Rhythm Versus Rate Control Therapy and Subsequent Stroke or Transient Ischemic Attack in Patients With Atrial Fibrillation

Summary—Despite anticoagulation, stroke remains a complication of atrial fibrillation. Several randomized controlled trials have compared rate and rhythm control approaches in patients with atrial fibrillation and demonstrated a similar impact on mortality, but most trials had inadequate sample size to assess their relative effect on stroke outcome. In the current observational study, we compared the rates of stroke/transient ischemic attack in patients treated with rhythm (n=16,325) or rate (n=41,193) control strategies in a large population-based cohort of patients with recently diagnosed atrial fibrillation. Crude stroke/transient ischemic attack incidence in the rhythm control group was 1.74 per 100 person-years in comparison with 2.49 in the rate control group (P<0.001). Although at baseline, patients receiving rhythm control therapy had fewer risk factors for stroke in comparison with patients receiving rate control therapy, the association between rhythm control treatment and lower stroke rates remained after multivariate analysis (adjusted hazard ratio, 0.80; 95% confidence interval, 0.74, 0.87) and propensity score analysis (adjusted hazard ratio, 0.77; 95% confidence interval, 0.68, 0.87), which balanced patients’ characteristics between groups. Once stratified by CHADS2 (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and previous stroke or transient ischemic attack) score, the rhythm control group had a lower stroke risk than the rate control group only for patients with high- and moderate-risk CHADS2 scores. The results of this study provide additional information to guide clinicians’ choice of treatment strategy by considering the outcome of stroke. This study may stimulate future large randomized trials comparing the effectiveness of rhythm versus rate control strategies on the risk of stroke and emphasizes the need for the development of new therapies for atrial fibrillation.

Conclusions—In comparison with rate control therapy, the use of rhythm control therapy was associated with lower rates of stroke/TIA among patients with atrial fibrillation, in particular, among those with moderate and high risk of stroke.1

Randomized Comparison of Sevoflurane Versus Propofol to Reduce Perioperative Myocardial Ischemia in Patients Undergoing Noncardiac Surgery

Summary—On the basis of promising evidence in patients undergoing on-pump coronary artery bypass graft surgery, the American College of Cardiology/American Heart Association guidelines recommend the use of volatile anesthetics as beneficial in hemodynamically stable patients at cardiovascular risk undergoing noncardiac surgery (class IIa recommendation). In the present randomized controlled trial, anesthesia maintenance with sevoflurane compared with propofol did not reduce the incidence of perioperative myocardial ischemia in patients with coronary artery disease or at risk for it undergoing major noncardiac surgery. In addition, the data did not suggest any effect of sevoflurane on postoperative N-terminal prohormone of brain natriuretic peptide release or on major adverse cardiac events at 12 months. These results are in agreement with observational data and data generated in a small randomized trial. This growing evidence questions the recommendation to preferentially use volatile anesthetics in noncardiac surgical patients at cardiac risk.

Conclusions—Compared with propofol, sevoflurane did not reduce the incidence of myocardial ischemia in high-risk patients undergoing major noncardiac surgery. The sevoflurane and propofol groups did not differ in postoperative NT-proBNP release, major adverse cardiac events at 1 year, or delirium.2

Effective Treatment of Edema and Endothelial Barrier Dysfunction With Imatinib

Summary—Endothelial barrier dysfunction is a major contributor to morbidity and mortality in the critically ill. Loss of the endothelial barrier follows exposure of the endothelium to inflammatory mediators and drives vascular leakage and edema formation. To date endothelial barrier function and vascular leakage still lack appropriate therapy. This study shows that imatinib—an US Food and Drug Administration–approved tyrosine kinase inhibitor—directly protects the endothelial barrier under inflammatory conditions. With the use of endothelial cells isolated from various vascular beds, it was shown that imatinib attenuates the loss of endothelial barrier on stimulation with inflammatory mediators. Imatinib protects against endothelial barrier dysfunction predominantly by inhibition of the tyrosine kinase Abl-related gene (Arg), a novel mediator of endothelial barrier disruption. The effect of imatinib on endothelial barrier was established in various mouse models of vascular leakage. Notably, imatinib attenuated vascular leakage in a murine model of sepsis, even when imatinib treatment was initiated considerable time after induction of sepsis. This study carries important clinical implications. First, imatinib may form a suitable therapy for treatment of diseases characterized by vascular leakage. The longstanding experience with imatinib, together
with the fact that imatinib concentrations used in this study parallel plasma values in cancer patients, are apparent advantages in this case. Logical first steps in further development of imatinib involve Phase I and II trials to evaluate safety and efficacy of imatinib in patients with profound vascular leakage. Second, the identification of Arg as a novel and drugable target opens perspectives for more specific pharmaceutical interventions.

