-metal stents was not significantly more effective than a 6-month clopidogrel regimen in reducing the composite of death due to any cause, myocardial infarction, cerebrovascular accident, or stent thrombosis. Two Korean studies have also previously reported a lack of benefit of either 12 or 24 months of clopidogrel therapy over 6 or 12 months of therapy, respectively. Therefore, altogether, the available evidence does not support the concept that the longer the duration of clopidogrel therapy after drug-eluting stent implantation, the better the outcomes. On the contrary, this study identifies the potential for harm with respect to major bleeding associated with prolonged use of dual-antiplatelet therapy.

Effect of Dietary Protein Supplementation on Blood Pressure: A Randomized, Controlled Trial

Summary—Observational epidemiological studies have reported an inverse association between dietary protein intake and blood pressure. We compared the effect of soy protein, milk protein, and complex carbohydrate supplementation on blood pressure in a randomized, double-blind crossover trial among 352 adults with prehypertension or stage 1 hypertension. The trial participants were assigned to take 40 g/d of soy protein, milk protein, or complex carbohydrate supplementation each for 8 weeks in a random order. A 3-week washout period was implemented between the interventions. Three blood pressure measurements were obtained at 2 baseline and 2 termination visits during each of the 3 intervention phases by use of a random-zero sphygmomanometer. Compared with carbohydrate controls, soy protein and milk protein supplementations were significantly associated with a −2.0 mm Hg (95% confidence interval −3.2 to −0.7 mm Hg, P = 0.002) and −2.3 mm Hg (−3.7 to −1.0 mm Hg, P = 0.0007) net change in systolic blood pressure, respectively. The results from this randomized, controlled trial indicate that both soy and milk protein intake reduce systolic blood pressure compared with
carbohydrate intake among patients with prehypertension and stage 1 hypertension. Furthermore, these findings suggest that partially replacing carbohydrate with soy or milk protein might be an important component of nutrition intervention strategies for the prevention and treatment of hypertension.

Conclusions—The results from this randomized, controlled trial indicate that both soy and milk protein intake reduce systolic BP compared with a high-glycemic-index refined carbohydrate among patients with prehypertension and stage 1 hypertension. Furthermore, these findings suggest that partially replacing carbohydrate with soy or milk protein might be an important component of nutrition intervention strategies for the prevention and treatment of hypertension.22

Effects of Interleukin-1β Inhibition With Canakinumab on Hemoglobin A1c, Lipids, C-Reactive Protein, Interleukin-6, and Fibrinogen: A Phase IIb Randomized, Placebo-Controlled Trial

Summary—Atherosclerosis in an inflammatory condition, and biomarkers of inflammation including CRP, IL-6, and fibrinogen associate with increased vascular risk. However, whether inhibiting inflammation will reduce vascular events is uncertain. One promising anti-inflammatory approach with potential relevance for cardiovascular disease is inhibition of the proinflammatory cytokine IL-1, particularly the IL-1β isoform that is secreted and acts locally but that also induces systemic effects. In a phase IIb randomized trial conducted among high-risk diabetic patients comparing placebo with canakinumab, a monoclonal antibody targeting IL-1β, we observed statistically significant dose-dependent reductions in all 3 of these inflammatory biomarkers without major effect on LDL-C or HDL-C. There were no differences in clinical adverse events between active and placebo patients, although a small increase in triglycerides was observed at higher canakinumab doses. These phase II trial data support the use of canakinumab as a potential therapeutic method to test directly the inflammatory hypothesis of atherosclerosis. Indeed, in part on the basis of these data, a large-scale multinational hard outcomes trial, CANTOS, is being conducted that will address directly whether inhibition of IL-1β with canakinumab can reduce recurrent vascular event rates in a high-risk secondary prevention population.

