Interleukin-1β inhibition and the prevention of recurrent cardiovascular events: Rationale and Design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

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Background Inflammation contributes to all phases of the atherothrombotic process, and patients with elevated inflammatory biomarkers such as high-sensitivity C-reactive protein (hsCRP) have increased vascular risk. Yet, it remains unknown whether direct inhibition of inflammation will reduce cardiovascular event rates.

Design The CANTOS will evaluate whether interleukin-1β (IL-1β) inhibition as compared with placebo can reduce rates of recurrent myocardial infarction, stroke, and cardiovascular death among stable patients with coronary artery disease who remain at high vascular risk due to persistent elevations of hsCRP (≥2 mg/L) despite contemporary secondary prevention strategies. Canakinumab is a human monoclonal antibody that selectively neutralizes IL-1β, a proinflammatory cytokine that plays multiple roles in the atherothrombotic process and that undergoes activation by the nucleotide-binding leucine-rich repeat-containing pyrin receptor 3 inflammasome, a process promoted by cholesterol crystals. Canakinumab significantly reduces systemic C-reactive protein and other inflammatory biomarker levels, is generally well tolerated, and is currently indicated for the treatment of inherited IL-1β driven inflammatory diseases such as the Muckle-Wells syndrome. In a multinational collaborative effort using an event-driven intention-to-treat protocol, CANTOS will randomly allocate 17,200 stable postmyocardial infarction patients with persistent elevation of hsCRP to either placebo or to canakinumab at doses of 50, 150, or 300 mg every 3 months, administered subcutaneously. All participants will be followed up over an estimated period of up to 4 years for the trial primary end point (nonfatal myocardial infarction, nonfatal stroke, cardiovascular death) as well as for other vascular events, total mortality, adverse events, and specific clinical end points associated with inflammation including new onset diabetes, venous thrombosis, and atrial fibrillation.

Summary If positive, CANTOS would confirm the inflammatory hypothesis of atherothrombosis and provide a novel cytokine-based therapy for the secondary prevention of cardiovascular disease and new-onset diabetes. (Am Heart J 2011;162:597-605.)

The inflammatory hypothesis of atherothrombosis and the role of hsCRP in clinical practice

Inflammation contributes to all phases of the atherothrombotic process including the rupture of plaques that underlies many acute ischemic events in the coronary and cerebral circulations. Components of both the innate and acquired immune systems contribute to atherosclerotic disease progression, and interactions between lipids and multiple facets of immune function promote premature atherogenesis and accelerate plaque fissuring. As comprehensively reviewed elsewhere, inflammatory mechanisms participate in diverse aspects of atherosclerosis including early cell adhesion, lesion propagation, matrix and collagen degradation, smooth muscle proliferation, heightened platelet reactivity, and thrombosis.1,2

For clinicians, translation of the inflammatory hypothesis of atherosclerosis has used emerging inflammatory biomarkers such as high-sensitivity C-reactive protein (hsCRP) as a method to identify individuals at high risk for both first and recurrent vascular events even in the absence of hyperlipidemia and other major vascular risk...
Epidemiologic data for hsCRP consistently demonstrate the pathophysiologic importance of inflammation as a target for intervention. In a comprehensive overview of >50 prospective cohort studies, the magnitude of risk associated with a 1 SD increase in hsCRP was found equal to or greater than that associated with a similar increase in risk due to hyperlipidemia or blood pressure. Furthermore, in this overview as in earlier studies, the strength of association and magnitude of reclassification of global vascular risk based on evaluation of hsCRP was at least as large as that achieved based on measurement of total and high-density lipoprotein cholesterol. Despite this large attributable risk (and in marked contrast to lipid-lowering and blood pressure-lowering therapies), it remains unknown whether inhibition of inflammation per se will lower vascular event rates, particularly in patient populations identified as having a persistent proinflammatory response despite use of all usual cardiovascular treatments.

The clinical and pathophysiologic need to test formally the inflammatory hypothesis of atherosclerosis is highlighted by several additional observations. First, despite the clear importance of low-density lipoprotein (LDL) cholesterol as a risk factor and the proven utility of LDL reduction as a therapeutic modality, half of all myocardial infection and stroke events occur among apparently healthy men and women with average or even low levels of cholesterol. Second, in almost all lipid-lowering trials completed to date, the relative risk reduction on vascular events associated with statin therapy has been largely independent of baseline LDL cholesterol. These data are intriguing, as statins, in addition to reducing cholesterol, also have anti-inflammatory effects independent of LDL lowering that may have clinical relevance.

