Survival Comparison of the Ross Procedure and Mechanical Valve Replacement With Optimal Self-Management Anticoagulation Therapy: Propensity-Matched Cohort Study

Summary: Survival in young adult patients after mechanical aortic valve replacement is reported to be significantly reduced compared with the general age- and gender-matched population. Prognosis of highly specialized self-management, better timing of surgery, and improved patient selection in recent years. In the absence of late mortality differences between comparable patients who received a mechanical aortic prosthesis and the Ross procedure, the weight of the prosthetic valve selection decision making process shifts toward quality of life and patient preference. Clinicians are therefore encouraged to systematically elicit patient preferences when discussing prosthetic valve selection in this young adult population.

Conclusions: In comparable patients, there is no late survival difference in the first postoperative decade for the Ross procedure over mechanical aortic valve replacement. In contrast to older reports, survival in these selected young adult patients closely resembles that of the general population, possibly as a result of highly specialized anticoagulation self-management. In the absence of late mortality differences between comparable patients who received a mechanical aortic prosthesis and the Ross procedure, the weight of the prosthetic valve selection decision making process shifts toward quality of life and patient preference. Clinicians are therefore encouraged to systematically elicit patient preferences when discussing prosthetic valve selection in this young adult population.

Dabigatran Versus Warfarin in Patients With Atrial Fibrillation: An Analysis of Patients Undergoing Cardioversion

Summary: Cardioversion in atrial fibrillation associated with an increased thromboembolic risk. The current recommendation is therapeutic anticoagulation with warfarin for at least 3 weeks before and 4 weeks after cardioversion; this recommendation is based on small nonrandomized observational and retrospective studies. Dabigatran is a novel oral direct thrombin inhibitor with rapid onset of action (peak levels in 2 hours) and a half-life of 12 to 17 hours. It was recently approved for stroke prevention in atrial fibrillation. The phase 3 Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial demonstrated that dabigatran 150 mg twice daily was superior to warfarin and dabigatran 110 mg twice daily was noninferior to warfarin for stroke prevention in atrial fibrillation. With 18,113 patients, RE-LY is the largest atrial fibrillation trial and provided a unique opportunity to evaluate the postcardioversion thromboembolic risk in patients who underwent cardioversion. A total of 1,983 cardioversions were performed during the RE-LY study: 647, 672, and 664 in the dabigatran 110 mg, dabigatran 150 mg, and warfarin groups, respectively. The frequencies of stroke and major bleeding within 30 days of cardioversion on the 2 doses of dabigatran were low and comparable to those on warfarin, with or without transesophageal echocardiography guidance. This posthoc analysis is the largest cardioversion experience to date and was the first to evaluate a novel anticoagulant in this setting. It also confirmed the efficacy and safety of warfarin in cardioversion in a large cohort of warfarin-treated patients. The 2 drugs are comparable, and dabigatran is a reasonable alternative to warfarin in patients requiring cardioversion.

Conclusions: This study is the largest cardioversion experience to date and the first to evaluate a novel anticoagulant in this setting. The frequencies of stroke and major bleeding within 30 days of cardioversion on the 2 doses of dabigatran were low and comparable to those on warfarin with or without transesophageal echocardiography guidance. Dabigatran is a reasonable alternative to warfarin in patients requiring cardioversion.

Incidence and Predictors of Early and Late Mortality After Transcatheter Aortic Valve Implantation in 663 Patients With Severe Aortic Stenosis

Summary: Transcatheter aortic valve implantation using the self-expandable CoreValve prosthesis was performed in 663 patients with severe aortic stenosis and high surgical risk in 14 Italian centers. Procedural success was 98% and intraprocedural mortality was 0.9%. The mortality rates at 30 days and 1 year were 5.4% and 15.0%, respectively. Early mortality was acceptably low compared with the anticipated risk calculated by means of the EuroSCORE and was strongly associated with the occurrence of procedural complications. Late mortality continued to occur from 30 days to 1 year after TAVI, primarily as the effect of postprocedural paravalvular aortic regurgitation ≥2+ and nonvalve related comorbidities such as cerebrovascular disease, chronic kidney disease and heart failure. Clinical and hemodynamic benefits observed acutely after TAVI were sustained at 1 year.
Conclusions: Benefit of TAVI with the CoreValve Revalving System is maintained over time up to 1 year, with acceptable mortality rates at various time points. Although procedural complications are strongly associated with early mortality at 30 days, comorbidities and postprocedural paravalvular aortic regurgitation ≥2+ mainly impact late outcomes between 30 days and 1 year.5

Safety of Percutaneous Left Atrial Appendage Closure: Results From the Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF (PROTECT AF) Clinical Trial and the Continued Access Registry

Summary: The Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF (PROTECT AF) study randomized atrial fibrillation (AF) patients at risk for stroke to either usual therapy (warfarin) or percutaneous left atrial appendage closure with the Watchman filter device. It was the first randomized study to demonstrate both the critical role of the left atrial appendage in the pathogenesis of AF-related stroke and the ability of a filter device to recapitulate the clinical benefit of warfarin. However, the procedural safety of this new invasive procedure was a source of concern. Based on PROTECT AF and the Continued Access Protocol Registry, a registry that has followed the trial, we assessed the safety of left atrial appendage closure, including the temporal distribution of safety events, the rate of events with increased experience, and the functional significance of these events. This analysis revealed that the safety events in the Watchman group are largely clustered early in the perioperative period and, after this point, the risk is minimal; that these safety events decrease in frequency with greater operator experience, particularly the rate of perioperative stroke and peri-cardial effusion/tamponade; and that the rates of events resulting in significant disability or death were statistically significantly lower for the Watchman device compared with warfarin therapy in PROTECT AF. This article suggests that despite a higher numeric rate of complications with Watchman implantation compared with warfarin, a more nuanced understanding of these data indicates that the safety of left atrial appendage closure is more favorable when one considers the differential functional impact of these events and the significant decrease in the frequency of events with operator experience.

Conclusion: As with all interventional procedures, there is a significant improvement in the safety of Watchman left atrial appendage closure with increased operator experience.4

Efficacy of Quantified Home-Based Exercise and Supervised Exercise in Patients With Intermittent Claudication: A Randomized Controlled Trial

Summary: A primary therapeutic goal for patients with peripheral artery disease and intermittent claudication is to regain lost ambulatory function through exercise rehabilitation. Medically supervised exercise programs are efficacious for improving claudication onset time and peak walking time, but more patients could benefit from an exercise program transported to the community setting (ie, home-based walking). However, home exercise has been poorly studied. This prospective, randomized, controlled clinical trial compared changes in claudication onset time, peak walking time, and daily ambulatory activity in peripheral artery disease patients with intermittent claudication after home-based exercise, supervised exercise, and usual-care control. Both exercise programs consisted of intermittent walking to near-maximal claudication pain for 12 weeks. We used a step activity monitor to address the primary flaw of previous home exercise programs by objectively measuring ambulatory cadences during home exercise sessions. Patients in home-based exercise completed 83% of their exercise sessions, averaging 42 minutes per session at a cadence of 37 strides per minute, and they increased claudication onset time, peak walking time, and daily ambulatory cadences apart from the exercise sessions. The changes in claudication onset time and peak walking time after home-based exercise were similar to those after supervised exercise, whereas the change in daily ambulatory cadences was greater. The clinical implication is that a home-based exercise program consisting of ambulatory monitoring, biweekly 15-minute meetings with staff, and feedback motivated patients to adhere to the program and may serve as a new model for improving claudication measures in more patients with less effort and fewer resources than a traditional supervised exercise program.

Conclusions: A home-based exercise program, quantified with a step activity monitor, has high adherence and is efficacious in improving claudication measures similar to a standard supervised exercise program. Furthermore, home-based exercise appears more efficacious in increasing daily ambulatory activity in the community setting than supervised exercise.5

Effect of Timing of Chronic Preoperative Aspirin Discontinuation on Morbidity and Mortality in Coronary Artery Bypass Surgery

Summary: The use of aspirin for patients with proven coronary artery disease is nearly ubiquitous, especially in those undergoing revascularization, whether percutaneous or surgical. The American Heart Association (AHA), American College of Cardiology (ACC), and Society of Thoracic Surgeons (STS) have given guidance as to the use of aspirin prior to coronary artery bypass grafting based on evidence mostly collected in the 1980s and 1990s. These guidelines are influenced by concerns of increased bleeding in the postoperative period and differ between societies. Thus, in the elective coronary artery bypass grafting population, aspirin is routinely discontinued up to 1 week prior to surgery. However, there is increasing concern that the discontinuation of aspirin, especially in patients with prior percutaneous coronary intervention, is linked to increased myocardial infarction, stroke, and death. More recently, there have been studies suggesting increased mortality in those who discontinue aspirin early before surgery. In our study of >4000 patients undergoing elective, isolated coronary artery bypass grafting, there was no significant difference between those with early discontinuation of aspirin (≥6 days before surgery) and late aspirin use (within 5 days) with regards to the composite outcome of in-hospital mortality, myocardial infarction, and stroke. Late use was associated with more intraoperative transfusion and postoperative transfusion but similar number of reoperations for bleeding. Thus, late use of aspirin results in no difference in the postoperative cardiovascular outcomes; however, there is an increased risk of bleeding and transfusion requirements.

