Blocking of Frizzled Signaling With a Homologous Peptide Fragment of Wnt3a/Wnt5a Reduces Infarct Expansion and Prevents the Development of Heart Failure After Myocardial Infarction

Summary: Myocardial infarction is one of the major causes of heart failure. The scar in the infarct area shows a progressive thinning in these patients, causing excessive dilatation of the entire left ventricle, which leads to pump failure. This dilatation can be attributed to the repetitive mechanical strain that the cardiac cycle places on the scar, causing wear of the extracellular matrix in the scar tissue. Previous work from our laboratory and others has highlighted the importance of myofibroblasts in the maintenance of this scar. The smooth muscle-like contractile properties of these cells provide a sustained contractile force that is subsequently anchored by the deposition of extracellular matrix. In this article, we propose the targeting of myofibroblasts as a novel therapeutic approach to prevent infarct-related heart failure. We have shown previously that myofibroblasts in the infarct area express Frizzled receptors. The receptors use Wnt proteins as their endogenous ligands. Here we describe a fragment of Wnt5a, named UM206, that blocks the interaction between Wnt and Frizzled with high affinity. When administered to infarcted mice, UM206 completely prevented heart failure development. Moreover, infarct thinning and left ventricular dilatation were significantly reduced by UM206, which may be explained by a 4-fold increase in myofibroblast numbers in the infarct area. This study shows that Frizzled blockers may be a novel drug class that can prevent heart failure development after myocardial infarction.

Conclusions: Blocking of Frizzled signaling reduces infarct expansion and preserves cardiac function after myocardial infarction. Our findings underscore the potential of Frizzled receptors as a target for pharmacotherapy of cardiac remodeling after myocardial infarction.

Mitogen-Activated Protein Kinase Inhibitors Improve Heart Function and Prevent Fibrosis in Cardiomyopathy Caused by Mutation in Lamin A/C Gene

Summary: Heart failure is responsible for considerable morbidity and mortality, and dilated cardiomyopathy (DCM) is a major cause. Molecular genetic studies have revealed mutations in various genes in patients with familial DCM, but the precise mechanisms of how they lead to heart muscle damage remain largely unknown. Mutations in LMNA encoding A-type nuclear lamins appear to be responsible for ~8% of cases of familial DCM, and patients with LMNA mutations have a poorer prognosis than those with DCM caused by mutations in most other genes. We have previously shown an abnormal activation of the extracellular signal-regulated kinase (ERK) and the c-jun N-terminal kinase (JNK) branches of the mitogen-activated protein kinase signaling cascade in hearts of mice with DCM caused by a mutation in Lmna. We now establish that treating these mice with chemical inhibitors of ERK and JNK after the onset of left ventricular dilatation and decreased cardiac ejection fraction, a time when human patients would be considered for therapy, improves cardiac function and significantly decreases myocardial fibrosis. These results provide proof of concept that pharmacological inhibitors of ERK and JNK signaling, some of which are currently in clinical development for other indications, could be studied in human clinical trials of patients with DCM caused by LMNA mutations.

Conclusion: Inhibitors of ERK and JNK signaling could potentially be used to treat humans with cardiomyopathy caused by LMNA mutations.

Separating the Mechanism-Based and Off-Target Actions of Cholesteryl Ester Transfer Protein Inhibitors With CETP Gene Polymorphisms

Summary: The inverse relationship between high-density lipoprotein cholesterol and risk of coronary heart disease suggests that therapeutic elevation of high-density lipoprotein cholesterol may provide an effective means of prevention of coronary heart disease. Pharmacological inhibition of cholesteryl ester transfer protein (CETP) leads to elevation in high-density lipoprotein cholesterol, but torcetrapib (the first-in-class CETP inhibitor) increased the risk of cardiovascular events in the ILLUMINATE trial (Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events), which may have resulted from an unexpected blood pressure–elevating effect of this agent. We used common genetic polymorphisms in the CETP gene to distinguish whether the hypertensive action of torcetrapib was mechanism based or off target, because a genetic study of these variants can be considered to be a type of natural randomized trial of a “clean” low-dose CETP inhibitor with no off-target actions. Common CETP gene polymorphisms and torcetrapib treatment had concordant effects on lipid and lipoprotein markers, including high-density lipoprotein cholesterol, but CETP gene variants had no effect on blood pressure. The blood pressure–elevating effect of torcetrapib appears to be an off-target action that is unlikely to be shared by chemically dissimilar CETP
Propranolol Decreases Tachycardia and Improves Symptoms in the Postural Tachycardia Syndrome: Less Is More

Summary: Postural tachycardia syndrome (POTS) is a disorder of chronic orthostatic intolerance that disproportionately affects women of childbearing age. It is characterized by a constellation of symptoms that occur during standing but resolve with sitting or lying down. A most striking feature of this disorder is the excessive increase in heart rate that occurs on standing in the absence of hypotension. Given the striking tachycardia, β-adrenergic blockers would seem like ideal treatments, but prior anecdotal and experimental experience has been disappointing. We report the first placebo-controlled trial of propranolol in POTS. A low dose of propranolol (20 mg) immediately decreased heart rate and orthostatic tachycardia and improved the orthostatic symptoms in patients with POTS. A higher dose of propranolol (80 mg) elicited more complete β-blockade with a further lowering of heart rate but did not further improve symptoms and may have made some symptoms worse. These data suggest that although low doses of propranolol are of benefit in POTS, higher doses might be counterproductive. These data also offer a potential explanation for the conflicting prior results of β-blockers in POTS.