Conclusions—Thus, imatinib prevents endothelial barrier dysfunction and edema formation via inhibition of Arg. These findings identify imatinib as a promising approach to permeability edema and indicate Arg as novel target for edema treatment.3

Endogenous and Natural Complement Inhibitor Attenuates Myocardial Injury and Arterial Thrombogenesis

Summary—Reperfusion of ischemic tissues induces tissue injury that is mediated by complement activation. We have identified a novel, endogenous, natural complement inhibitor that displaces the 3 serine proteases (ie, mannos-binding lectin/ficolin-associated serine protease-1, -2, and -3) from the mannos-binding lectin complex in a dose-dependent manner. Furthermore, at pharmacologic concentrations, mannos-binding lectin-associated protein-1 prevents arterial thrombogenesis, as well as myocardial injury after ischemia and reperfusion in vivo. The mannos-binding lectin complex has been associated with several clinical diseases, and mannos-binding lectin-associated protein-1 may represent a novel molecular mechanism to modulate its activity in vivo.

Conclusions—Our results suggest that the natural, endogenous inhibitor MAP-1 effectively inhibits lectin pathway activation in vivo. MAP-1 at pharmacological doses represents a novel therapeutic approach for human diseases involving the lectin pathway and its associated MASPs.4

Dipeptidyl Peptidase-4 Modulates Left Ventricular Dysfunction in Chronic Heart Failure via Angiogenesis-Dependent and -Independent Actions

Summary—Dipeptidyl peptidase-4 (DPP4) is a serine protease with a primary function of truncating various bioactive molecules such as incretin hormones, angiogenic chemokines, inflammatory cytokines, denatured collagen, and brain natriuretic peptide. To date, the pathophysiological significance of DPP4 in the processes of diabetes mellitus, malignancy, and inflammation has been well recognized and well established; however, the role of DPP4 in the pathogenesis of cardiovascular disease remained unclear until as recently as several years ago, when the first report demonstrated the protective role of DPP4 inhibition in acute myocardial infarction. The present study highlights a novel pathophysiological role for DPP4 in diastolic left ventricular dysfunction and raises the possibility of using DPP4 as a diagnostic surrogate and a therapeutic target for chronic heart failure. One of the primary interpretations drawn from the present study is that the coronary microcirculation is essential for diastolic left ventricular dysfunction development, in which DPP4 may play a pathophysiological role by regulating coronary angiogenesis. Diabetes mellitus has been postulated to exacerbate heart failure, and the comorbidity of diabetic retinopathy, ie, diabetic microvascularopathy, has been suggested to be associated with the increased incidence of heart failure in patients with diabetes mellitus. Thus, the present study proposes another therapeutic benefit of the small-molecule DPP4 inhibitors in reducing the incidence of heart failure in patients with diabetes mellitus.

Conclusions—DPP4 inhibition reverses DHF via membrane-bound DPP4/stromal cell-derived factor-1α-dependent local actions on angiogenesis and circulating DPP4/glucagon-like peptide-1-mediated inotropic actions. Myocardium-derived DPP4 activity in coronary sinus can be monitored by peripheral vein sampling, which partly correlates with DHF index; thus, circulating DPP4 may potentially serve as a biomarker for monitoring DHF.5

Missed Opportunities: Despite Improvement in Use of Cardioprotective Medications Among Patients With Lower-Extremity Peripheral Artery Disease, Underuse Remains