Conclusions: Among patients undergoing isolated coronary artery bypass graft surgery, late discontinuation of aspirin resulted in no difference in postoperative cardiovascular outcomes; however, there was an increased transfusion requirement. Thus, we recommend weighing the risks and benefits of late aspirin use in these patients.6

Timeliness of Tissue-Type Plasminogen Activator Therapy in Acute Ischemic Stroke: Patient Characteristics, Hospital Factors, and Outcomes Associated With Door-to-Needle Times Within 60 Minutes

Summary: Tissue-type plasminogen activator (tPA) is a proven intervention for acute ischemic stroke patients. The benefits of intravenous tPA in acute ischemic stroke are time dependent, and guidelines recommend an arrival to treatment initiation (door-to-needle) time of ≤60 minutes. Despite the proven benefits, guidelines recommendations, and explicit goals for timely administration of tPA, the frequency, patient and hospital characteristics, temporal trends, and outcomes of ischemic stroke with door-to-needle times ≤60 minutes have not been well studied. Data from 25 504 acute ischemic stroke patients treated with tPA within 3 hours of symptom
onset from 2003 to 2009 in 1082 hospitals participating in the Get With the Guidelines–Stroke Program were analyzed to determine frequency, patient and hospital characteristics, and temporal trends in patients treated with door-to-needle times ≤60 minutes. Only 26.6% of tPA-treated patients had a door-to-needle time ≤60 minutes. Patient factors most strongly associated with door-to-needle time ≤60 minutes were younger age, male gender, white race, and no prior stroke. Hospital factors associated with ≤60-minute door-to-needle times included greater annual volumes of tPA-treated stroke patients. The proportion of patients with door-to-needle times ≤60 minutes varied widely by hospital and increased modestly from 19.5% in 2003% to 29.1% in 2009. Despite similar stroke severity, in-hospital mortality was lower and symptomatic intracranial hemorrhage was less frequent for patients with door-to-needle times ≤60 minutes compared with patients with door-to-needle times >60 minutes. These findings support the need for a targeted initiative to improve the timeliness of reperfusion in acute ischemic stroke.7

Is Hypothermia After Cardiac Arrest Effective in Both Shockable and Nonshockable Patients?: Insights From a Large Registry

Summary: Neurological outcome in out-of-hospital cardiac arrest remains poor, even for patients in whom a successful return of spontaneous circulation has been obtained. Therapeutic mild hypothermia could improve neurological outcome, particularly in patients with shockable initial rhythm (ie, ventricular fibrillation or pulseless tachycardia). However, its benefit is not well established in patients with nonshockable rhythms. In a tertiary center in Paris, France, therapeutic mild hypothermia has been progressively implemented over the last decade, regardless of the presented rhythm, in 457 of 708 shockable patients (65%) and in 261 of 437 nonshockable patients (60%). Overall, 342 of 1145 patients (30%) achieved a favorable outcome at hospital discharge, 274 of 708 shockable patients (39%) and 68 of 437 nonshockable patients (16%), respectively. Therapeutic mild hypothermia was associated with a nearly 2-fold improvement in favorable neurological outcome in shockable patients (adjusted odds ratio, 1.90; 95% confidence interval, 1.18–3.06) whereas no significant association was found in nonshockable patients (adjusted odds ratio, 0.71; 95% confidence interval, 0.37–1.36). Therefore, these findings support and strongly encourage the routine practice of therapeutic mild hypothermia in agreement with international guidelines in patients with ventricular fibrillation/ventricular tachycardia as initial rhythm. However, the benefit of hypothermia in nonshockable patients is still debatable. Further clinical investigations such as randomized trials are warranted to test new and different schemes of hypothermia in the most severely brain damaged patients, with the aim to reinforce its potential efficiency.8

Conclusions: Fewer than one-third of patients treated with intravenous tPA had door-to-needle times ≤60 minutes, with only modest improvement over the past 6.5 years. These findings support the need for a targeted initiative to improve the timeliness of reperfusion in acute ischemic stroke.7

Permanent Pacemaker Insertion After CoreValve Transcatheter Aortic Valve Implantation: Incidence and Contributing Factors (the UK CoreValve Collaborative)

Summary: Transcatheter aortic valve implantation has entered mainstream interventional cardiology as a treatment for aortic stenosis in patients with prohibitively high operative risk. This is a growing cohort of patients globally, given the increased longevity and prevalence of significant comorbidities. The CoreValve Revalving system (CoreValve Medtronic, Luxembourg) is 1 of the 2 prostheses currently in use, and it has been noted to be associated with an increased need for permanent pacemaker implantation. This study represents the largest analysis of the rates of permanent pacemaker implantation in patients receiving a CoreValve implant and uses clinical ECG data to create an electroanatomic model to explain the phenomenon. Consideration of these factors as addressed in this study has not only implications for the future designs of transcatheter aortic valve implantation devices but also immediate clinical impact on the standard of care of this increasingly numerous patient group.

Conclusion: One third of patients undergoing a CoreValve transcatheter aortic valve implantation procedure require a permanent pacemaker within 30 days. Periprocedural atrioventricular block, balloon predilatation, use of the larger CoreValve prosthesis, increased intraventricular septum diameter and prolonged QRS duration were associated with the need for permanent pacemakers.9

Risk of Upper Gastrointestinal Bleeding With Low-Dose Acetylsalicylic Acid Alone and in Combination With Clopidogrel and Other Medications

Summary: Clinical trials have shown that low-dose acetylsalicylic acid (ASA) and clopidogrel are associated with an increased risk of upper gastrointestinal bleeding (UGIB). Other medications that are commonly coadministered with low-dose ASA and clopidogrel can also increase the risk of UGIB. However, few studies have quantified the risk of UGIB associated with specific combinations of these therapies in the general population. We used The Health Improvement Network (a UK primary care database) to identify 2049 patients with a UGIB diagnosis in 2000 to 2007 and 20 000 controls with no UGIB diagnosis. We evaluated drug use in these patients and estimated the relative risk (RR) of UGIB associated with various medications. We found that the RR of UGIB was 1.80 (95% confidence interval [CI], 1.59–2.03) in users of low-dose ASA and 1.67 (95% CI, 1.24–2.24) in users of clopidogrel. Compared with low-dose ASA monotherapy, the risk of UGIB was significantly increased when low-dose ASA was coadministered with clopidogrel (RR, 2.08; 95% CI, 1.34–3.21), oral anticoagulants (RR, 2.00; 95% CI, 1.15–3.45), low-medium-dose nonsteroidal anti-inflammatory drugs (RR, 2.63; 95% CI, 1.93–3.60), high-dose nonsteroidal anti-inflammatory drugs (RR, 2.66; 95% CI, 1.88–3.76), or high-dose oral corticosteroids (RR, 4.43; 95% CI, 2.10–9.34). Our findings confirm that low-dose ASA and clopidogrel are associated with an increased risk of UGIB in the general population and show that the risk of UGIB is increased further in patients using combination therapies. These factors should be taken into account when assessing the risk-to-benefit ratio of low-dose ASA.

Conclusions: Use of low-dose ASA is associated with an almost 2-fold increase in the risk of UGIB compared with nonuse. This risk is increased further in individuals taking low-dose ASA along with clopidogrel, oral anticoagulants, nonsteroidal anti-inflammatory drugs, or high-dose oral corticosteroids.10

Impact of Oral Sildenafil on Exercise Performance in Children and Young Adults After the Fontan Operation: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

Summary: Children and young adults with functional single-ventricle physiology have decreased exercise capacity as a result of an inability to normally increase transpulmonary blood flow during exercise. A medication capable of decreasing pulmonary vascular
Association of Incident Cardiovascular Disease With Progression of Sleep-Disordered Breathing

Conclusions: In this cohort, sildenafil significantly improved ventilatory efficiency during peak and submaximal exercise. There was also a suggestion of improved oxygen consumption at the anaerobic threshold in 2 subgroups. These findings suggest that sildenafil may be an important agent for improving exercise performance in children and young adults with single-ventricle physiology after the Fontan operation. However, the long-term safety and efficacy of sildenafil in this patient population remain unknown.