Conclusions: Low-dose oral propranolol significantly attenuated tachycardia and improved symptoms in POTS. Higher-dose propranolol did not further improve, and may worsen, symptoms.

DITPA (3,5-Diiodothyropropionic Acid), a Thyroid Hormone Analog to Treat Heart Failure: Phase II Trial Veterans Affairs Cooperative Study

Summary: This was a randomized, placebo-controlled, phase II trial designed to evaluate the safety of and provide preliminary data on the potential efficacy of 3,5-diiodothyropropionic acid in patients with stable congestive heart failure. Although the trial was stopped early because of increased side effects at the dose we chose, the data do show beneficial hemodynamic effects of a thyroid hormone analog in the treatment of congestive heart failure. The use of a thyroid hormone analog to treat congestive heart failure is a new and different conceptual approach to the treatment of heart failure because the presumed mechanism of action of the thyroid hormone analog is to alter the molecular composition of the heart and vasculature. If the outcome in patients with congestive heart failure is to be improved, different approaches must be examined that include structural and molecular targets as opposed to attempts to achieve more and more neurohormonal blockade.

Conclusions: DITPA improved some hemodynamic and metabolic parameters, but there was no evidence for symptomatic benefit in congestive heart failure.

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 insulotropic 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 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 physiological 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 a concomitant reduction in atherosclerosis and support a therapeutic role for these agents in preventing cardiovascular complications in type II diabetes mellitus.

Conclusion: 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.

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 LC1699 significantly lowers blood pressure in patients with mild to moderate hypertension. The compound was safe and well tolerated. Aldosterone synthase inhibition with LC1699 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 include elucidation of the effects of partial suppression of cortisol synthesis.

Conclusions: Aldosterone synthase inhibition with LC1699 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.
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 prenatatal 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 (SVT) to a normal rhythm and in slowing both atrial fibrillation and SVT to better-tolerated ventricular rates and therefore might be considered first to treat significant fetal tachyarrhythmia.

Pharmacological Suppression of Hepatic ATP-Binding Cassette Transporter 1 Activity in Mice Reduces High-Density Lipoprotein Cholesterol Levels but Promotes Reverse Cholesterol Transport

Summary: Plasma levels of high-density lipoprotein cholesterol (HDL-C) do not always reflect the dynamic process of reverse cholesterol transport (RCT) from macrophage to bile and feces and the risk of atherosclerosis. For example, mice lacking the hepatic HDL receptor scavenger receptor class B type I have markedly elevated HDL-C levels but impaired RCT and increased atherosclerosis. The ATP-binding cassette transporter 1 (ABCA1) is expressed in the liver, and by exporting cholesterol out of the liver to the HDL protein, apolipoprotein A-I plays a critical role in maintaining plasma HDL-C levels. However, the relationship of hepatic ABCA1 to RCT and atherosclerosis remains poorly understood. Because hepatic ABCA1 pumps cholesterol from the liver into the blood instead of the bile, it might reduce the rate at which the liver excretes HDL-derived cholesterol. Probucol is a drug that reduces HDL-C levels but also, paradoxically, reduces atherosclerosis and xanthomas. We tested the hypothesis that probucol inhibits hepatic ABCA1 activity, thereby reducing HDL-C levels but promoting RCT from macrophages. In studies in mice lacking the hepatic HDL receptor scavenger receptor class B type I, probucol substantially reduced HDL-C but significantly increased macrophage RCT. Furthermore, probucol significantly enhanced the excretion of HDL-derived cholesterol into the feces. Probucol markedly inhibited ABCA1-dependent cholesterol efflux from mouse primary hepatocytes, and this effect was shown to be responsible for the effect of probucol on increasing the fecal excretion of HDL-derived cholesterol in vivo. These results provide an explanation for the beneficial effects of probucol on atherosclerosis despite its HDL-lowering effects and suggest that inactivation of hepatic ABCA1 leads to increased RCT despite reducing plasma HDL-C levels.

Conclusions: We demonstrate that pharmacological inhibition of hepatic ABCA1 activity with probucol reduced HDL-C levels but promoted RCT through diversion of HDL-derived cholesterol from efflux back into plasma instead to excretion in the bile. These results explain the beneficial effects of probucol on atherosclerosis and xanthomas despite its HDL-lowering effects and suggest that inactivation of hepatic ABCA1 leads to increased RCT despite reducing plasma HDL-C levels.