Conclusions—Canakinumab, a human monoclonal antibody that neutralizes interleukin-1β, significantly reduces inflammation without major effect on low-density lipoprotein cholesterol or high-density lipoprotein cholesterol. These phase II trial data support the use of canakinumab as a potential therapeutic method to test directly the inflammatory hypothesis of atherosclerosis.23

Comparison of Everolimus-Eluting and Sirolimus-Eluting Coronary Stents: 1-Year Outcomes from the Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial (RESET)

Summary—Several recent randomized trials comparing everolimus-eluting stents (EES) and sirolimus-eluting stents (SES) reported similar outcomes. However, only 1 trial was powered for a clinical end point, and no trial was powered for evaluating target-lesion revascularization. Randomized Evaluation of Sirolimus-eluting versus Everolimus-eluting stent Trial is a prospective multicenter randomized, open-label trial comparing EES with SES in Japan. The trial was powered for evaluating noninferiority of EES relative to SES in terms of target-lesion revascularization. From February and July 2010, 3197 patients were randomly assigned to receive either EES (1597 patients) or SES (1600 patients). At 1 year, the primary efficacy end point of target-lesion revascularization occurred in 65 patients (4.3%) in the EES group, and in 76 patients (5.0%) in the SES group, demonstrating noninferiority of EES to SES (Pnoninferiority<0.0001, and \( P_{\text{noninferiority}}=0.34 \)). Cumulative incidence of definite stent thrombosis was low and similar between the 2 groups (0.32% versus 0.38%; \( P=0.77 \)). One-year clinical and angiographic outcome after EES implantation was noninferior to and not different from that after SES implantation in a stable coronary artery disease population with relatively less complex coronary anatomy. One-year clinical outcome after both EES and SES use was excellent with a low rate of target-lesion revascularization and a very low rate of stent thrombosis. Clinical follow-up will be continued up to 3 years. Future studies comparing different drug-eluting stents should focus more on patients with complex coronary artery disease to discern meaningful differences in safety and efficacy outcomes.

Conclusions—One-year clinical and angiographic outcome after EES implantation was noninferior to and not different from that after SES implantation in a stable coronary artery disease population with relatively less complex coronary anatomy. One-year clinical outcome after both EES and SES use was excellent with a low rate of target-lesion revascularization and a very low rate of stent thrombosis.24

Early Developmental Outcome in Children With Hypoplastic Left Heart Syndrome and Related Anomalies: The Single Ventricle Reconstruction Trial

Summary—Survival to adulthood is becoming a reality for patients with hypoplastic left heart syndrome and related single right ventricle anomalies treated with staged palliation from the Norwood operation to the Fontan procedure. We assessed neurodevelopment at age 14 months in the 15-center, randomized Single Ventricle Reconstruction trial by using the Psychomotor Development Index and Mental Development Index of the Bayley Scales of Infant Development—Second Edition. We found a high prevalence of neurodevelopmental impairment in patients with hypoplastic left heart syndrome and related single right ventricle anomalies. Lower Bayley Scales of Infant Development—Second Edition scores at age 14 months were predicted by both innate patient factors and measures of greater severity of illness. Patient factors that portended greater risk included the presence of genetic syndromes or other anomalies, lower maternal education, and lower birth weight. Patients with a more complicated postoperative course following the Norwood procedure also had worse outcomes, as indicated by independent risk factors of longer postoperative mechanical ventilation or hospital stay. Between Norwood discharge and age 12 months, a greater number of complications were also associated with worse development, a novel finding that highlights ongoing brain vulnerability and opportunities for intervention. Neither the type of systemic-to-pulmonary-artery shunt nor bypass-related variables were predictors of Bayley Scales of Infant Development—Second Edition scores in multivariable analyses. Thus, patient characteristics and indices of greater severity of illness were the factors most highly associated with later neurodevelopmental outcome. Substantial improvement in neurodevelopmental outcome in this vulnerable population is thus likely to require inclusion of interventions that occur outside the operating room.

Conclusions—Neurodevelopmental impairment in Norwood survivors is more highly associated with innate patient factors and overall...
Randomized Comparison of Everolimus-Eluting and Sirolimus-Eluting Stents in Patients Treated With Percutaneous Coronary Intervention: The Scandinavian Organization for Randomized Trials With Clinical Outcome IV (SORT OUT IV)