Do Postmarketing Surveillance Studies Represent Real-World Populations?: A Comparison of Patient Characteristics and Outcomes After Carotid Artery Stenting

Conclusions: Participants in postmarketing surveillance studies for carotid artery stenting have different clinical and procedural characteristics and lower mortality compared with nonparticipants. Extrapolating results from postmarketing surveillance studies of carotid artery stenting to larger real-world settings should be done only with great caution.13

Effects of Optimal Medical Treatment With or Without Coronary Revascularization on Angina and Subsequent Revascularizations in Patients With Type 2 Diabetes Mellitus and Stable Ischemic Heart Disease

Conclusions: Participants in postmarketing surveillance studies for carotid artery stenting have different clinical and procedural characteristics and lower mortality compared with nonparticipants. Extrapolating results from postmarketing surveillance studies of carotid artery stenting to larger real-world settings should be done only with great caution.13

Clinical Benefit of Statin Pretreatment in Patients Undergoing Percutaneous Coronary Intervention: A Collaborative Patient-Level Meta-Analysis of 13 Randomized Studies

Conclusions: Participants in postmarketing surveillance studies for carotid artery stenting have different clinical and procedural characteristics and lower mortality compared with nonparticipants. Extrapolating results from postmarketing surveillance studies of carotid artery stenting to larger real-world settings should be done only with great caution.13
Conclusions: High-dose statin pretreatment leads to a significant reduction in periprocedural myocardial infarction and 30-day adverse events in patients undergoing percutaneous coronary intervention. This strategy should be considered in all patients with planned percutaneous coronary intervention.13

Frequency and Predictors of Stent Thrombosis After Percutaneous Coronary Intervention in Acute Myocardial Infarction

Summary: The prospective, multicenter, randomized Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial included 3602 patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention who were randomized to heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy. Stents were implanted in 3202 patients, including 2261 who received drug-eluting stents and 861 who received only bare metal stents. Definite or probable stent thrombosis within 2 years, occurred in 4.4% of patients, including 0.9% acute events, 1.6% subacute events, 1.0% late events, and 1.1% very late events. The 2-year cumulative rates of stent thrombosis were similar with both drug-eluting stents and bare metal stents, as well as in patients randomized to bivalirudin monotherapy versus heparin plus glycoprotein IIb/IIIa inhibitor. Acute stent thrombosis occurred more frequently in patients assigned to bivalirudin compared with heparin plus a glycoprotein IIb/IIIa inhibitor, whereas stent thrombosis after 24 hours occurred less frequently in patients with bivalirudin compared with heparin plus a glycoprotein IIb/IIIa inhibitor. Prerandomization heparin and a 600-mg clopidogrel loading dose were independent predictors of reduced acute and subacute stent thrombosis, respectively. Optimizing adjunct pharmacology, including early antithrombin therapy and preloading with a potent antiplatelet therapy, may further reduce stent thrombosis in ST-segment elevation myocardial infarction, thereby improving event-free survival in these high-risk patients.

Conclusions: Stent thrombosis is not uncommon within the first 2 years after primary percutaneous coronary intervention in ST-segment elevation myocardial infarction, and occurs with similar frequency in patients receiving drug-eluting stents versus bare metal stents and bivalirudin alone versus heparin plus a glycoprotein IIb/IIIa inhibitor. Optimizing adjunct pharmacology including early antithrombin therapy and preloading with a potent antiplatelet therapy may further reduce stent thrombosis in ST-segment elevation myocardial infarction.16

Transmural Heterogeneity and Remodeling of Ventricular Excitation-Contraction Coupling in Human Heart Failure

Summary: Excitation-contraction coupling is a complex process mediated by a network of proteins that control ionic currents, cell signaling, calcium handling, and sarcomeric mechanics. The 2 hallmarks of excitation-contraction coupling preceding mechanical contraction are the transmembrane action potential and intracellular calcium transient. Numerous studies in animal models have significantly advanced our understanding of the fundamental mechanisms of excitation-contraction coupling at the molecular, cellular, and whole-heart levels. However, the extrapolation of these findings to clinical practice is limited by the lack of functional human data. Our study provides, for the first time in medical history, such functional data: simultaneous recordings of action potentials and calcium transients from the human left ventricular tissue of nonfailing and failing hearts. We found that the nonfailing human left ventricle has a transmural gradient of calcium transient kinetics, with the calcium transient being longer at the endocardial than at the epicardial layers of the ventricular wall. A decrease in this gradient in the failing heart reversed the normal sequence of relaxation. We also found that heart failure leads to significant changes in calcium dynamics, manifesting as a biphasic calcium entry into the cytosol. Downregulation of sarcoplasmic reticulum Ca2+-ATPase 2a depends on the origin and anatomic location, which might explain the inconsistency in the literature on the subject. Transmural heterogeneity indicates that the anatomic location must be considered in studies of molecular remodeling of excitation-contraction coupling. Our study confirms some of the earlier findings in animal models but contradicts others. Thus, extrapolation of findings from animal models to humans should be done with caution.

Conclusions: For the first time, we present direct experimental evidence of transmural heterogeneity of excitation-contraction coupling and calcium handling in human hearts. End-stage heart failure is associated with the heterogeneous remodeling of excitation-contraction coupling and calcium handling.17

Development of a Squalene Synthase Inhibitor for the Treatment of Hypercholesterolemia

Summary: Elevated low-density lipoprotein cholesterol is the cornerstone of coronary artery disease prevention, and although statins have provided enormous advances, there remains an unmet need for new effective, well-tolerated, safe low-density lipoprotein cholesterol-lowering drugs. This report summarizes the phase 2 and 3 results from the lapaquistat clinical program, which was halted at an advanced stage as a result of potential hepatic safety issues. Lapaquistat acetate is a squalene synthase inhibitor, a step after the statins, investigated for the treatment of hypercholesterolemia. Data were pooled from 12 studies (n=6151) lasting 6 to 96 weeks. Trials were randomized, double-blind, parallel, and placebo or active controlled with lapaquistat monotherapy or coadministration with other lipid-altering drugs. All studies included lapaquistat 100 mg daily; 5 included 50 mg; and 1 included 25 mg. The main outcome measure was low-density lipoprotein cholesterol, secondary lipid/metabolic parameters, and overall safety. Lapaquistat 100 mg significantly decreased low-density lipoprotein cholesterol by 21.6% in monotherapy and 18.0% in combination with a statin. It also significantly reduced C-reactive protein. Total adverse events were higher for lapaquistat than placebo, although individual events were similar. At 100 mg, alanine aminotransferase values ≥3 times the upper limit of normal on ≥2 consecutive visits increased (2.0%–2.7% versus 0.3%–0.7% for placebo or low-dose atorvastatin). Two patients receiving lapaquistat 100 mg met the Hy Law criteria of alanine aminotransferase elevation plus increased total bilirubin. Squalene synthase inhibition with lapaquistat, alone or in combination with statins, effectively lowered low-density lipoprotein cholesterol and C-reactive protein. Elevations in alanine aminotransferase combined with a rare increase in bilirubin presented potential hepatic safety issues, resulting in termination of development. The lapaquistat experience illustrates the current challenges in lipid-altering drug development.

Conclusions: Squalene synthase inhibition with lapaquistat acetate, alone or in combination with statins, effectively lowered low-density lipoprotein cholesterol in a dose-dependent manner. Elevations in alanine aminotransferase, combined with a rare increase in bilirubin, presented potential hepatic safety issues, resulting in termination of development. The lapaquistat experience illustrates the current challenges in lipid-altering drug development.18

Declining Stroke and Vascular Event Recurrence Rates in Secondary Prevention Trials Over the Past 50 Years and Consequences for Current Trial Design

Summary: Formal analysis of secondary stroke prevention trials over the last 5 decades confirms that vascular event rates in control arms have declined substantially. Annual recurrent stroke rates in control arms fell from 8.71% in trials launched in the 1960s to 6.10% in the 1970s, 5.41% in the 1980s, 4.04% in the 1990s, and 4.98% in the 2000s. Annual event rates for fatal stroke decreased from 2.87±1.04% in the 1960s to 0.36±0.14% in the 2000s, and those for...
major vascular events declined from 10.91 ± 1.29% in the 1960s to 6.29 ± 0.68% in the 2000s. Multivariate analysis suggests that increasing antithrombotic use and lower blood pressures were the most important drivers of vascular event rate reduction. The sample size required for adequately powered trials more than doubled during the study period. If a continued linear decline is assumed, the annual recurrent stroke rate in trial control arms in the coming decade is projected to be 2.25%, and control group sample size requirements would increase to 15,983 patients for a trial designed to detect a 20% relative risk reduction in the frequency of recurrent stroke, with 2 years of follow-up, 80% power, and 5% α error. The introduction into clinical practice of successive waves of therapies with proven efficacy in stroke prevention has been notably successful, resulting in a substantial decline in the rate of recurrent vascular events in the control arms of secondary stroke prevention trials. Consequently, trials of new therapies are more arduous, requiring ever larger sample sizes to confirm treatment efficacy, and clinical investigators must cope with the paradox of progress.