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% versus 12.7% in the acetylcysteine and placebo groups, respectively; relative risk, 1.00; 95% confidence interval, 0.81–1.25; 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.

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 $>230$ 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 platelet reactivity below this threshold merits investigation.11

n-3 Polyunsaturated Fatty Acids in the Prevention of Atrial Fibrillation Recurrences After Electric Cardioversion: A Prospective, Randomized Study

Summary: Atrial fibrillation (AF) is the most common sustained arrhythmia and represents a growing burden on the healthcare system. The prevalence of AF increases with age and has been estimated at 3.8% in persons $>60$ years of age and at 9.0% in those $\geq 80$ years of age. Atrial fibrillation is associated with considerable morbidity and mortality, related mainly to increased risk of thromboembolic events and of new-onset or worsening heart failure. Treatment of AF remains controversial. Although rhythm control and rate control strategies seem to provide comparable results, restoration and maintenance of sinus rhythm would be the preferable pathophysiological approach. However, current pharmacological antiarrhythmic therapies have limited efficacy and poor safety profiles, and invasive or surgical treatments are indicated only in a minority of patients and are not free of failure and procedural risks.

In this study, we tested the efficacy of n-3 polyunsaturated fatty acids in the prevention of AF recurrences in 199 patients with persistent AF on amiodarone and a renin-angiotensin inhibitor. Participants were randomized to n-3 polyunsaturated fatty acids 2 g/d or placebo followed, after at least 4 weeks, by direct current cardioversion. At 1 year, the probability of maintenance of sinus rhythm was significantly higher in the n-3 polyunsaturated fatty acids group than in the placebo group. Our results indicate that the addition of n-3 polyunsaturated fatty acids 2 g/d in patients with persistent AF and structural heart disease and on amiodarone and a renin-angiotensin inhibitor may exert beneficial effects in the prevention of AF recurrence.

Conclusions: In patients with persistent atrial fibrillation on amiodarone and a renin-angiotensin-aldosterone system inhibitor, the addition of n-3 PUFAs 2 g/d improves the probability of the maintenance of sinus rhythm after direct current cardioversion. Our data suggest that n-3 PUFAs may exert beneficial effects in the prevention of atrial fibrillation recurrence. Further studies are needed to confirm and expand our findings.12

Ticagrelor Compared With Clopidogrel by Geographic Region in the Platelet Inhibition and Patient Outcomes (PLATO) Trial

Summary: In the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor prevented the composite of cardiovascular death, myocardial infarction, and stroke better than clopidogrel in a broad acute coronary syndrome population, without increased risk of overall major bleeding. Preplanned analyses examined variation in the treatment effect in relation to 31 demographic and patient characteristics and found a nominally significant interaction of treatment with region. Clopidogrel was associated with a nonsignificant trend of better outcome in North America, whereas ticagrelor was associated with better outcome in the other regions combined. Lower maintenance doses of aspirin were used in the other regions. Of 37 baseline and postrandomization factors explored with Cox regression and separately with landmark techniques, only aspirin dose explained a substantial fraction of the regional interaction; however, given the limitations of these post hoc analyses, the play of chance remains an alternative explanation. Despite robust statistical techniques, a randomized clinical trial is the definitive approach to understanding the dose of aspirin and outcomes with ticagrelor and clopidogrel. Current guidelines for the management of patients with acute coronary syndromes recommend low-dose maintenance aspirin; during potent P2Y12 inhibition with ticagrelor in patients with acute coronary syndromes, low-dose maintenance aspirin is associated with favorable outcomes.

Conclusions: The regional interaction could arise from chance alone. Results of 2 independently performed analyses identified an underlying statistical interaction with aspirin maintenance dose as a possible explanation for the regional difference. The lowest risk of cardiovascular death, myocardial infarction, or stroke with ticagrelor compared with clopidogrel is associated with a low maintenance dose of concomitant aspirin.13

Downregulation of Kv7.4 Channel Activity in Primary and Secondary Hypertension

Summary: Hypertension is a major risk factor for a number of cardiovascular diseases and is the leading cause of mortality worldwide. Hypertension is characterized by an increase in peripheral resistance and is associated with remodeling of the blood vessel architecture, which contributes to the maintenance of elevated blood pressure in the longer term. Recently, voltage-dependent potassium channels encoded by the KCNQ gene family (Kv7.1 through Kv7.5) have been identified in rodent and human vascular smooth muscle, in which they are important regulators of membrane potential and hence vascular contractility. The present study shows that in normotensive rats and mice, structurally different Kv7 activators relaxed mesenteric resistance vessels and thoracic aorta and improved coronary perfusion considerably. Strikingly, the vasorelaxant effects of these agents were markedly attenuated in tissues from spontaneously hypertensive rats and angiotensin II–infused hypertensive mice, and the effect on coronary perfusion was negligible. These impaired functional responses were associated with a downregulation of KCNQ4 gene expression and reduced production of Kv7.4 protein. Downregulation of KCNQ4 and the loss of this antispasmodenic mechanism appear to be a common feature of hypertensive blood vessels, which provides considerable new insight into the pathogenesis of hypertension. Strategies for restoring KCNQ4 could be therapeutically beneficial.