Summary—Among drug-eluting stents released to date, the sirolimus-eluting stent has demonstrated the least amount of late lumen loss, but its efficacy and safety have not been compared head-to-head with the next-generation everolimus-eluting stent. The Scandinavian Organization for Randomized Trials With Clinical Outcome IV (SORT OUT IV) trial compared the everolimus-eluting stent with the sirolimus-eluting stent in patients with coronary artery disease. The primary end point was a composite of safety (cardiac death, myocardial infarction, definite stent thrombosis) and efficacy (target vessel revascularization) parameters. A total of 1390 patients were assigned to receive the everolimus-eluting stent and 1384 patients to the sirolimus-eluting stent. At the 9-month follow-up, 4.9% of the patients treated with the everolimus-eluting stent compared with 5.2% of the patients treated with the sirolimus-eluting stent experienced the primary end point (P for noninferiority=0.01). At the 18-month follow-up, this difference remained. The rate of definite stent thrombosis was higher in the sirolimus-eluting group compared with the everolimus-eluting group (0.9% versus 0.2%). The everolimus-eluting stent was found to be noninferior to the sirolimus-eluting stent.

Conclusions—The everolimus-eluting stent was found to be noninferior to the sirolimus-eluting stent.

Atrial Fibrillation Catheter Ablation Versus Surgical Ablation Treatment (FAST): A 2-Center Randomized Clinical Trial

Summary—Catheter ablation (CA) and minimally invasive surgical ablation (SA) have become accepted therapy for atrial fibrillation (AF). This study describes the first randomized clinical trial comparing the efficacy and safety of CA and SA during 12 months of follow-up. One hundred twenty-four patients with atrial fibrillation drug-refractory atrial fibrillation with left atrial dilatation and hypertension (42 patients, 33%) or failed prior CA (82 patients, 67%) were randomized to CA (63 patients) or SA (61 patients). CA consisted of linear antral pulmonary vein isolation and optional additional lines. SA consisted of bipolar radiofrequency isolation of the bilateral pulmonary vein, ganglionated plexi ablation, and left atrial appendage excision with optional additional lines. Follow-up at 6 and 12 months was performed by ECG and 7-day Holter recording. The primary end point, freedom from left atrial arrhythmia >30 seconds without antiarrhythmia drugs after 12 months, was 36.5% for CA and 65.6% for SA (P=0.0022). There was no difference in effect for subgroups, which was also consistent at both sites. The primary safety end point of significant adverse events during the 12-month follow-up was significantly higher for SA than for CA (n=21 [34.4%] versus n=10 [5.9%]; P=0.027), driven mainly by procedural complications such as pneumothorax and bleeding. In the CA group, 1 patient died at 1 month of subarachnoid hemorrhage while on vitamin K antagonists. The results indicate that in atrial fibrillation patients with dilated left atrial and hypertension or failed prior CA, SA is superior in achieving freedom from left atrial arrhythmias after 12 months of follow-up at the cost of a higher procedural serious adverse event rate. These findings may guide physicians and patients in choosing between these invasive treatments for atrial fibrillation.

Conclusions—In atrial fibrillation patients with dilated left atrium and hypertension or failed prior atrial fibrillation CA, SA is superior to CA in achieving freedom from left atrial arrhythmias after 12 months of follow-up, although the procedural adverse event rate is significantly higher for SA than for CA.

Coronary Artery Bypass Surgery With or Without Mitral Valve Annuloplasty in Moderate Functional Ischemic Mitral Regurgitation: Final Results of the Randomized Ischemic Mitral Evaluation (RIME) Trial

Summary—The role of mitral valve repair (MVR) during coronary artery bypass grafting (CABG) in patients with moderate ischemic mitral regurgitation is uncertain. We randomized 73 patients referred for CABG with moderate ischemic mitral regurgitation and an ejection fraction >30% to receive either CABG plus MVR (34 patients) or CABG only (39 patients). At 1 year, patients in the CABG plus MVR group had a significantly greater improvement in functional capacity as measured by peak oxygen consumption, and greater left ventricular reverse remodeling as measured by the left ventricular end-systolic volume index, reduction in mitral regurgitation severity, and B-type natriuretic peptide levels, compared with the CABG-only group. However, operation duration, blood transfusion, intubation duration, and hospital stay duration were greater in the CABG plus MVR group. There was also a trend toward higher complication rates in the CABG plus MVR group, although this was not statistically significant. Deaths at 30 days and 1 year were similar in both groups, as was the incidence of hospitalization for heart failure. The results of this study support the addition of MVR to CABG in patients with moderate ischemic mitral regurgitation undergoing CABG, but the benefits of the combined procedure must be balanced against a possible increased risk of morbidity in the perioperative period. The impact of these benefits on longer term clinical outcomes remains to be defined.