Conclusions: Recurrent stroke and vascular event rates have declined substantially over the last 5 decades, with improved blood pressure control and more frequent use of antiplatelet therapy as the leading causes. Considerably larger sample sizes are now needed to demonstrate incremental improvements in medical secondary prevention.19

Sensitivity of the Aortic Dissection Detection Risk Score, a Novel Guideline-Based Tool for Identification of Acute Aortic Dissection at Initial Presentation: Results From the International Registry of Acute Aortic Dissection

Summary: Acute aortic dissection is known to be an underrecognized condition at presentation, yet the mortality associated with delayed or missed diagnosis is substantial. The American Heart Association, American College of Cardiology, and other professional societies recently published the 2010 thoracic aortic disease guidelines, which include recommendations for the initial bedside screening of at-risk patients. The goal of these recommendations is to improve physician recognition and facilitate prompt diagnostic testing in those at risk. In our study, we modified this guideline-based screening tool to define the aortic dissection detection risk score, which divides patients into low-, intermediate-, and high-risk groups on the basis of historical and examination features. We then tested the aortic dissection detection risk score for sensitivity among 2538 patients enrolled in the International Registry of Acute Aortic Dissection. Our results indicate that the aortic dissection detection risk score is 95.7% sensitive for the detection of acute aortic dissection and may help to facilitate prompt evaluation if applied at the bedside. Additional studies are needed to determine the specificity of the aortic dissection detection risk score and provide prospective validation.

Conclusions: The clinical risk markers proposed in the 2010 thoracic aortic disease guidelines and their application as part of the acute dissection detection risk score comprise a highly sensitive clinical tool for the detection of acute aortic dissection.20

Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation: An Analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial

Summary: The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial in patients with atrial fibrillation and at least 1 additional risk factor for stroke demonstrated that dabigatran 110 mg twice a day compared with warfarin was associated with a similar risk of stroke or systemic embolism and a lower risk of major bleeding, and that dabigatran 150 mg twice a day compared with warfarin was associated with a lower risk of stroke or systemic embolism compared with warfarin was associated with a lower risk of major bleeding in those aged <75 years and a similar risk in those aged ≥75 years. Dabigatran 150 mg twice a day compared with warfarin was associated with a lower risk of major bleeding in those aged <75 years and a trend toward higher risk of major bleeding in those aged ≥75 years. The interaction between treatment and age was evident for extracranial bleeding but not for intracranial bleeding, which was consistently reduced with dabigatran compared with warfarin irrespective of age. These results suggest that in patients with atrial fibrillation and at least 1 additional risk factor for stroke who are aged <75 years, the higher dabigatran dose might be preferable, whereas in older patients, the lower dabigatran dose might be considered a means to reduce the risk of bleeding.

Conclusions: In patients with atrial fibrillation at risk for stroke, both doses of dabigatran compared with warfarin have lower risks of both intracranial and extracranial bleeding in patients aged <75 years. In those aged ≥75 years, intracranial bleeding risk is lower but extracranial bleeding risk is similar or higher with both doses of dabigatran compared with warfarin.21

Cost-Effectiveness of Dabigatran for Stroke Prophylaxis in Atrial Fibrillation

Summary: Each year, in the United States alone, atrial fibrillation causes >50,000 strokes and $12 billion in medical expenditure. Thus, safe and cost-effective stroke prevention is critical to the atrial fibrillation population. Dabigatran etexilate was developed with the hope that it would be as effective as warfarin, but safer and easier to administer. The Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) found that dabigatran 150 mg twice daily was superior to warfarin in the prevention of ischemic stroke. On the basis of results from RE-LY, the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE), and other trials, we developed a decision-analysis model to compare the cost and quality-adjusted survival of various antithrombotic therapies. Dabigatran 150 mg (twice daily) was cost-effective in atrial fibrillation populations at high risk of hemorrhage or high risk of stroke unless international normalized ratio control with warfarin was excellent. Warfarin was cost-effective in moderate-risk atrial fibrillation populations unless international normalized ratio control was poor.

Conclusions: Dabigatran 150 mg (twice daily) was cost-effective in atrial fibrillation populations at high risk of hemorrhage or high risk of stroke unless international normalized ratio control with warfarin was excellent. Warfarin was cost-effective in moderate-risk atrial fibrillation populations unless international normalized ratio control was poor.22

Differences in Admitting Hospital Characteristics for Black and White Medicare Beneficiaries With Acute Myocardial Infarction

Summary: Recent research has identified differential access to high-quality hospital care as an important, perhaps primary, factor associated with racial disparities in the treatment of acute myocardial infarction. However, the reasons why minorities are more often treated at hospitals with relatively lower quality of care are not fully understood. We examined the relationship between patient race, distance, and admissions to hospitals with particular characteristics (eg, provision of revascularization services, quality ranks) available to patients within defined hospital markets. We found that, after accounting for distance from home to available hospitals, black patients were overall less likely to be admitted to the closest
hospitals, to hospitals with revascularization programs, and to high-quality hospitals. In secondary analyses limited to black and white patients living in similar ZIP codes, these differences were attenuated and not statistically significant. Our findings suggest that differences in admissions to hospitals with particular characteristics are not driven exclusively by race, but also by characteristics of the environment in which patients live. Such local context factors may include economic factors, community culture (e.g., perceived discrimination, high levels of distrust in the healthcare system), and physician referral practices. Practicing physicians need to be aware of and sensitive to such potential local barriers in access to high-quality care.

**Conclusions:** Differences in admissions to revascularization and high-quality hospitals may contribute to disparities in acute myocardial infarction care. These differences may be due in part to residential ZIP code characteristics.23

**Blood Pressure Targets in Subjects With Type 2 Diabetes Mellitus/Impaired Fasting Glucose: Observations From Traditional and Bayesian Random-Effects Meta-Analyses of Randomized Trials**

**Summary:** Most guidelines for treatment of hypertension, including the seventh report of the Joint National Committee, recommend an aggressive blood pressure goal of <130/80 mm Hg for patients with diabetes mellitus. However, the evidence on which the guidelines are based is limited. In our analyses of 13 randomized trials with 37,736 participants, we noted that in patients with type 2 diabetes mellitus, a systolic blood pressure treatment goal of 130 to 135 mm Hg is acceptable. However, with more aggressive goals (<135 mm Hg), we observed target organ heterogeneity in that the risk of stroke continued to fall, but there was no benefit regarding the risk of other macrovascular or microvascular (cardiac, renal, and retinal) events, and the risk of serious adverse events even increased.

**Conclusions:** The present body of evidence suggests that in patients with type 2 diabetes mellitus/impaired fasting glucose/impaired glucose tolerance, a systolic blood pressure treatment goal of 130 to 135 mm Hg is acceptable. However, with more aggressive goals (<135 mm Hg), we observed target organ heterogeneity in that the risk of stroke continued to fall, but there was no benefit regarding the risk of other macrovascular or microvascular (cardiac, renal and retinal) events, and the risk of serious adverse events even increased.24

**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 -28.4–27.4 m], P=0.97) or between those given simvastatin (n=32) or placebo (n=33; placebo-corrected difference -27.6 m [95% confidence interval -59.6–4.3 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.

**Conclusion:** 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.25

**Cardiac Dysfunction and Noncardiac Dysfunction as Precursors of Heart Failure With Reduced and Preserved Ejection Fraction in the Community**

**Summary:** In our prospective study of a large, community-based sample, antecedent subclinical cardiac and noncardiac major organ system dysfunction was associated with risk of future heart failure. The presence of asymptomatic left ventricular systolic and diastolic dysfunction preceded and increased the risk of incident heart failure by >2-fold and >30%, respectively. With adjustment for cardiac dysfunction, the presence of subclinical renal impairment, airflow limitation, or anemia was each associated with >30% increased risk of incident heart failure. Notably, the significant risk factors differed according to the type of incident heart failure (preserved versus reduced ejection fraction). Antecedent left ventricular systolic dysfunction, subclinical renal impairment, and lower hemoglobin concentrations were associated with a higher incidence of heart failure with reduced ejection fraction, whereas antecedent diastolic dysfunction and baseline airflow obstruction were related positively to the risk of future heart failure with preserved ejection fraction. This study provides longitudinal evidence for the progressive nature of heart failure as emphasized in current heart failure guidelines and underscores the potential importance of noncardiac risk factors in predisposing to the manifestation of overt heart failure. The implications for the early identification of individuals at risk of heart failure and potential strategies to prevent progression to overt heart failure deserve further study.