Conclusions: In 2 different rat and mouse models of hypertension, the functional impact of Kv7 channels was dramatically downregulated.14
Rhesus Macaques Develop Metabolic Syndrome With Reversible Vascular Dysfunction Responsive to Pioglitazone

Summary: The metabolic syndrome (MetS) is a constellation of clinical features that include central obesity, hypertension, athero-
genic dyslipidemia, and insulin resistance and is clinically important both because of its prevalence and because it increases the risk for cardiovascular disease and type 2 diabetes mellitus (T2D). However, the concept remains controversial, and there is a need for better understanding of how MetS predisposes to cardiovascular disease and T2D. Here, we devised and implemented a strategy to establish a spontaneous nonhuman primates model of MetS, investigated the emergence of MetS in relation to vascular dysfunction, and determined the response to an established pharmacological treatment for diabetes mellitus. By identifying MetS-predisposed animals among 408 rhesus monkeys of 12.7 years age and acclimating them to standardized laboratory conditions for 18 months, we established a nonhuman primates model of spontaneous MetS that faithfully reproduced salient features of human MetS. During the transition from pre-MetS to onset MetS, individual components of MetS emerged together, indicating common shared underlying processes rather than simultaneous occurrence of independent risk factors. Importantly, vascular dysfunction (60% impairment of flow-mediated dilation of brachial artery) tracked with development of MetS. Pioglitazone, a peroxisome proliferator–activated receptor γ agonist, reversibly improved atherogenic dyslipidemia and insulin resistance and fully restored flow-mediated dilation with persistent effect, suggesting the benefit for early treatment of MetS before frank T2D develops. This unique nonhuman primate model of MetS, as demonstrated here, should be highly valuable in mechanistic and translational studies on the pathogenesis of MetS in relation to cardiovascular disease and T2D.

Conclusions: Coemergence of metabolic and cardiovascular components during MetS progression and complete normalization of vascular dysfunction with peroxisome proliferator-activated receptor γ agonists suggest shared underlying mechanisms rather than separate processes, arguing for the benefit of early intervention of MetS components. Predictive nonhuman primate (NHP) models of MetS should be highly valuable in mechanistic and translational studies on the pathogenesis of MetS in relation to cardiovascular disease and diabetes mellitus.15

Renin-Angiotensin-Aldosterone Genotype Influences Ventricular Remodeling in Infants With Single Ventricle

Summary: The Pediatric Heart Network conducted a pharmacoge-
netic study as part of a multicenter randomized, controlled trial of enalapril versus placebo in single-ventricle infants to assess if renin-angiotensin-aldosterone system (RAAS)–upregulation genotypes influence the response to enalapril. This represents the first pharmacogenetic study of enalapril in a congenital heart disease population. One-hundred fifty-four infants with single ventricle were genotyped and followed up until 14 months of age. Patients with RAAS-upregulation genotypes had persistent increase in ventricular mass and volume despite volume-unloading surgery (ie, superior cavopulmonary connection). Enalapril did not decrease ventricular mass or volume in either genotype group. Patients with high-risk genotypes had lower weight and height at enrollment, and the height impairment persisted in high-risk patients who were receiving enalapril whereas patients receiving placebo normalized their height by 14 months. The high-risk genotype group also showed mild but persistent renal dysfunction. In summary, patients with RAAS-upregulation genotypes failed to show reverse remodeling in response to volume-unloading surgery, had persistent growth abnormalities, especially with enalapril, and had persistent renal dysfunction. These patients may need earlier superior cavopulmonary connection to facilitate reversal of ventricular dilation and hypertrophy before the remodeling becomes irreversible. Because neither enalapril nor surgery showed significant benefit in high-risk genotype patients, there is a need to develop newer therapies in at-risk patients.

Conclusions: Renin-angiotensin-aldosterone system–upregulation genotypes were associated with failure of reverse remodeling after superior cavopulmonary connection surgery, less improvement in renal function, and impaired somatic growth, the latter especially in patients receiving enalapril. Renin-angiotensin-aldosterone system genotype may identify a high-risk subgroup of single ventricle patients who fail to fully benefit from volume-unloading surgery. Follow-up is warranted to assess long-term impact.16

Duration of Treatment With Nonsteroidal Anti-Inflammatory Drugs and Impact on Risk of Death and Recurrent Myocardial Infarction in Patients With Prior Myocardial Infarction: A Nationwide Cohort Study