Conclusions—Adding mitral annuloplasty to CABG in patients with moderate ischemic MR may improve functional capacity, left ventricular reverse remodeling, MR severity, and B-type natriuretic peptide levels, compared with CABG alone. The impact of these benefits on longer term clinical outcomes remains to be defined.

Clinical and Angiographic Risk Stratification and Differential Impact on Treatment Outcomes in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial

Summary—In this report, we examine angiographic and clinical risk scores in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial to test the hypothesis that differences in the end points of death and myocardial infarction and the composite end points of death/myocardial infarction/stroke and cardiac death/myocardial infarction observed between coronary revascularization and intensive medical therapy might be related to coronary disease extent and clinical characteristics. In the group of patients in whom percutaneous coronary intervention was chosen as the preferred revascularization option, there were no treatment differences between an initial strategy of indicated coronary intervention or intensive medical therapy regardless of angiographic or clinical risk score. This was not the case in the patients in whom coronary artery bypass graft surgery was selected as the preferred revascularization option because there...
was an increasing benefit of coronary artery bypass graft surgery in terms of reduction of cardiac end points in the highest-angiographic-risk patients, particularly in those with high clinical risk scores. Our findings indicate that among patients with diabetes mellitus and stable ischemic heart disease, a strategy of prompt coronary artery bypass graft surgery is preferred to an initial strategy of intensive medical therapy for those with extensive coronary artery disease or impaired left ventricular function to reduce the rates of myocardial infarction and death/myocardial infarction/stroke.

Conclusions—Among patients with diabetes mellitus and stable ischemic heart disease, a strategy of prompt coronary artery bypass graft surgery significantly reduces the rate of death/myocardial infarction MI/stroke in those with extensive coronary artery disease or impaired left ventricular function.30

Periprocedural Bleeding and Thromboembolic Events With Dabigatran Compared With Warfarin: Results From the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Randomized Trial

Summary—The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial demonstrated that dabigatran is well-tolerated and that, compared with warfarin, dabigatran 150 mg BID is more effective at preventing stroke and systemic embolism, whereas dabigatran 110 mg BID is associated with a lower risk of major bleeding. However, because dabigatran does not yet have a specific antidote, and its anticoagulant effect is currently difficult to precisely measure, there is concern that dabigatran may increase the risk of bleeding in patients undergoing invasive procedures, particularly if performed on an emergency basis. The RE-LY trial highlights the importance of this scenario, because 25% of patients underwent at least 1 surgery or invasive procedure within 2 years. This analysis of periprocedural outcomes from RE-LY includes data on >7500 surgeries and procedures, making it the largest evaluation of any anticoagulant strategy in the periprocedural setting. The open-label design of RE-LY allowed a real-world evaluation of the periprocedural management or anticoagulation and demonstrated that dabigatran-treated patients were 4 times more likely to have their procedure completed within 48 hours of the discontinuation of anticoagulation than patients treated with warfarin. Overall, there was no detectable difference in the rate of minor, major, or fatal bleeding between patients treated with warfarin in comparison with either dose of dabigatran, nor was there any difference in the risk of thromboembolic events. In comparison with patients receiving warfarin, the rates of major bleeding with both doses of dabigatran were also similar in the subgroups of patients having major surgery and those having surgery on an emergency basis.

Conclusions—Dabigatran and warfarin were associated with similar rates of periprocedural bleeding, including patients having urgent surgery. Dabigatran facilitated a shorter interruption of oral anticoagulation.30

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.31

Does Initial Shunt Type for the Norwood Procedure Affect Echocardiographic Measures of Cardiac Size and Function During Infancy?: The Single Ventricle Reconstruction Trial