**Conclusions:** Antecedent cardiac dysfunction and noncardiac organ dysfunction are associated with increased incidence of heart failure, supporting the notion that heart failure is a progressive syndrome and underscoring the importance of noncardiac factors in its occurrence.26

**Cost-Effectiveness of Statin Therapy for Primary Prevention in a Low-Cost Statin Era**

**Summary:** This cost-effectiveness analysis sought to identify whether expanded use of statins for primary prevention would be cost-effective or even cost-saving in an era of generic, low-cost statins. Assuming that statins are universally available at a cost of $4/mo and efficacious in all persons >35 years of age, treatment thresholds of low-density lipoprotein cholesterol >160 mg/dL for low-risk persons (0–1 risk factor), >130 mg/dL for moderate-risk persons (≥2 risk factors and 10-year risk <10%), and >100 mg/dL for moderately high-risk persons (≥2 risk factors and 10-year risk ≥10%) would reduce annual healthcare costs by $430 million compared with Adult Treatment Panel III guidelines. Lowering thresholds to >130 mg/dL for persons with 0 risk factors and >100 mg/dL for persons with 1 risk factor and treating all moderate- and moderately high-risk persons would further lower CHD burden for $9900 per quality-adjusted life-year compared with Adult Treatment Panel III guidelines. These findings were insensitive to known and hypothetical side effects, but were sensitive to large reductions in efficacy of statins or a long-term discontinuity burden for which a patient would trade 80 days of life to avoid 30 years of statins. Low-cost statins are cost-effective for most persons with even modestly elevated cholesterol or any coronary heart disease risk factors if they do not mind taking a pill daily.

**Conclusions:** Low-cost statins are cost-effective for most persons with even modestly elevated cholesterol or any coronary heart
Mortality and Readmission of Patients With Heart Failure, Atrial Fibrillation, or Coronary Artery Disease Undergoing Noncardiac Surgery: An Analysis of 38,047 Patients

Summary: Heart failure (HF), coronary artery disease (CAD) and atrial fibrillation (AF) are the 3 most common chronic cardiovascular conditions, affecting a broad cross-section of the population. An increasing number of patients with HF, CAD, and AF survive longer and undergo noncardiac surgery. Although the perioperative risk for the patients with CAD has been well described, the risk for patients with HF or AF is less well defined. Using a cohort of >37,000 patients with HF, CAD, or AF from Alberta, Canada, we found that the risk for 30-day postoperative mortality was 3 times higher for those with HF compared with those with CAD, and nearly twice as high for AF compared with CAD. This difference persisted even after adjustment for patient and hospital variables. Even minor procedures carried significantly more risk than previously appreciated. Although current perioperative risk prediction models place greater emphasis on CAD than HF or AF, patients with HF or AF have a significantly higher risk of postoperative mortality than patients with CAD.

Conclusions: Although current perioperative risk prediction models place greater emphasis on CAD than HF or AF, patients with HF or AF have a significantly higher risk of postoperative mortality than patients with CAD, and even minor procedures carry a risk higher than previously appreciated.

One-Year Outcomes of Cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) Registry: The European Registry of Transcatheter Aortic Valve Implantation Using the Edwards SAPIEN Valve

Summary: Cohort 1 of the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) Registry describes the outcomes at 30 days and 1 year of >1,000 consecutive patients undergoing transcatheter aortic valve implantation using the Edwards SAPIEN valve. The 30-day results have previously been published and have established the procedural results of the technique in a large group of patients in a multicenter registry. The 1-year data describe the outcomes in the largest group of transcatheter aortic valve implantation patients at this time point. This combined data will allow the interventional community to adequately consent transcatheter aortic valve implantation patients on the basis of robust data and will also be a benchmark against which future patient groups and any new devices may be measured.

Conclusion: The SOURCE Registry is the largest consecutively enrolled registry for transcatheter aortic valve implantation procedures. It demonstrates that with new transcatheter aortic techniques excellent 1-year survival in high-risk and inoperable patients is achievable and provides a benchmark against which future transcatheter aortic valve implantation cohorts and devices can be measured.

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.

Prognostic Value of Admission Glycosylated Hemoglobin and Glucose in Nondiabetic Patients With ST-Segment–Elevation Myocardial Infarction Treated With Percutaneous Coronary Intervention

Summary: Measurement of admission glucose and hemoglobin A1c (HbA1c) in acute myocardial infarction may identify patients with disturbed glucose metabolism and an increased risk for adverse outcome. Although HbA1c and glucose are related, they can differentiate between mechanisms of adverse outcome. Admission glucose is related to increased hemodynamic stress, whereas HbA1c identifies patients with higher long-term cardiovascular risk, possibly by abnormal long-term glucose levels. Early identification of these patient groups enables the initiation of specific intervention strategies and may help us develop strategies to improve prognosis in these high-risk patient groups. This is of particular importance because there is a global increase in the number of patients suffering from cardiovascular disease with underlying insulin resistance, prediabetes, and overt diabetes mellitus. Both glucose and HbA1c should be measured in patients admitted with ST-segment–elevation myocardial infarction.

Conclusions: In nondiabetic patients with ST-segment–elevation myocardial infarction, both elevated admission glucose and HbA1c levels were associated with adverse outcome. Both of these parameters reflect different patient populations, and their association with outcome is probably due to different mechanisms. Measurement of both parameters enables identification of these high-risk groups for aggressive secondary risk prevention.

Dose Response Between Physical Activity and Risk of Coronary Heart Disease: A Meta-Analysis

Summary: Physical activity has clearly been shown to decrease the risk of developing coronary heart disease. However, the dose-response relation (How much activity is needed? What level of risk reduction is associated with specified levels of activity? Does the risk continue to decrease at higher levels of activity?) is less clear. This is the first meta-analysis of epidemiological studies to quantify the dose-response relation, examining both the specific amounts of physical activity and associated risk reductions for coronary heart disease (Previous meta-analyses have quantified only risk reductions, not the specific doses of activity required). We found that individuals who engaged in the equivalent of 150 minutes/wk of...
Cardiac Resynchronization Therapy as a Therapeutic Option in Patients With Moderate-Severe Functional Mitral Regurgitation and High Operative Risk

Summary: In heart failure patients with ischemic or nonischemic cardiomyopathy, functional mitral regurgitation (MR) is a frequent finding that has important prognostic implications. Functional MR can be treated surgically by means of restrictive annuloplasty with or without additional surgical left ventricular remodeling. However, the beneficial effect of this procedure on long-term mortality has not been clearly demonstrated, and many of these patients may not be referred for or are denied mitral valve surgery because of the high operative mortality risk. The current study sought to investigate the effect of cardiac resynchronization therapy (CRT) on moderate-severe functional MR and whether the reduction in severity of MR after CRT positively influenced long-term prognosis. In 85 heart failure patients with moderate-severe functional MR, a significant reduction in extent of MR was observed after CRT, and particularly 42 patients (49%) improved ≥1 grade of MR. Importantly, improvement in MR was a strong independent prognostic factor of improved survival (hazard ratio, 0.35, P=0.043). These findings demonstrate that CRT may improve MR in heart failure patients with moderate-severe functional MR and high risk for surgery. Secondly, the current study showed for the first time that the improvement in MR results in superior survival during long-term follow-up independently of other known prognostic factors. Therefore, CRT may yield a valuable therapeutic option for heart failure patients with moderate-severe functional MR but with a high operative risk.

Conclusions: Cardiac resynchronization therapy is a potential therapeutic option in heart failure patients with moderate-severe functional MR and high risk for surgery. Improvement in MR results in superior survival after CRT.

Platelet Reactivity and Cardiovascular Outcomes After Percutaneous Coronary Intervention: A Time-Dependent Analysis of the Gauging Responsiveness With a VerifyNow P2Y12 Assay: Impact on Thrombosis and Safety (GRAVITAS) Trial

Summary: A variable pharmacodynamic response to clopidogrel has been well documented, and an association between high on-treatment reactivity while patients are receiving clopidogrel and adverse clinical outcomes after percutaneous coronary intervention has been shown in prospective, observational studies. In the Gauging Responsiveness With a VerifyNow P2Y12 Assay: Thrombosis and Safety (GRAVITAS) trial, high-dose clopidogrel was not superior to standard-dose clopidogrel in preventing cardiovascular events after percutaneous coronary intervention in patients with high on-treatment reactivity, defined as on-treatment reactivity ≥230 P2Y12 reaction units according to the VerifyNow P2Y12 platelet function test. The aim of this analysis was to examine the relationship between outcomes and on-treatment reactivity over the course of the trial. In the 2796 patients with evaluable platelet function data, on-treatment reactivity <208 P2Y12 reaction units at randomization or during follow-up was associated with a lower risk of cardiovascular death, myocardial infarction, and stent thrombosis, even after adjustment for other predictors of outcome. The treatment strategy of high-dose clopidogrel achieved this level of reactivity in <50% of patients. These findings support the prognostic utility of serial platelet function testing after percutaneous coronary intervention, including in patients with stable coronary artery disease, and suggest that in patients who display high on-treatment reactivity while receiving standard-dose therapy, double-dose clopidogrel is largely ineffective in achieving a level of on-treatment reactivity associated with improved outcome. Therefore, the safety and efficacy of alternative approaches using more potent P2Y12 inhibitors in patients with high on-treatment reactivity merit further investigation.