Summary—One of the main goals for treatment of peripheral artery disease (PAD) is risk factor modification and secondary prevention of vascular events by initiating cardioprotective pharmacotherapies. Studies investigating temporal trends and longitudinal use of cardioprotective agents after incident diagnosis of PAD have been limited. With the use of Danish nationwide administrative registries, which capture medication adherence, we demonstrate a significant temporal improvement from 2000 to 2007 in the use of any antiplatelet and statin therapy after incident diagnosis of PAD. However, the use of these medications is modest, such that by 18 months after incident diagnosis, nearly half of patients with PAD alone are not taking any antiplatelet or statin therapy. After adjustment, patients with incident PAD and a history of coronary artery disease are more likely to take cardioprotective medications than patients with incident coronary artery disease alone (no history of PAD). Meanwhile, patients with PAD alone have nearly half the adjusted odds of taking any antiplatelet in comparison with patients with coronary artery disease alone. Although use of cardioprotective medications improved after publication of the American College of Cardiology/American Heart Association PAD guidelines in 2005, the adjusted odds of any antiplatelet use among patients with PAD alone, compared with patients with coronary artery disease alone, was nearly 35% less, and statin use was 20% less in a more contemporary period (2005–2007). The present analysis underscores the need for systemwide improvements to improve adherence to secondary prevention in this population.

Conclusions—Despite improvement in the use of cardioprotective medications over time, patients with PAD alone remain less likely than those with CAD alone to use these agents.6

Activity of the Estrogen-Metabolizing Enzyme Cytochrome P450 1B1 Influences the Development of Pulmonary Arterial Hypertension

Summary—Pulmonary arterial hypertension (PAH) is a fatal condition with diverse origins that converge to promote pathological changes in the pulmonary vasculature. The nature of these origins is intriguing and stems from genetic and environmental factors to secondary risk factor–related disease. Estrogen is one such risk factor that has been causally related to PAH; however, the causation remains obscure. In this study, we have identified that the estrogen-metabolizing enzyme cytochrome P450 1B1 (CYP1B1) controls the formation of estrogen-derived mitogenic metabolites to drive vascular cell mitogenesis and PAH. Central to this, we report that CYP1B1 is robustly upregulated in 2 independent forms of clinical
Histone Deacetylation Inhibition in Pulmonary Hypertension: Therapeutic Potential of Valproic Acid and Suberoylanilide Hydroxamic Acid

Summary—Histone deacetylases (HDACs) have emerged as key targets to reverse aberrant epigenetic changes associated with cancer and autoimmune disease, and HDAC inhibitors show promise as antineoplastic and antiinflammatory agents. We examined the pattern of HDAC expression in lungs from patients with pulmonary arterial hypertension and investigated the effect of HDAC inhibition on the reversal of pulmonary hypertension in a rat model. Coupled to this, we explored the effects on mechanisms (proliferation, apoptosis, and inflammation) relevant to the pathology of pulmonary arterial hypertension in human and animal cell model systems. Our results demonstrate that increased HDAC activity contributes to the vascular pathology of pulmonary hypertension. The effectiveness of the HDAC inhibitors valproic acid and suberoylanilide hydroxamic acid in models of pulmonary arterial hypertension supports a therapeutic strategy based on HDAC inhibition in pulmonary arterial hypertension.

Conclusions—Increased HDAC activity contributes to the vascular pathology of pulmonary hypertension. The effectiveness of HDAC inhibitors, valproic acid, and suberoylanilide hydroxamic acid, in models of pulmonary arterial hypertension supports a therapeutic strategy based on HDAC inhibition in pulmonary arterial hypertension.

Patterns of Use of Perioperative Angiotensin-Converting Enzyme Inhibitors in Coronary Artery Bypass Graft Surgery With Cardiopulmonary Bypass: Effects on In-Hospital Morbidity and Mortality

Summary—Despite significant improvement in both surgical and medical management of coronary artery bypass graft patients, many experience significant perioperative morbidity that adversely affects quality of life and length of hospitalization and increases resource use. Angiotensin-converting enzyme inhibitors (ACEIs) have been proven effective in the care of cardiovascular patients with hypertensive heart disease and congestive heart failure; however, effect of ACEI on survival in patients undergoing coronary artery bypass graft surgery is equivocal. Unfortunately, ACEI treatment is usually held up before coronary artery bypass graft, primarily because of historical reports linking it to hemodynamic instability during the perioperative period and a larger need for vasoactive drug use and fluid administration. To address these issues, we designed a prospective, international, multi-institutional study that allowed determination of the impact of the current practice pattern of ACEI use on morbidity and mortality after coronary artery bypass graft surgery. We showed that continuation of ACEI therapy early after surgery or adding ACEI de novo postoperatively can be associated with marked improvement in cardiovascular and renal outcomes. Conversely, a practice of withdrawing ACEI treatment postoperatively is associated with poor in-hospital nonfatal outcomes. The associated improvement in outcomes with ACEI therapy was not surprising, given the well-known benefits of blocking the renin-angiotensin-aldosterone system; however, it is alarming to learn that clinicians chose to continue discontinue ACEI therapy in nearly 50% of patients after cardiac surgery. The present work confirms that acute withdrawal of ACEI therapy may be particularly harmful in the context of cardiac surgery, and attention to restore ACEI therapy soon after operation should be encouraged.