Summary: Recently, there has been increased awareness of aug-
mented cardiovascular risk associated with use of nonsteroidal anti-inflammatory drugs (NSAIDs), especially among patients with established cardiovascular disease. Earlier studies have indicated acute or subacute effects of both the selective cyclooxygenase-2 inhibitors and nonselective NSAIDs on the cardiovascular system. These adverse events were closely tied to the timing of taking the drugs, and most patients were receiving treatment for a short period of time. However, at present, there is a lack of data on the impact of NSAID treatment duration on cardiovascular risk. The present study addresses the risk of all NSAIDs in a selected population of post–myocardial infarction patients. We present a comprehensive analysis of the effect of duration of NSAID treatment on risk of death or recurrent myocardial infarction in a nationwide cohort of myo-
cardial infarction survivors. We found that short-term treatment with most NSAIDs was associated with increased and instantaneous cardiovascular risk. Particularly worrying was the fact that the widely used nonselective NSAID diclofenac was associated with early and higher cardiovascular risk than the selective cyclooxygenase-2 inhibitor rofecoxib, which was withdrawn from the market in 2004 owing to its unfavorable cardiovascular risk profile. Our results indicate that there is no apparent safe therapeutic window for NSAIDs in patients with prior myocardial infarction and challenge the current recommendations of short-term use of NSAIDs as being safe. We believe this message is important, and should be distributed as widely as possible to clinicians taking care of patients with cardiovascular disease.

Conclusions: Even short-term treatment with most NSAIDs was associated with increased risk of death and recurrent myocardial infarction in patients with prior myocardial infarction. Neither short- nor long-term treatment with NSAIDs is advised in this population, and any NSAID use should be limited from a cardiovascular safety point of view.17

Use of Angiotensin Receptor Blockers and the Risk of Cancer

Summary: A meta-analysis of randomized trials published in June 2010 suggested that use of angiotensin receptor blockers (ARBs) may be associated with an increased risk of cancer, lung cancer in particular. Because millions of patients use ARBs, monitoring their safety is of immediate clinical importance. Using individual-level data from registries in Denmark, including, for example, information on filled drug prescriptions and cancer diagnoses, we conducted a nationwide cohort study to compare the rates of incident cancer among users of ARBs and angiotensin-converting enzyme inhibitors. In an analysis including >100 000 users of ARBs and >200 000 users of angiotensin-converting enzyme inhibitors, we found no evidence of an increased risk of cancer overall associated with ARB
Clinical Benefit of Statin Pretreatment in Patients Undergoing Percutaneous Coronary Intervention: A Collaborative Patient-Level Meta-Analysis of 13 Randomized Studies

Summary: In this collaborative patient-level meta-analysis of 13 randomized, controlled trials (n=33,44 patients), we demonstrated that short-term pretreatment with high-dose statins reduces the incidence of perioperative myocardial infarction and early major adverse cardiac events in patients undergoing percutaneous coronary intervention. This outcome improvement was irrespective of clinical presentation, chronic statin therapy, or antithrombotic treatment, and was more pronounced in patients with high baseline inflammatory status. Our results strengthen the concept that the clinical benefit provided in the short-term by high-dose statins is due to pleiotropic effects. These data suggest that a strategy of early initiation of high-dose statins should be implemented routinely in patients who are candidates for percutaneous coronary intervention, and guideline committees should consider updates to incorporate this novel strategy for perioperative percutaneous coronary intervention prevention of ischemic events.

Conclusions: High-dose statin pretreatment leads to a significant reduction in perioperative 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.19

Upstream Clopidogrel Use and the Efficacy and Safety of Early Eptifibatide Treatment in Patients With Acute Coronary Syndrome: An Analysis From the Early Glycoprotein IIb/IIIa Inhibition in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome (EARLY ACS) Trial

Summary: In the Early Glycoprotein IIb/IIIa Inhibition in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome (EARLY ACS) trial, routine early eptifibatide before angiography was not superior to delayed provisional use during percutaneous coronary intervention but led to more bleeding. The efficacy and safety of early eptifibatide in the setting of upstream clopidogrel use is unknown. In this study of 9166 non–ST-segment elevation acute coronary syndrome patients who underwent coronary angiography in the EARLY ACS trial, we found that early preprocedure use of eptifibatide did not improve short-term ischemic outcomes but may be associated with a reduction in 30-day ischemic risk after upstream treatment with clopidogrel. The addition of clopidogrel accentuated bleeding risks associated with early eptifibatide use. These findings lend support to the concept of enhanced value for additive antiplatelet therapies, and future investigations are needed to identify those patients who may benefit from more intensive platelet inhibition without a significant excess in bleeding risk.