Conclusions: In the GRAVITAS trial, achievement of on-clopidogrel reactivity <208 P2Y12 reaction units at 12 to 24 hours after percutaneous coronary intervention or during follow-up was associated with a lower risk for cardiovascular events. The efficacy of an
individualized strategy to target a level of on-treatment reactivity below this threshold merits investigation.\textsuperscript{35}

**Comparative Effectiveness of Exercise Electrocardiography With or Without Myocardial Perfusion Single Photon Emission Computed Tomography in Women With Suspected Coronary Artery Disease: Results From the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) Trial**

**Summary:** There is a paucity of prospective, randomized trials as well as a compelling need for higher levels of scientific evidence, including targeted, prospective comparative effectiveness research, to more rigorously address the outpatient diagnostic evaluation of patients with suspected coronary artery disease. In particular, the evaluation of women with suspected coronary artery disease remains a conundrum because of their atypical symptom presentation, which often results in varied diagnostic practice patterns. The What Is the Optimal Method for Ischemia Evaluation in Women trial was designed to compare the effectiveness of the standard exercise tolerance test (ETT) versus exercise myocardial perfusion imaging (MPI) for predicting 2-year event-free survival for women with suspected coronary artery disease at intermediate pretest coronary artery disease likelihood who are capable of performing exercise. A total of 824 women were randomized to a standard ETT or exercise MPI. At 2 years, there was no difference in major adverse cardiovascular events (ETT, 98.0%; MPI, 97.7%; P = 0.59). Compared with ETT alone, index testing costs were higher for the exercise MPI group (P < 0.001), whereas downstream procedural costs were slightly lower (P = 0.008). Overall, the cumulative diagnostic cost saving was 48% for the ETT compared with the exercise MPI group (P < 0.001). In conclusion, in low-risk, symptomatic women capable of exercise, a nonimaging strategy employing standard ETT was as effective in predicting clinical outcomes and more cost efficient than a strategy of initial exercise MPI.

**Conclusions:** In low-risk, exercising women, a diagnostic strategy that uses ETT versus exercise MPI yields similar 2-year post test outcomes while providing significant diagnostic cost savings. The ETT with selective follow-up testing should be considered as the initial diagnostic strategy in symptomatic women with suspected coronary artery disease.\textsuperscript{36}

**Role of Cardiovascular Magnetic Resonance as a Gatekeeper to Invasive Coronary Angiography in Patients Presenting With Heart Failure of Unknown Etiology**

**Summary:** Identifying the underlying etiology in patients with new onset heart failure and no overt features of underlying coronary artery disease, eg, angina, can be challenging. Invasive coronary angiography (CA) carries tangible risks and does not provide tissue characterization. In this prospective study of 120 patients (powered to display noninferiority), late gadolinium enhanced cardiovascular magnetic resonance (LGE-CMR) showed equivalence to CA when determined against a gold standard consensus panel who considered data from all the investigations. Diagnoses ascribed by LGE-CMR and CA were also validated against clinical outcomes at a median of 3.7 years. LGE-CMR is ideally placed as a gatekeeper to CA because it is safer, uniquely provides biventricular function and tissue characterization data, and is economically viable. LGE-CMR and CA were equivalent in diagnostic accuracy (97% versus 95%) and the data suggests that 73% of patients would have appropriately avoided CA, being spared the risks and costs of this investigation. Importantly, no patient with prognostically important coronary artery disease would have been denied CA and any subsequent revascularization as LGE-CMR had a negative predictive value of 100%. The data also suggests the need for a paradigm shift in the classification of patients with heart failure to reflect not just coronary anatomy, but also myocardial tissue characterization. This study therefore challenges the traditional dichotomy of ischemic versus nonischemic cardiomyopathy by revealing subgroups of patients with features of both ischemic and nonischemic etiologies.

**Conclusion:** This study showed that LGE-CMR is a safe, clinically effective, and potentially economical gatekeeper to CA in patients presenting with heart failure of uncertain etiology.\textsuperscript{37}

**Mechanisms of Myocardial Infarction in Women Without Angiographically Obstructive Coronary Artery Disease**

**Summary:** There is no angiographically demonstrable obstructive coronary artery disease in a substantial proportion of patients with myocardial infarction, particularly women. Plaque rupture has long been hypothesized to be a cause of myocardial infarction with nonobstructive coronary artery disease. We sought to determine the mechanism(s) of myocardial infarction in this setting using intravascular ultrasound and cardiac MRI performed within 1 week. Fifty women were enrolled with median worst coronary angiographic stenosis of 20% and median peak troponin of 1.60 ng/mL. Plaque disruption (rupture and/or ulceration) was found on blinded core laboratory intravascular ultrasound review in 38% of patients tested. Late gadolinium enhancement (LGE) was identified in 39% and abnormal T2 signal in 53% of women undergoing cardiac MRI. The most common LGE pattern was ischemic (transmural/subendocardial). Nonischemic (midmyocardial/subepicardial) and mixed LGE patterns were also observed. T2 signal hyperintensity was common and LGE was infrequent among patients with plaque disruption. We hypothesize that vasospasm of, embolism to, or flush occlusion of a branch vessel caused myocardial infarction in patients with an ischemic LGE pattern but without plaque disruption. Intravascular ultrasound and cardiac MRI provided complementary information in this cohort and together revealed abnormalities in 35 of 50 patients (70%). In this study, the first prospective evaluation using intravascular ultrasound and cardiac MRI in women with acute myocardial infarction and without obstructive coronary artery disease at angiography, we have demonstrated that plaque disruption is a frequent finding. We have also shown that LGE commonly identifies the location and pattern of myocardial damage and that acute myocardial edema is frequently present in these patients.

**Conclusions:** Plaque rupture and ulceration are common in women with myocardial infarction without angiographically demonstrable obstructive coronary artery disease. In addition, LGE is common in this cohort of women, with an ischemic pattern of injury most evident. Vasospasm and embolism are possible mechanisms of ischemic LGE without plaque disruption. Intravascular ultrasound and cardiac MRI provide complementary mechanistic insights into female myocardial infarction patients without obstructive coronary artery disease and may be useful in identifying potential causes and therapies.\textsuperscript{38}

**Predicting the Restenosis Benefit of Drug-Eluting Versus Bare Metal Stents in Percutaneous Coronary Intervention**

**Summary:** Drug-eluting stents for percutaneous coronary intervention decrease the risk of restenosis compared with bare metal stents. However, they are costlier, require prolonged dual antiplatelet therapy, and provide the most benefit in patients at highest risk for restenosis. To assist physicians in targeting drug-eluting stent use in patients at the highest risk for target vessel revascularization, we developed and validated a model to predict target vessel revascularization from a contemporary population-based registry in Massachusetts based on commonly collected clinical and angiographic variables that are obtainable before percutaneous coronary intervention.

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The ability of the model to discriminate 1-year target vessel revascularization risk among percutaneous coronary intervention patients was significantly better than a simpler model based on the presence of diabetes mellitus, stent length, and stent diameter (c statistic, 0.66 versus 0.60; integrated discrimination index, 0.013; P<0.001). The predicted reduction in target vessel revascularization associated with drug-eluting stents used ranged from as little as 1.2% (95% confidence interval, 0.9 to 1.6) to 15.9% (95% confidence interval, 13.0 to 18.4), depending on patient characteristics. Because the predicted benefit associated with drug-eluting stents varies broadly among patients, this predictive model may be used to support the optimal use of drug-eluting stents in a prospective fashion and to engage patients in the decision-making process before coronary intervention.

Conclusions: A predictive model using commonly collected variables can identify patients who may derive the greatest benefit in target vessel revascularization reduction from drug eluting stents. Whether use of the model improves the safety and cost-effectiveness of drug eluting stents use should be tested prospectively.30

Causes of Delay and Associated Mortality in Patients Transferred With ST-Segment–Elevation Myocardial Infarction

Summary: Regional ST-segment–elevation myocardial infarction systems are being developed to improve timely access to primary percutaneous coronary intervention (PCI). System delays may diminish the mortality benefit achieved with primary PCI in ST-segment–elevation myocardial infarction patients, but the specific reasons for and clinical impact of delays in patients transferred for PCI are unknown. We report the frequency, magnitude, and clinical impact of specific delays that occur at the referral hospital, during transport, and at the PCI hospital for 2034 patients transferred for PCI in a regional ST-segment–elevation myocardial infarction system. Despite the use of evidence-based strategies to improve treatment times, delays still occurred frequently within the ST-segment–elevation myocardial infarction system. Delays occurred most frequently at the referral hospital, and were most often due to awaiting transport and emergency department delays. Delays occurred less frequently during transport or at the PCI center. Diagnostic dilemmas and nondiagnostic initial ECGs led to delays of the greatest magnitude but had limited or no impact on mortality. Delays caused by out-of-hospital cardiac arrest and/or cardiogenic shock had the highest impact on in-hospital mortality. In these high-risk patients, the delay rarely led to the cardiac arrest or cardiogenic shock; instead, the critical nature of the patient’s illness resulted in the delay. These results have implications for the design of regional ST-segment–elevation myocardial infarction systems and may affect the current American College of Cardiology/American Heart Association guidelines for time to treatment in transferred patients.