Conclusions—Increased CYP1B1-mediated estrogen metabolism promotes the development of PAH, likely via the formation of metabolites, including 16α-hydroxyestrone. Collectively, this study reveals a possible novel therapeutic target in clinical PAH.

Histone Deacetylation Inhibition in Pulmonary Hypertension supports a therapeutic strategy based on HDAC inhibition in pulmonary arterial hypertension. The effectiveness of the HDAC inhibition relevant to the pathology of pulmonary arterial hypertension and investigated the effect of HDAC inhibition on the reversal of pulmonary hypertension in a rat model. Coupled to this, we explored the effects on mechanisms (proliferation, apoptosis, and inflammation) relevant to the pathology of pulmonary arterial hypertension in human and animal cell model systems. Our results demonstrate that increased HDAC activity contributes to the vascular pathology of pulmonary hypertension. The effectiveness of the HDAC inhibitors valproic acid and suberoylanilide hydroxamic acid in models of pulmonary arterial hypertension supports a therapeutic strategy based on HDAC inhibition in pulmonary arterial hypertension.

Conclusions—Increased HDAC activity contributes to the vascular pathology of pulmonary hypertension. The effectiveness of HDAC inhibitors, valproic acid, and suberoylanilide hydroxamic acid, in models of pulmonary arterial hypertension supports a therapeutic strategy based on HDAC inhibition in pulmonary arterial hypertension.

Suppression of Arterial Thrombosis Without Affecting Hemostatic Parameters With a Cell-Penetrating PAR1 Pepducin

Summary—Antiplatelet therapy is of paramount importance in the effective treatment of patients with acute coronary syndrome and those undergoing percutaneous coronary intervention. Thrombin is the most potent platelet activator. The thrombin receptor PAR1 has emerged as an important new therapeutic target to inhibit platelet function in patients with acute coronary syndrome undergoing percutaneous coronary intervention. We describe the development of PZ-128, a first-in-class PAR1 inhibitor that targets the cytoplasmic loops of the receptor. PZ-128 rapidly suppressed PAR1-induced platelet aggregation and arterial thrombosis in guinea pigs and baboons and was synergistic to oral clopidogrel. PZ-128 did not affect bleeding or coagulation in nonhuman primates or in blood from patients undergoing percutaneous coronary intervention. Platelet function returned to baseline 24 hours after PZ-128 infusion. PAR1 inhibition by PZ-128 appears to be a novel promising therapy for patients with acute coronary syndrome. Planned clinical trials will establish where this novel class of medication fits into our therapeutic armamentarium.

Conclusions—Our study suggests that withdrawal of ACEI treatment after coronary artery bypass graft surgery is associated with nonfatal in-hospital ischemic events. Furthermore, continuation of ACEI or de novo ACEI therapy early after cardiac surgery is associated with improved in-hospital outcomes.

C1q/Tumor Necrosis Factor-Related Protein-3, a Newly Identified Adipokine, Is a Novel Antiapoptotic, Proangiogenic, and Cardioprotective Molecule in the Ischemic Mouse Heart

Summary—Cardiovascular disease remains a leading cause of mortality worldwide. Although improved reperfusion strategies have led to declined death rates after acute myocardial infarction, both the
Tumor Necrosis Factor-α–Mediated Downregulation of the Cystic Fibrosis Transmembrane Conductance Regulator Drives Pathological Sphingosine-1-Phosphate Signaling in a Mouse Model of Heart Failure

Summary—This study brings forth the novel concept that changes in vascular cystic fibrosis transmembrane conductance regulator expression underlie the enhancement of vascular tone in heart failure. We identify the cystic fibrosis transmembrane conductance regulator as a critical regulatory site for S1P signaling; its tumor necrosis factor-α–dependent downregulation in heart failure underlies its enhancement in microvascular tone. This molecular mechanism potentially represents a novel and highly strategic therapeutic target for cardiovascular conditions involving inflammation.