Summary—Hypoplastic left heart syndrome is a common form of functional single-ventricle congenital heart disease and is associated with significant morbidity/mortality. A National Heart, Lung, and Blood Institute Pediatric Heart Network study, the Single Ventricle Reconstruction trial, randomized initial surgical Norwood palliation in 549 infants with hypoplastic left heart syndrome to either a rightventricle–pulmonary artery shunt or a modified Blalock-Taussig shunt to determine the optimal surgical approach. The primary result of the trial found better 1-year transplant-free survival in subjects who received a right ventricle–pulmonary artery shunt compared with those who had a modified Blalock-Taussig shunt. This study compared 2-dimensional echocardiographic indices to assess the effect of initial shunt type at 4 stages during the trial (at baseline preoperatively, early after the Norwood procedure, immediately before the second-stage surgical procedure, and at 14 months of age). We found that differences in neoaoartic annular size and flow patterns between shunt types when the shunts are in place can likely be explained by the different physiologies created rather than by intrinsic differences in cardiac function. After the shunt was removed at the second-stage surgery, echocardiographic indices were similar between the 2 groups, including measures of right ventricular function, cardiac and vascular dimensions, neoaoartic and tricuspid dimensions and valve function, and neoaoartic flow patterns. This lack of shunt-related differences in echocardiographic indices of cardiac and vascular function in survivors of the Norwood procedure at 14 months suggests that the best initial surgical pathway for infants with hypoplastic left heart syndrome remains unclear and emphasizes the importance of longitudinal follow-up of this unique cohort.

Conclusions—Indices of cardiac size and function after the Norwood procedure are similar for modified Blalock-Taussig shunt and RVPAS by 14 months of age. Interstage differences between shunt types can likely be explained by the physiology created when the shunts are in place rather than by intrinsic differences in cardiac function.32
Pacemaker Therapy in Patients With Neuromodulated 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 ≥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 ≈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 ≥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.35

Myocardial Ischemic Events in Patients With Atrial Fibrillation Treated With Dabigatran or Warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) Trial

Summary—Dabigatran etexilate is a novel, potent, competitive, and reversible direct thrombin inhibitor that recently has been compared with warfarin for prevention of thromboembolic events in 18,113 patients with nonvalvular atrial fibrillation (Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY trial]). At a dose of 110 mg twice daily, dabigatran had similar efficacy as warfarin in preventing stroke and systemic embolism but lower rates of major hemorrhage. At a dose of 150 mg twice daily, dabigatran was associated with lower rates of stroke and systemic embolism than warfarin but similar rates of major hemorrhage. This post hoc study evaluated the incidence of myocardial ischemic events, including myocardial infarction (MI), in the 3 treatment arms. MI occurred at annual rates of 0.82% and 0.81% with dabigatran 110 mg or 150 mg BID compared with 0.64% in patients taking warfarin (hazard ratio 1.29, 95% confidence interval 0.96–1.75, P=0.09 for dabigatran 110 mg; hazard ratio 1.27, 95% confidence interval 0.94–1.71, P=0.12 for dabigatran 150 mg). Events prespecified as “net clinical benefit” (all strokes, systemic embolism, MI, pulmonary embolism, major bleeding, and all-cause death) occurred at a rate of 7.34% per year with dabigatran 110 mg, 7.11% per year with dabigatran 150 mg, and 7.91% per year with warfarin (hazard ratio 0.92, 95% confidence interval 0.84–1.01, P=0.09 for dabigatran 110 mg; 0.90, 95% confidence interval 0.82–0.99, P=0.02 for dabigatran 150 mg). In conclusion, in patients with atrial fibrillation, there was a nonsignificant increase in MIs with dabigatran compared with warfarin, but other myocardial ischemic events were not increased. The net clinical benefit favors dabigatran over warfarin in patients with or without a baseline history of MI or coronary artery disease.

Conclusions—There was a nonsignificant increase in MI with dabigatran compared with warfarin, but other myocardial ischemic events were not increased. Treatment effects of dabigatran were consistent in patients at higher and lower risk of myocardial ischemic events.34

Impact of the Presence and Extent of Incomplete Angiographic Revascularization After Percutaneous Coronary Intervention in Acute Coronary Syndromes: The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) Trial