Conclusions: Treatment delays occur even in efficient systems for ST-segment–elevation myocardial infarction care. The clinical impact of specific delays in interhospital transfer for PCI varies according to the cause of the delay.40

Comparison of Transplacental Treatment of Fetal Supraventricular Tachyrhythmias With Digoxin, Flecainide, and Sotalol: Results of a Nonrandomized Multicenter Study

Summary: Fetal atrial flutter and supraventricular tachycardia may result in low cardiac output and death. Consequently, maternal antiarrhythmic treatment is offered in most affected pregnancies. This retrospective multicenter study is the first to compare the efficacy and safety of transplacental digoxin, flecainide, and sotalol, the most commonly used drugs to treat fetal tachyarrhythmia. In the absence of fetal hydrops, arrhythmia-related mortality was 0%, suggesting that transplacental antiarrhythmic therapy is safe and effective regardless of the drug chosen. In fetal hydrops, however, when rapid heart rate control becomes a matter of urgency to improve the chances of survival, the rate of arrhythmia-mediated death was 17%. We found that the fetal response to drug therapy was significantly associated with the type of tachycardia, fetal state, and choice of antiarrhythmic. Atrial flutter, fetal hydrops, and an incessant arrhythmia pattern were independently associated with slower cardioversion rates. Flecainide and digoxin were associated with increased likelihood of conversion of fetal supraventricular tachycardia to a normal rhythm and significantly greater slowing of ventricular rates of persistent atrial flutter/supraventricular tachycardia than sotalol. The highest rate of prenatal atrial flutter termination was observed with sotalol, albeit this was achieved in only about half of the sotalol-treated patients. Flecainide or digoxin might therefore be considered first to treat significant fetal tachyarrhythmia, perhaps in combination with sotalol to treat poorly tolerated atrial flutter. Our results may also be useful in improving our understanding of the potentials and limitations of antiarrhythmic drug therapy and, in persistent arrhythmia, helping to define a treatment period after which an alternative management should be considered.

Conclusion: Flecainide and digoxin were superior to sotalol in converting supraventricular tachyarrhythmias to a normal rhythm and in slowing both atrial fibrillation and supraventricular tachyarrhythmias to better-tolerated ventricular rates and therefore might be considered first to treat significant fetal tachyarrhythmia.41

Cardiac Magnetic Resonance Imaging Pericardial Late Gadolinium Enhancement and Elevated Inflammatory Markers Can Predict the Reversibility of Constrictive Pericarditis After Anti-Inflammatory Medical Therapy: A Pilot Study

Summary: Constrictive pericarditis (CP) is a disabling disease and usually requires pericardiectomy to relieve heart failure symptoms. Reversible cases of CP after anti-inflammatory therapy have been described, but there is no known method to predict the reversibility. We report our pilot study to assess whether cardiac MRI (CMR) pericardial late gadolinium enhancement (LGE) can predict the reversibility of CP after a course of anti-inflammatory therapy. Twenty-nine patients received anti-inflammatory medications after CMR. Fourteen patients had resolution of CP, whereas 15 had persistent CP. We report the frequency and impact of specific delays that occurred at the referral hospital, during transport, and at the PCI hospital for 2034 patients transferred for PCI in a regional ST-segment–elevation myocardial infarction system. Despite the use of evidence-based strategies to improve treatment times, delays still occurred frequently within the ST-segment–elevation myocardial infarction system. Delays occurred most frequently at the referral hospital, and were most often due to awaiting transport and emergency department delays. Delays occurred less frequently during transport or at the PCI center. Diagnostic dilemmas and nondiagnostic initial ECGs led to delays of the greatest magnitude but had limited or no impact on mortality. Delays caused by out-of-hospital cardiac arrest and/or cardiogenic shock had the highest impact on in-hospital mortality. In these high-risk patients, the delay rarely led to the cardiac arrest or cardiogenic shock; instead, the critical nature of the patient’s illness resulted in the delay. These results have implications for the design of regional ST-segment–elevation myocardial infarction systems and may affect the current American College of Cardiology/American Heart Association guidelines for time to treatment in transferred patients.

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Health-Related Quality of Life After Transcatheter Aortic Valve Replacement in Inoperable Patients With Severe Aortic Stenosis

Summary: Many patients with severe aortic stenosis do not undergo surgical valve replacement because of prohibitive operative risk. In a cohort of such patients, the Placement of Aortic Transcatheter Valves (PARTNER) trial recently showed that transcatheter aortic valve replacement increased 12-month survival by an absolute margin of 20% but was associated with increased risks of vascular complications and stroke compared with standard therapy, which included balloon aortic valvuloplasty in the majority of subjects. In this trial, quality of life was assessed prospectively with the Kansas City Cardiomyopathy Questionnaire and the Short Form-12 General Health Survey. We found that the overall summary score of the Kansas City Cardiomyopathy Questionnaire, the primary quality-of-life end point, improved 20 to 30 points on a 100-point scale 1, 6, and 12 months after transcatheter aortic valve replacement, whereas the improvement in the control group was 10 to 12 points at 1 and 6 months and only 4 points at 12 months. Similar patterns were observed for the other quality-of-life measures. Thus, during the first year after intervention, quality of life was substantially better in the transcatheter aortic valve replacement group than in the control group in this clinical trial population.

Conclusions: Among inoperable patients with severe aortic stenosis, compared with standard care, transcatheter aortic valve replacement resulted in significant improvements in health-related quality of life that were maintained for at least 1 year.

Isolated Low Levels of High-Density Lipoprotein Cholesterol Are Associated With an Increased Risk of Coronary Heart Disease: An Individual Participant Data Meta-Analysis of 23 Studies in the Asia-Pacific Region

Summary: This study, comprising information from >220 000 individuals from the Asia-Pacific region, describes a novel and potentially important form of dyslipidemia. Low levels of high-density lipoprotein cholesterol (HDL-C) have been independently associated with increased cardiovascular risk. Some earlier observational studies have suggested the existence of such a distinct type of dyslipidemia with low HDL-C occurring in the absence of elevated levels of other lipid fractions, ie, isolated low HDL-C. This phenotype has been postulated to be especially prevalent among Asian populations. Individuals with this form of lipid abnormality are usually not considered to be candidates for lipid-lowering medication because of their comparatively normal levels of total and low-density lipoprotein cholesterol. This study compared the prevalence of isolated low HDL-C in Asian and non-Asian populations and determined whether the risk of coronary heart disease and stroke was elevated in individuals with this form of lipid abnormality. Findings from this study indicated a substantially higher prevalence of isolated low HDL-C among Asians (22.4%) compared with non-Asians (14.5%) that was unlikely to be explained by differences in the background rates of lipid-lowering medication, cigarette smoking, and alcohol use. Both nonsolinated low HDL-C and isolated low HDL-C were associated with increased risk of coronary heart disease but not stroke. Compared with non-Asians, the relationship between isolated low HDL-C and subsequent risk of coronary heart disease was stronger in Asians. In this group, it was associated with the same magnitude of coronary risk (~60%) as low levels of HDL-C combined with other lipid abnormalities.

Conclusion: Isolated low HDL-C is a novel lipid phenotype that appears to be more prevalent among Asian populations, in whom it is associated with increased coronary risk. Further investigation into this type of dyslipidemia is warranted.

Derivation and Validation of a Simple Exercise-Based Algorithm for Prediction of Genetic Testing in Relatives of LQTS Probands

Summary: Diagnosis of long-QT syndrome (LQTS) is relatively straightforward in patients with overt QT prolongation or symptoms based on existing clinical criteria; however, diagnosis may be challenging in asymptomatic relatives of patients with established LQTS, especially in the context of normal or borderline QT prolongation. Accurate identification of LQTS carriers in this subgroup is important because they remain at significant risk of life-threatening cardiac events. Although genetic testing can identify LQTS carriers where there is a known familial mutation, such an approach may be costly and subject to availability. Postural and exercise provocation has been explored as a means of amplifying phenotypic characteristics, especially in so-called silent mutation carriers. In the present study, differential QT response during exercise was exploited to predict LQTS carriers among first-degree relatives of probands with an established diagnosis of LQTS. A simple 3-step screening algorithm was derived based on resting corrected QT interval, 4-minute recovery corrected QT interval, and 1-minute recovery corrected QT interval. Subsequent external validation in an independent cohort demonstrated a high degree of accuracy for predicting LQTS carriers, and a moderate degree of accuracy for predicting LQTS subtype compared with genetic testing as a gold standard. The screening algorithm appears useful as an interim test while formal genetic results are awaited, or as a diagnostic test in centers where genetic testing is unavailable.