Global Variation in the Prevalence of Elevated Cholesterol in Outpatients With Established Vascular Disease or 3 Cardiovascular Risk Factors According to National Indices of Economic Development and Health System Performance

Summary—The exponential rise in cardiovascular disease over the past decade has placed a tremendous burden on the health and economic development of countries worldwide, with unprecedented demands for an effective response from governments and other stakeholders in global health. From a large, multinational registry of outpatients with established cardiovascular disease or ≥3 risk factors, we used data from 53,570 individuals from 36 countries to examine the relationship between country-level economic and health system factors and the risk of elevated cholesterol (total cholesterol levels >200 mg/dL). The analysis was performed separately for patients with versus without previous history of hyperlipidemia; a higher proportion of the total variability in elevated cholesterol was at the country level for patients with (12.1%) versus without (7.4%) history of hyperlipidemia. Among patients with history of hyperlipidemia, after adjusting for patient-level demographic and clinical characteristics and average fat consumption at the country level, countries in the highest tertile of gross national income or World Health Organization index of health system achievement were found to have significantly lower odds of elevated cholesterol than those in each of the lower 2 tertiles, and the odds of elevated cholesterol was higher for countries in higher versus lower tertile of out-of-pocket health expenditures. No significant associations between country-level factors and elevated cholesterol were found for patients without history of hyperlipidemia. These results support the need for strengthening efforts toward effective cardiovascular disease prevention and control and may provide insight for health policy setting at the national level.

Conclusions—Global variations in the prevalence of elevated cholesterol among patients with history of hyperlipidemia are associated with socioeconomic development, health system management, and cost-effectiveness. Patient population and, if efficacious, could be implemented rapidly at the national level.
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, 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). In conclusion, in patients at higher and lower risk of myocardial ischemic events.

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.

The Bispecific SDF1-GPVI Fusion Protein Preserves Myocardial Function After Transient Ischemia in Mice

Summary—Heart failure is the major serious complication of myocardial infarction. Circulating bone-marrow–derived stem cells play a critical role in repair mechanisms of infarcted myocardium and limit disease progression and heart failure. Clinical trials suggest that regenerative mechanisms of the diseased myocardium can be supported by administration of autologous bone-marrow–derived stem cells. One major limitation of the stem cell–based treatment option is low and undirected accumulation of cells with high regenerative potential at the site of injured myocardium. Bispecific recombinant molecules that target both structures of the diseased myocardial microcirculation and distinct circulating bone-marrow–derived stem cells such as SDF1-GPVI have been shown to be of great potential to augment peripheral recruitment of stem cells toward diseased myocardium. These molecules have been proven to limit heart failure and preserve myocardium in disease-related mouse models. These molecules may be a promising strategy to promote myocardial repair and to preserve cardiac function after myocardial infarction.

Conclusions—These results indicate that administration of SDF1-GPVI may be a promising strategy to treat myocardial infarction to promote myocardial repair and to preserve cardiac function.

Evaluation of Multiple Biomarkers of Cardiovascular Stress for Risk Prediction and Guiding Medical Therapy in Patients With Stable Coronary Disease