Conclusions: Routine early eptifibatide use, compared with delayed provisional use, may be associated with lower 30-day ischemic risk in non-ST-elevation acute coronary syndrome patients also treated with clopidogrel before angiography. The benefit–risk ratio of intensive platelet inhibition with combined early use of antiplatelet agents needs further evaluation in prospective randomized trials.20

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 CABG, 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.21

Microsomal Prostaglandin E2 Synthase-1 Modulates the Response to Vascular Injury

Summary: Nonsteroidal anti-inflammatory drugs specific for the inhibition of cyclooxygenase-2 (COX-2) confer a risk of myocardial infarction and stroke. Microsomal (m) prostaglandin (PG) E2 synthase (S)-1 represents an alternative anti-inflammatory target downstream of COX-2. Inhibition of mPGES-1 may be less likely to predispose patients to thrombotic events than inhibition of COX-2. Despite the risk of myocardial infarction conferred by celecoxib in placebo-controlled trials, preliminary evidence suggests that in patients receiving platelet inhibitors to limit this risk, restenosis might be reduced by this purposefully designed nonsteroidal anti-inflammatory drug selective for inhibition of COX-2. Here, we demonstrate that deletion of mPGES-1 in mice attenuates neointimal hyperplasia after vascular injury. Both suppression of PGE2 and redirection of the accumulated PGH2 substrate to PGL2 may contribute to dysregulated expression of tenascin-C, an extracellular matrix glycoprotein, resulting in impaired vascular smooth muscle cell migration and proliferation in the knockouts. These studies raise the possibility of mPGES-1 inhibition as a strategy to limit restenosis after percutaneous coronary intervention. However, a limitation may prove to be the contrasting effect on myocardial remodeling after coronary ligation. Although mPGES-1 inhibitors might be expected to confer a diminished risk of myocardial infarction and mortality after myocardial infarction compared with COX-2 inhibitors, the
Conclusions: Deletion of mPGES-1 in mice attenuates neointimal hyperplasia after vascular injury, in part by regulating tenasin-C expression. This raises for consideration the therapeutic potential of mPGES-1 inhibitors as adjuvant therapy for percutaneous coronary intervention.

Inhibition of p38 Mitogen-Activated Protein Kinase Improves Nitric Oxide–Mediated Vasodilatation and Reduces Inflammation in Hypercholesterolemia

Summary: Hypercholesterolemia is associated with impaired vaso-motor endothelial function, which is a recognized surrogate marker of outcome. We tested the hypothesis that a novel p38 MAP kinase inhibitor, losmapimod, could improve nitric oxide–mediated responses in such a cohort. We demonstrated for the first time that moderate blockade of this pathway improved endothelial-dependent and -independent nitric oxide–mediated vasodilatation in addition to reducing systemic inflammation, as evidenced by an almost 60% reduction in high-sensitivity C-reactive protein, without alteration in cholesterol levels. Inhibition of p38 may be an attractive target in patients with underlying vascular inflammation.

Conclusions: Losmapimod improves nitric oxide–mediated vasodilatation in hypercholesterolemic patients, which is consistent with findings in previous translational animal models. These data support the hypothesis that attenuating the inflammatory milieu by inhibiting p38 MAPK activity improves NO activity. This suggests p38 MAPK as a novel target for patients with cardiovascular disease.

Clinical Events as a Function of Proton Pump Inhibitor Use, Clopidogrel Use, and Cytochrome P450 2C19 Genotype in a Large Nationwide Cohort of Acute Myocardial Infarction: Results From the French Registry of Acute ST-Elevation and Non–ST-Elevation Myocardial Infarction (FAST-MI) Registry

Summary: Over the past months, there has been an intense scientific debate on the potential clinical impact of proton pump inhibitor use in patients treated with clopidogrel. There is a potential for drug-drug interactions because many proton pump inhibitors are metabolized by or are inhibitors of the cytochrome P450 2C19 (CYP2C19) enzyme. The stakes are considerable, given the huge number of patients treated with these medications. Specifically, the impact of CYP2C19 genetic polymorphisms on clinical outcomes in patients receiving a proton pump inhibitor and clopidogrel has not been evaluated. Overall, proton pump inhibitor use was not associated with an increased risk for any of the main outcomes (in-hospital and 1-year survival, 1-year myocardial infarction– and stroke-free survival, 1-year major ischemic events in hospital survival, in-hospital bleeding and transfusion) in either the overall population or any of the subgroups tested. One of the key new findings of the present analysis is that there was no clinically relevant association in adverse cardiovascular events or mortality among patients with no or 1 CYP2C19 loss-of-function allele. Thus, in this population, the results do not support the avoidance of proton pump inhibitor use for those patients receiving clopidogrel who are at increased risk of gastrointestinal bleeding. However, because of the low number of patients and resultant large confidence interval ranges, the possibility that a higher early risk may exist in patients with 2 CYP2C19 variant alleles cannot be dismissed and needs further clinical studies. We believe that these results are important for physicians in charge of these patients.

Conclusion: Proton pump inhibitor use was not associated with an increased risk of cardiovascular events or mortality in patients administered clopidogrel for recent MI, whatever the CYP2C19 genotype, although harm could not be formally excluded in patients with 2 loss-of-function alleles.