Conclusions: A simple algorithm that incorporates resting and exercise-recovery QTc is useful in identifying LQTS in asymptomatic relatives.

High-Molecular-Weight and Total Adiponectin Levels and Incident Symptomatic Peripheral Artery Disease in Women: A Prospective Investigation

Summary: Lower-extremity peripheral artery disease (PAD) is a manifestation of atherosclerosis that has received considerably less clinical and research attention than coronary or cerebrovascular disease. PAD shares many risk factors with other cardiovascular diseases, including smoking, diabetes mellitus, hypertension, and hyperlipidemia; however, less is known about how PAD differs from atherosclerosis of other vascular territories. Studies of biomarkers and future disease risk can improve our ability to detect patients at heightened risk and our understanding of disease pathogenesis and, by extension, may identify potential novel modalities for treatment. Adiponectin is secreted from adipose tissue and is known to be inversely correlated with future diabetes mellitus risk. It may also be antiatherogenic. This study is the first to examine the relationship between adiponectin and PAD as a specific vascular end point. A large population of initially healthy women aged ≥45 years without existing cardiovascular disease was studied. After traditional cardiovascular risk factors were taken into account, women with high-molecular-weight or total adiponectin levels in the highest tertile had a 59% (high-molecular-weight) or 63% (total) reduced risk for future symptomatic PAD (intermittent claudication or lower-extremity revascularization) compared with women with levels in the lowest tertile. Given the lack of a consistently demonstrated relationship between adiponectin and other cardiovascular end points, this striking result, if confirmed, suggests a unique relationship of adiponectin in PAD development that may reflect a more prominent role of adipokines in peripheral atherosclerosis.

Conclusions: Total and high-molecular-weight adiponectin are inversely associated with incident PAD among initially healthy women. These prospective data support a protective role for this adipokine in peripheral atherosclerosis development.
Statin Use in Outpatients With Obstructive Coronary Artery Disease

Summary: In the large, contemporary Practice Innovation and Clinical Excellence (PINNACLE) outpatient registry, we examined rates of guideline-based treatment with lipid-lowering therapy in 38,775 patients with obstructive coronary artery disease (defined as history of myocardial infarction or prior coronary revascularization) and without contraindications to statin therapy. We found that 78% of patients were receiving guideline-based treatment with statins, 5% were treated only with nonstatin lipid-lowering medications, and 17% of patients were not treated with any lipid-lowering therapy at all. Among untreated patients, half had low-density lipoprotein cholesterol (LDL-C) levels ≥100 mg/dL. Despite multiple clinical trials that have shown that statin therapy reduces cardiovascular morbidity and mortality in this population, a substantial number of high-risk patients remained untreated with statins despite elevated levels of LDL-C. We also found that half of untreated patients had LDL-C levels <100 mg/dL. Although appearing to have reached established LDL-C treatment “targets” for secondary prevention, these patients were not receiving guideline-based care because they were not treated with any lipid-lowering therapy. Our data suggest that some physicians may be making decisions about lipid management for these patients on the basis of baseline LDL-C levels alone rather than on the basis of clinical trial evidence, which has demonstrated a consistent benefit with statin therapy in secondary prevention regardless of baseline LDL-C levels. These findings highlight important opportunities to improve the use of statin therapy in outpatients at high risk for recurrent cardiovascular events.

Conclusions: Despite robust clinical trial evidence, a substantial number of patients with obstructive coronary artery disease remain untreated with statins. A small proportion were treated with nonstatin therapy, and 1 in 6 patients was simply untreated; half of the untreated patients had low-density lipoprotein cholesterol values <100 mg/dL. These findings illustrate important opportunities to improve lipid management in outpatients with obstructive coronary artery disease.

Prevalence and Significance of Alterations in Cardiac Structure and Function in Patients With Heart Failure and a Preserved Ejection Fraction

Summary: The purpose of this study was to examine the prevalence and pattern of structural remodeling and alterations in function present in patients with heart failure and a preserved ejection fraction (HFPEF) and to determine whether there was an association among changes in cardiac structure, function, morbidity, and mortality. An echocardiographic substudy of the Irbesartan in Heart Failure with Preserved Ejection Fraction trial (I-PRESERVE) enrolled 745 patients. Structural remodeling and diastolic dysfunction was present in the majority of patients with HFPEF. Structural remodeling and diastolic dysfunction predicted clinical outcomes. Increased left ventricular mass, mass/volume ratio, and left atrial size were independently associated with an increased risk of morbidity and mortality. These findings may be pivotal to the development of improved diagnostic criteria and prognostic assessment of patients with HFPEF. For example, the inclusion of measurements of left ventricular mass, geometry, and diastolic function could be added to the diagnostic criteria for HFPEF and could be used to predict the risk of morbidity and mortality in patients with HFPEF. With these data, studies could be developed to test the hypothesis that the reversal of these changes in left ventricular structure and function would result in reduced morbidity and mortality in patients with HFPEF. Taken together, these findings serve to enhance our understanding of the pathophysiology underlying clinical heart failure in these patients with HFPEF.

Conclusions: Left ventricular hypertrophy or concentric remodeling, left atrial enlargement, and diastolic dysfunction were present in the majority of patients with HFPEF. Left ventricular mass and left atrial size were independently associated with an increased risk of morbidity and mortality. The presence of structural remodeling and diastolic dysfunction may be useful additions to diagnostic criteria and provide important prognostic insights in patients with HFPEF.

Survival After Open Versus Endovascular Thoracic Aortic Aneurysm Repair in an Observational Study of the Medicare Population

Summary: Using Medicare claims from 1998 to 2007, we examined short and long-term survival of patients with descending thoracic aortic aneurysms (TAA) following open surgical repair and endovascular repair (TEVAR). Overall, we studied 12,573 patients who underwent open repair, and 2,732 patients who underwent TEVAR. Perioperative mortality was lower in patients undergoing TEVAR compared with open repair for both intact (6.1% versus 7.1%, P = 0.07) and ruptured TAA (28% versus 46%, P = 0.001). However, patients with intact TAA selected for TEVAR had significantly worse survival than open patients at one year (87% open, 82% TEVAR, P = 0.001) and five years (72% open, 62% TEVAR, P = 0.001), and analyses adjusting for patient-level comorbidities produced similar results. Therefore, although perioperative mortality is lower with TEVAR, patients selected for TEVAR have worse long-term survival than patients selected for open repair in our observational analysis of Medicare patients. Future work is needed to determine if these deaths are due to the selection of high-risk patients for TEVAR, or due to late device-related complications from the TEVAR itself.

Conclusions: Although perioperative mortality is lower with TEVAR, Medicare patients selected for TEVAR have worse long-term survival than patients selected for open repair. The results of this observational study suggest that higher-risk patients are being offered TEVAR and that some do not benefit on the basis of long-term survival. Future work is needed to identify TEVAR candidates unlikely to benefit from repair.

The Diagnostic Value of Physical Examination and Additional Testing in Primary Care Patients With Suspected Heart Failure

Summary: The initial diagnosis of new nonacute heart failure is as difficult as it is important, especially in settings where more advanced diagnostic tests, notably echocardiography, are not readily available. This diagnostic study demonstrates the importance of history taking and, in particular, physical examination in a large cohort of 721 patients suspected of having nonacute heart failure, 207 (28.7%) of whom were diagnosed with heart failure. When a primary care physician is confronted with a patient suspected of having nonacute heart failure, a diagnostic rule including age, objective evidence of prior coronary artery disease, use of a loop diuretic, displaced apex beat, basal or more pulmonary rales, irregularly irregular pulse, heart murmur suggestive of mitral regurgitation, pulse rate, and elevated jugular venous pressure, plus a single additional test, the NT-proBNP plasma level, can accurately predict the presence or absence of heart failure numerically. The rule had comparable performance in 2 validation datasets. Chest x-ray or ECG can be used in addition to or instead of the NT-proBNP measurement depending on local availability and other patient characteristics. It remains important for diagnosticians to maintain basic physical examination skill.

Conclusions: In this study, we estimated the quantitative diagnostic contribution of elements of the history and physical examination in the diagnosis of heart failure in primary care outpatients, which may help to improve clinical decision making. The largest additional quantitative diagnostic contribution to those elements was provided by measurement of NT-proBNP. For daily practice, a diagnostic rule was derived that may be useful to quantify the probability of heart failure in patients with new symptoms suggestive of heart failure.
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