Summary—The benefit of angiotensin-converting enzyme inhibitors in low-risk patients with stable coronary artery disease without heart failure remains controversial, and current practice guidelines note that it is reasonable but not recommended to use angiotensin-converting enzyme inhibitors when cardiovascular risk factors are well controlled and revascularization has been performed. We now demonstrate that elevated levels of 3 novel biomarkers of cardiovascular stress, midregional pro-atrial natriuretic peptide, midregional pro-adrenomedullin, and C-terminal pro-endothelin-1, are associated with the subsequent risk of cardiovascular death and heart failure independently of clinical factors (adjusted hazard ratios per 1-SD increase of 1.97, 1.48, and 1.47, respectively; P ≤ 0.002 for each biomarker). Furthermore, elevated levels of these biomarkers identified patients in whom therapy with an angiotensin-converting enzyme inhibitor resulted in a significant reduction in the risk of cardiovascular death or heart failure. Specifically, trandolapril significantly reduced the risk of cardiovascular death or heart failure in patients who had elevated levels of ≥2 biomarkers (hazard ratio, 0.53; 95% confidence interval, 0.36–0.80), whereas there was no benefit in patients with elevated levels of 0 or 1 biomarker (hazard ratio, 1.09; 95% confidence interval, 0.74–1.59; Pinteraction = 0.012). Thus, in patients with stable coronary artery disease and preserved left ventricular ejection fraction, elevated levels of novel biomarkers of cardiovascular stress identify patients who are at higher risk of cardiovascular death and heart failure and may be useful to select patients who derive significant benefit from angiotensin-converting enzyme inhibitor therapy.

Conclusions—In patients with stable coronary artery disease and preserved left ventricular ejection fraction, our results suggest that elevated levels of novel biomarkers of cardiovascular stress may help identify patients who are at higher risk of cardiovascular death and heart failure and may be useful to select patients who derive significant benefit from angiotensin-converting enzyme inhibitor therapy.

Determinants and Consequences of Renal Function Variations With Aldosterone Blocker Therapy in Heart Failure Patients After Myocardial Infarction: Insights From the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study

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

Conclusions—In patients with heart failure after acute myocardial infarction and receiving standard medical care, an early decline in eGFR is not uncommon and is associated with poor long-term outcome. Eplerenone induced a moderately more frequent early decline in eGFR, which did not affect its clinical benefit on cardiovascular outcomes.19

Summary—Natriuretic peptides have long been viewed as compensatory hormones that are upregulated in the setting of heart failure, affording beneficial cardiac and hemodynamic effects. Yet a recent large randomized trial with recombinant B-type natriuretic peptide (nesiritide) failed to reduce mortality or rehospitalization in heart failure patients. We tested whether unsuspected proadrenergic effects might oppose the anticipated benefits of natriuretic peptides. We report that brain natriuretic peptide increases norepinephrine release in the guinea pig heart ex vivo, an effect that is further enhanced in ischemia/reperfusion. In addition, natriuretic peptides elicit catecholamine exocytosis in sympathetic nerve terminals isolated from the guinea pig heart and in nerve growth factor–differentiated rat pheochromocytoma PC12 cells, a model of sympathetic nerve endings. This proexocytotic effect is likely due to a protein kinase G–mediated inhibition of phosphodiesterase type 3. This increases intraneuronal cyclic AMP levels and protein kinase A activity, which culminates in increased intracellular calcium and norepinephrine release. Notably, these effects occur at concentrations of natriuretic peptides reached at cardiac sympathetic nerve endings in advanced congestive heart failure. We propose that this proadrenergic action may counteract any beneficial cardiac and hemodynamic effects of increasing natriuretic peptide levels in congestive heart failure and thus explain the ineffectiveness of nesiritide as a cardiac failure medication.19

Conclusions—Our results show that natriuretic peptides, at concentrations likely to be reached at cardiac sympathetic nerve endings in advanced congestive heart failure, promote norepinephrine release via a protein kinase G–induced inhibition of phosphodiesterase type 3–mediated cAMP hydrolysis. We propose that this proadrenergic action may counteract the beneficial cardiac and hemodynamic effects of natriuretic peptides and thus explain the ineffectiveness of nesiritide as a cardiac failure medication.19

Ulinastatin, a Urinary Trypsin Inhibitor, for the Initial Treatment of Patients With Kawasaki Disease: A Retrospective Study

Summary—The present study is the first report demonstrating that ulinastatin (UTI), a urinary trypsin inhibitor, is associated with fewer patients requiring additional rescue treatment and reduction of coronary artery lesions in the treatment of Kawasaki disease (KD). UTI, which protects tissues and organs against neutrophil-mediated injury, has been clinically used for the treatment of circulatory shock, septic shock, and acute respiratory distress syndrome. The results of our retrospective study suggested the usefulness of UTI as an initial treatment of KD, although UTI has been used mainly as an additional rescue treatment for patients refractory to initial treatment. Considering the pathological finding of neutrophils in the early stage of KD, clinical use of UTI may be more beneficial in initial treatment than in additional rescue treatment. Moreover, initial treatment with a combination of intravenous immunoglobulin and UTI may reduce not only the occurrence of coronary artery lesions but also the number of patients requiring additional rescue treatment, leading to possible benefits in total cost. No adverse events associated with UTI were observed in the present study. We consider that UTI is an effective candidate for intensive initial treatment to improve the clinical course and coronary outcome among patients with KD. Further study and a randomized prospective trial are needed to confirm the clinical benefits of UTI.