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

Summary: Cardioversion in atrial fibrillation is 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 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 1983 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.

Ticagrelor versus Clopidogrel in Acute Coronary Syndromes in Relation to Renal Function: Results From the Platelet Inhibition and Patient Outcomes (PLATO) Trial

Summary: Among patients with acute coronary syndromes, any degree of impairment of renal function is associated with a worse prognosis but also an increased bleeding risk, which may alter the risk-benefit ratio with antiplatelet therapies. The Platelet Inhibition and Patient Outcomes (PLATO) trial investigated the effects of ticagrelor compared with clopidogrel in a broad population of patients with non–ST-segment elevation acute coronary syndromes, regardless of the intended management strategy. Patients with chronic kidney disease, defined as a baseline creatinine clearance <60 mL/min, constituted 21% of those with baseline creatinine measurements (15 202). The numeric absolute (and relative) risk reductions of the primary composite end point and total mortality by ticagrelor versus clopidogrel were 4.7% (23%) and 4.0% (28%) in patients with chronic kidney disease and 1% (10%) and 0.5% (11%) in patients with normal renal function. The incidence of major bleeding did not differ significantly between the ticagrelor and clopidogrel groups in patients with normal renal function or in patients with chronic kidney disease. Thus, ticagrelor is a more effective antiplatelet agent than clopidogrel in acute coronary syndrome patients regardless of renal function, and the benefits are
larger in those with poor renal function without any need for dose reduction to prevent major bleeding. Given the high prevalence of renal dysfunction among patients with atherosclerotic disease and the associated elevated risk of ischemic and bleeding complications, ticagrelor provides an important opportunity to substantially improve outcome in patients with acute coronary syndromes and impaired renal function.

Conclusions: In acute coronary syndrome patients with chronic kidney disease, ticagrelor compared with clopidogrel significantly reduces ischemic end points and mortality without a significant increase in major bleeding but with numerically more non-procedure-related bleeding.26

Enalapril in Infants With Single Ventricle: Results of a Multicenter Randomized Trial

Summary: Infants with complex heart lesions that lead to single-ventricle physiology are at risk for abnormalities in ventricular systolic and diastolic function and for poor growth. Extrapolation of data from the adult literature has led to the empirical use of angiotensin-converting enzyme inhibitor therapy in this population; however, its efficacy has never been studied. The Pediatric Heart Network conducted a multicenter, double-blind, placebo-controlled trial involving 230 infants with single-ventricle physiology randomized to receive enalapril (target dose 0.4 mg · kg⁻¹ · d⁻¹) or placebo and followed up to 14 months of age. Overall, the majority of the study population had normal ventricular function and no clinical heart failure at 14 months of age, regardless of the treatment group. Growth was significantly impaired, and there were neurodevelopmental abnormalities noted. The incidence of death or transplantation was 13% and did not differ between treatment groups. Administration of enalapril did not improve somatic growth, ventricular function, or heart failure severity. The results of this randomized trial do not support the routine use of enalapril in this population.

Conclusions: Administration of enalapril to infants with single-ventricle physiology in the first year of life did not improve somatic growth, ventricular function, or heart failure severity. The results of this randomized trial do not support the routine use of enalapril in this population.

Evaluation of a New Heparin Agent in Percutaneous Coronary Intervention: Results of the Phase 2 Evaluation of M118 IN pErcticaNeus Coronary intErvention (EMINENCE) Trial

Summary: M118 is a novel low–molecular-weight heparin that has been rationally designed to capture the desired attributes of both unfractionated heparin and low–molecular-weight heparin: Potent activity against both factor Xa and IIa, predictable pharmacokinetics after both intravenous and subcutaneous administration, ability to be monitored by use of point-of-care coagulation assays, and reversibility with protamine sulfate. We performed a phase 2 randomized trial to evaluate the safety and feasibility of M118 in the setting of elective percutaneous coronary intervention. The results of the EMINENCE trial demonstrate that M118 is well tolerated and feasible to use as an anticoagulant during percutaneous coronary intervention. It exhibits a dose-dependent increase in the activated clotting time and is noninferior to unfractionated heparin with respect to a broad composite of end points that reflect complications related to percutaneous coronary intervention. In addition to clinical outcomes, angiographic outcomes were excellent and comparable between unfractionated heparin and M118. Although a range of doses of intravenous M118 was comparable to unfractionated heparin at preventing a broad composite of percutaneous coronary intervention–related complications, we conclude that a dose range of 75 to 100 IU/kg appears most promising and should be tested further in a phase 3 trial.