Summary—The prevalence and clinical significance of incomplete coronary revascularization (ICR) in patients with acute coronary syndromes treated with percutaneous coronary intervention (PCI) are unknown. Prior studies have reported conflicting data owing to the lack of randomized clinical trial data, varying definitions of ICR, and substantial baseline differences between patients in whom complete revascularization is versus is not achieved. In the present study, using the large-scale Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial database, ICR after PCI was variably defined if any lesion with diameter stenosis cutoffs ranging from ≥30% to ≥70% with reference vessel diameter ≥2.0 mm (assessed at an independent angiographic core laboratory) remained after PCI. The prevalence of ICR after PCI varied widely from 17% to 75% of patients, depending on the threshold of angiographic percent diameter stenosis used to define ICR. Regardless of the threshold percent diameter stenosis used to define ICR, the presence of ICR after PCI was strongly associated with 1-year major adverse cardiovascular events, driven by increased rates of myocardial infarction and ischemia-driven unplanned repeat revascularization in patients with ICR, with numerically greater but nonsignificantly different rates of mortality. Thus, a strong relationship between ICR and major adverse cardiovascular events exists after PCI in acute coronary syndromes. A large-scale, randomized trial is thus warranted and required to determine whether a complete revascularization strategy (either single procedure or staged) is capable of reducing MACE compared with a selective ICR approach (whether angiographically or functionally guided) in acute coronary syndromes.

Conclusions—Depending on the threshold of percent DS, ICR was present in 17% to 75% of patients with acute coronary syndromes after percutaneous coronary intervention. Regardless of the threshold, ICR was strongly associated with 1-year myocardial infarction, ischemia-driven unplanned revascularization, and major adverse cardiac events.35

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.26

Low-Density Lipoprotein Cholesterol–Lowering Effects of AMG 145, a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease in Patients With Heterozygous Familial Hypercholesterolemia: The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) Randomized Trial

Summary—Heterozygous familial hypercholesterolemia, a dominant genetic disorder found in 0.2% of the population, results in early coronary artery disease. Current lipid-lowering therapy fails to achieve optimal low-density lipoprotein cholesterol (LDL-C) goals in many patients. We evaluated AMG 145, a fully human monoclonal antibody against PCSK9, to reduce LDL-C in heterozygous familial hypercholesterolemia patients already on maximally tolerated lipid-lowering therapy and LDL-C >2.6 mmol/L (100 mg/dL). The phase 2, double-blind, placebo-controlled trial randomized 168 patients (56 placebo, 56 AMG 145 350 mg, 56 AMG 145 420 mg) to every 4 weeks subcutaneous injections for 12 weeks. The primary end point was percentage change in LDL-C, measured by ultracentrifugation, from baseline at Week 12. Safety assessments included adverse events and laboratory tests. LDL-C reduction (least squares mean [standard error (SE))] was 43 (3)% and 55 (3)% for AMG 145 350 mg and 420 mg, respectively, compared with 1 (3)% increase with placebo (P<0.001 for both dose groups). AMG 145 420 mg every 4 weeks resulted in 89% of patients reaching LDL-C levels of <2.6 mmol/L (100 mg/dL) and 65% achieving <1.8 mmol/L (70 mg/dL), respectively, compared with 2% and 0% of placebo subjects, respectively. There was a significant dose-dependent reduction in lipoprotein (a) with AMG 145 therapy of 23% and 32% compared with placebo. Serious adverse events (not considered treatment-related) occurred in 2 patients on AMG 145. We conclude that AMG 145 administered every 4 weeks yields rapid and substantial reductions in LDL-C with minimal adverse events and good tolerability in patients with heterozygous familial hypercholesterolemia and elevated LDL-C despite intensive lipid-lowering therapy.

Conclusions—AMG 145 administered every 4 weeks yielded rapid and substantial reductions in LDL-C in heterozygous familial hypercholesterolemia patients despite intensive statin use, with or without ezetimibe, with minimal adverse events and good tolerability.11

Improving Blood Pressure Control Through a Clinical Pharmacist Outreach Program in Patients With Diabetes Mellitus in 2 High-Performing Health Systems: The Adherence and Intensification of Medications Cluster Randomized, Controlled Pragmatic Trial

Summary—We studied the implementation and clinical outcomes of a state-of-the-art, intensive pharmacist-led intervention seeking to improve blood pressure control in a high-risk population (patients with diabetes mellitus, persistent hypertension, and documented medication adherence or management problems) in 2 high-performing healthcare systems (Kaiser Permanente and the Veterans Affairs Health System). In the short term, the program improved blood pressure control in comparison with usual care, but, by 6 months after the program’s completion, patients receiving usual care had on average achieved similar systolic blood pressure improvements (mean of 10 mm Hg decrease). In such high-performing healthcare systems, the programs already put into place to achieve the impressive 80% rates of blood pressure control in these systems may be demonstrating best
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.

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.

References


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