Conclusions—UTI was associated with fewer patients requiring additional rescue treatment and reduction of CAL in this retrospective study.20

Sildenafil and B-Type Natriuretic Peptide Acutely Phosphorylate Titin and Improve Diastolic Distensibility In Vivo

Summary—Reduced left ventricular diastolic compliance contributes to the pathophysiology of heart failure with preserved ejection fraction, a disease entity with no effective therapy. In vitro studies suggest that cGMP may have favorable effects on diastolic function, in part via activation of cGMP-dependent protein kinase and titin phosphorylation. Phosphodiesterase-5A degrades cGMP, whereas nitric oxide and natriuretic peptides enhance cGMP production. We studied the effects of short-term treatment with sildenafil (a phosphodiesterase-5A inhibitor) and brain natriuretic peptide on diastolic function in vivo (pressure-volume analysis) and on skin blood flow (thermocouple measurements). Brain natriuretic peptide and sildenafil increased arterial capacitance and decreased left ventricular diastolic stiffness. In vivo, plasma cGMP levels and left ventricular diastolic and systolic capacitance were increased and ex vivo measurements of cardioventricular passive stiffness were decreased during serial treatment with sildenafil and with brain natriuretic peptide. These functional changes were associated with increases in titin phosphorylation without effects on troponin I, troponin T, phospholamban, myosin light chain, or myosin binding protein C phosphorylation. These data suggest that therapies elevating cGMP may provide benefit in the treatment of heart failure with preserved ejection fraction and support further investigation of short- or long-term administration of cGMP-enhancing therapies in this syndrome.

Conclusions—Short-term cGMP-enhancing treatment with sildenafil and BNP improves left ventricular diastolic distensibility in vivo, in part by phosphorylating titin.21

Long-Term Dipeptidyl-Peptidase 4 Inhibition Reduces Atherosclerosis and Inflammation via Effects on Monocyte Recruitment and Chemotaxis

Summary—The incretin hormones glucagon-like peptide and glucose-dependent insulotropin polypeptide play a key role in the regulation of postprandial glycemia and satiety. Incretin hormones are inactivated by the exopeptidase dipeptidyl-peptidase 4 (DPP-4). Both small-molecule inhibitors of DPP-4 and DPP-4–resistant incretin analogs are increasingly common treatments for type II diabetes. Incretin hormone analogs are increasingly common treatments for type II diabetes. Incretin hormone analogs are increasingly common treatments for type II diabetes. Incretin hormone analogs are increasingly common treatments for type II diabetes.
diabetes mellitus, although their effects in reducing long-term cardiovascular complications remain to be established. An expanding list of potential beneficial effects of DPP-4 inhibition on the cardiovascular system includes glucagon-like peptide–mediated effects on cardioprotective pathways, nitric oxide–dependent vasodilation, and non–glucagon-like peptide effects that relate to a pathophysiological role for DPP-4 in regulating inflammation. In this study, we investigated the net effects of long-term DPP-4 inhibition with alogliptin in a model of atherosclerosis and insulin resistance. DPP-4 activity was increased in atherosclerosis with a reduction in response to treatment. DPP-4 inhibition improved insulin resistance, blood pressure, and visceral adiposity with reductions in atherosclerosis and inflammation (evidenced by a reduction in plaque and adipose inflammatory macrophage content) and a shift to an alternately activated macrophage phenotype. DPP-4 inhibition prevented monocyte migration and actin polymerization in vitro via Rac-dependent mechanisms and prevented in vivo migration of labeled monocytes to the aorta in response to exogenously administered tumor necrosis factor-α and DPP-4. These data support a net effect of DPP-4 inhibition in reducing adipose and vascular inflammation with a concomitant reduction in atherosclerosis and support a therapeutic role for these agents in preventing cardiovascular complications in type II diabetes mellitus.