Conclusions: This phase 2 randomized trial demonstrates that M118 is well tolerated and feasible to use as an anticoagulant in patients undergoing elective percutaneous coronary intervention and forms the basis for further investigation of this agent in ischemic heart disease.28

Effect of Rosiglitazone on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease: The Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients With Cardiovascular History Trial

Summary: The thiazolidinedione class of drugs has many favorable metabolic and vascular anatomic effects in people with type 2 diabetes mellitus. Whereas the Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients With Cardiovascular History (APPROACH) trial did not show a clear reduction in coronary atherosclerosis versus glipizide, its results are consistent with other studies of rosiglitazone and pioglitazone that did suggest reduced carotid and coronary atherosclerosis. Moreover, the large randomized outcomes trials of the thiazolidinediones that have been completed to date are consistent with the hypothesis that (1) pioglitazone may reduce cardiovascular outcomes compared with placebo and (2) the effect of rosiglitazone on cardiovascular outcomes is similar to that of metformin and to that of sulfonylureas. With the exception of fluid retention and pulmonary edema, these trial findings support the importance of clearly testing the cardiovascular effects of both of these drugs within 1 trial. The Thiazolidinedione Intervention With Vitamin D Evaluation (TIDE) trial is a large placebo-controlled trial of 16,000 participants that is currently assessing the cardiovascular effects of both thiazolidinediones versus placebo when added to current therapy. It will also clearly evaluate whether either of the 2 thiazolidinediones differ with respect to cardiovascular outcomes and will clearly determine whether either or both of these drugs prevents, promotes, or has a neutral effect on serious cardiovascular outcomes.

Conclusions: Rosiglitazone did not significantly decrease the primary end point of progression of coronary atherosclerosis more than glipizide in patients with type 2 diabetes mellitus and coronary atherosclerosis.

Intracoronary Eptifibatide Bolus Administration During Percutaneous Revascularization for Acute Coronary Syndromes With Evaluation of Platelet Glycoprotein IIb/IIIa Receptor Occupancy and Platelet Function: The Intracoronary Eptifibatide (ICE) Trial

Summary: Eptifibatide administered intravenously may improve cardiac outcomes in selected patients during percutaneous coronary intervention. We evaluated the strategy of intracoronary bolus administration of eptifibatide to achieve higher levels of glycoprotein IIb/IIIa receptor occupancy in the local coronary bed, an effect that may dissociate coronary thrombus and hence improve coronary flow. Platelet glycoprotein IIb/IIIa receptor occupancy in the coronary sinus was significantly greater with intracoronary versus intravenous administration: first bolus, 94±2% versus 51±15% (P<0.001); second bolus, 99±2.2% versus 91.4% (P<0.001), respectively. Microvascular perfusion was significantly improved as measured by the corrected thrombolysis in myocardial infarction frame count with intracoronary versus intravenous administration: pre–percutaneous coronary intervention, 36 (median) (25th and 75th percentiles, 16 and 64) versus 31 (25th and 75th percentiles, 23 and
Conclusions: Intracoronary bolus administration of epifibatide during percutaneous coronary intervention in patients with acute coronary syndromes results in higher local platelet glycoprotein Ib/IIa receptor occupancy and better microcirculatory flow with an improved corrected thrombolysis in myocardial infarction frame count. This approach requires further study and confirmation of its potential to reduce major adverse cardiac events.

Myocardial Ischemia/Reperfusion Injury Is Mediated by Leukocytic Toll-Like Receptor-2 and Reduced by Systemic Administration of a Novel Anti–Toll-Like Receptor-2 Antibody

Summary: Over the past few decades, many molecular targets have been studied to limit the excessive tissue loss that occurs during the reperfusion phase after ischemia. This so-called myocardial ischemia/reperfusion injury limits the full potential of reperfusion therapy. Unfortunately, successful clinical translation of preclinical promises remains to be established. Our understanding of the pathogenesis of myocardial ischemia/reperfusion injury became much clearer with the discovery of Toll-like receptors (TLRs). The role of innate immunity in cardiac ischemia appeared to be more pivotal than we thought. More important, TLRs hold great promise as a therapeutic target within the innate immune system, also beyond cardiac ischemia/reperfusion injury. Administration of a TLR2 antagonist just 5 minutes before reperfusion reduces infarct size and improves cardiac performance and geometry. Furthermore, antagonizing TLR2 reduces inflammation and cell death after infarction. Our results reappraised the critical role of TLRs in cardiac ischemia and elucidated the mechanisms by which TLR2 mediates myocardial ischemia/reperfusion injury. Our results establish TLR2 as a novel therapeutic target for the treatment of acute myocardial infarction, even when it is initiated in the late ischemic period. For this reason, we provide a rationale for anti-TLR2 treatment initiated either in the ambulance or in the catheterization laboratory before reperfusion.

Conclusions: Circulating TLR2 expression mediates myocardial ischemia/reperfusion injury. Antagonizing TLR2 just 5 minutes before reperfusion reduces infarct size and preserves cardiac function and geometry. Anti-TLR2 therapy exerts its action by reducing leukocyte influx, cytokine production, and proapoptotic signaling. Hence, monoclonal anti-TLR2 antibody is a potential candidate as an adjunctive therapy in patients with myocardial infarction.

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