Conclusions—DPP-4i exerts antiatherosclerotic effects and reduces inflammation via inhibition of monocyte activation/chemotaxis. These findings have important implications for the use of this class of drugs in atherosclerosis.12

Effects of a Novel Aldosterone Synthase Inhibitor for Treatment of Primary Hypertension: Results of a Randomized, Double-Blind, Placebo- and Active-Controlled Phase 2 Trial

Summary—A growing body of literature links aldosterone to the development and/or progression of a variety of cardiovascular disease processes, including endothelial dysfunction, hypertension, ventricular remodeling, and congestive heart failure. Blockade of the mineralocorticoid receptor with antagonists such as spironolactone has shown benefit in blunting or reversing many of the unfavorable effects attributed to aldosterone. An alternative approach to blocking the effects of aldosterone is to prevent its production by inhibiting aldosterone synthase. The present findings indicate that inhibition of aldosterone synthase with the novel compound LCI699 significantly lowers blood pressure in patients with mild to moderate hypertension. The compound was safe and well tolerated. Aldosterone synthase inhibition with LCI699 was accompanied by suppression of adrenocorticotropic hormone–stimulated release of cortisol in a proportion of subjects, indicating partial inhibition of 11β-hydroxylase. Overall, the present results indicate that aldosterone synthase inhibition may represent a novel and effective approach to lowering high blood pressure. Additional studies are needed to determine whether there is differential antihypertensive and/or cardiovascular benefit of suppressing aldosterone production compared with blocking activation of the mineralocorticoid receptor. Such testing will need to elucidate the effects of partial suppression of cortisol synthesis.

Conclusions—Aldosterone synthase inhibition with LCI699 significantly lowered clinic and ambulatory blood pressure. A minority of subjects developed blunted adrenocorticotropic hormone–stimulated release of cortisol. These results support additional research to evaluate use of aldosterone synthase inhibition in primary hypertension and/or patients characterized by aldosterone excess.21

Comparison of Transplacental Treatment of Fetal Supraventricular Tachyarrhythmias 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.

Conclusions—Flecainide and digoxin were superior to sotalol in converting SVT to a normal rhythm and in slowing both AF and SVT to better-tolerated ventricular rates and therefore might be considered first to treat significant fetal tachyarrhythmia.24

Acetylcysteine for Prevention of Renal Outcomes in Patients Undergoing Coronary and Peripheral Vascular Angiography: Main Results From the Randomized Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT)

Summary—Contrast-induced acute kidney injury is associated with the need for dialysis, prolonged hospitalization, and mortality. Its incidence in patients with risk factors (kidney failure, diabetes mellitus, or advanced age) varies between 9% and 38%. Previous acetylcysteine trials had substantial risk of bias and were underpowered. We conducted a randomized trial of acetylcysteine versus placebo in 2308 patients at risk for contrast-induced acute kidney injury (age >70 years, renal failure, diabetes mellitus, heart failure, or hypotension) undergoing an intravascular angiographic procedure. Allocation was concealed; patients, health staff, and outcome assessors were blinded, and analysis followed the intention-to-treat principle. We administered 1200 mg of acetylcysteine or placebo every 12 hours, twice before and twice after the angiography. We found no effect of acetylcysteine on contrast-induced acute kidney injury, the primary end point (12.7% vs 12.7% in the acetylcysteine and placebo groups, respectively; relative risk, 1.00; 95% confidence interval, 0.81 to 1.25; P=0.97). There was also no effect on any of the secondary outcomes or for any subgroup. We conducted a meta-analysis to assess
the results of the Acetylcysteine for Contrast-Induced Nephropathy Trial in the context of 45 trials on the same subject and found a huge variation in the effect on contrast-induced acute kidney injury, although those with adequate methodological criteria did not show any clinical benefit of acetylcysteine. In conclusion, our trial, the largest conducted to date, showed that acetylcysteine is ineffective to prevent contrast-induced acute kidney injury. Therefore, we do not recommend routine use of acetylcysteine for patients undergoing angiography.

Conclusions—In this large randomized trial, we found that acetylcysteine does not reduce the risk of contrast-induced acute kidney injury or other clinically relevant outcomes in at-risk patients undergoing coronary and peripheral vascular angiography.15

References


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