As initially observed a decade ago in the CARE trial of secondary prevention, the relative benefit of pravastatin is greater in the presence of inflammation than in its absence. Furthermore, as shown retrospectively in the AFCAPS/TexCAPS trial of lovastatin and then prospectively in the JUPITER trial of rosuvastatin, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase therapy is highly effective at reducing vascular event rates among apparently healthy individuals with low levels of LDL cholesterol who, nonetheless, have heightened vascular risk based on elevated hsCRP levels. Of relevance to the inflammatory hypothesis of atherothrombosis, in the JUPITER trial, both absolute vascular risk and the magnitude of absolute risk reduction associated with rosuvastatin increased with increasing levels of baseline hsCRP but not with baseline LDL cholesterol. In addition, the magnitude of relative risk reduction observed in JUPITER (a trial that enrolled based on inflammation) was greater than that observed in all prior statin trials (that largely enrolled based on hyperlipidemia).

Multiple prospective cohort studies also demonstrate the importance of hsCRP as an independent predictor of recurrent vascular risk in secondary prevention. Equally important, analyses of several randomized trials including PROVE IT, A to Z, and JUPITER consistently indicate that achieving low levels of hsCRP contributes to event reduction in a manner analogous to achieving low levels of LDL cholesterol. For example, in the PROVE IT trial comparing atorvastatin with pravastatin, those with on-treatment levels of hsCRP >2 mg/L had substantially higher risks of recurrent cardiovascular events when compared with those who achieved on-treatment hsCRP levels <2 mg/L (Figure 1). Supporting the clinical concept of dual targets, the PROVE IT and A to Z trials (secondary prevention) as well as JUPITER (primary prevention) demonstrate that the greatest clinical benefits from statin therapy accrue among those who reduce hsCRP levels as well as LDL cholesterol.

Analyses of the CORONA trial of rosuvastatin conducted among high-risk patients with congestive heart failure also add clinically relevant data regarding the utility of hsCRP in secondary prevention as a method to identify patient groups at high inflammatory risk who preferentially benefit from therapy. In CORONA, statin therapy produced no benefit in those with baseline hsCRP levels <2 mg/L yet did statistically significantly reduce all prespecified trial end points among those with
hsCRP >2 mg/L. Indeed, had stratification been done by hsCRP on an a priori basis, the CORONA trial would have been reported as a positive rather than null trial. 

Yet, such analyses of statin trials cannot definitively evaluate whether lowering inflammation alone would lower vascular risk due to the statins’ ability to affect both inflammation and lipid levels. Similarly, randomized trial data suggesting that aspirin has greater clinical benefits among those with elevated hsCRP support but does not prove the inflammatory hypothesis, as aspirin has primary antiplatelet as well as anti-inflammatory effects. 

The accumulating laboratory and clinical data summarized above, however, do provide the scientific basis for proceeding with a series of novel “cardiovascular inflammation reduction trials” designed to test directly whether known anti-inflammatory agents without concomitant effects on cholesterol or platelet function can reduce cardiovascular events. One particularly promising approach to this issue is inhibition of interleukin-1β (IL-1β), a potent proinflammatory cytokine that plays multiple roles in the atherothrombotic process.

### The interleukin-1 family and effects on systemic inflammatory disorders

Interleukins are critical mediators of the systemic inflammatory response. Of the inflammatory molecules implicated in atherothrombosis, interleukin-1 (IL-1) plays a particularly prominent role. The IL-1 gene family encodes 3 major proteins: IL-1α and IL-1β (that exert proinflammatory effects by binding to the IL-1 type 1 receptor) and IL-1 receptor antagonist (IL-1Ra; an endogenous inhibitor that competitively blocks binding of IL-1α and β to the IL-1 type I receptor). The balance of pro- and anti-inflammatory effects mediated through IL-1 and IL-1Ra also depends upon the IL-1 type II receptor that acts as a “decoy receptor” and does not lead to signal transduction. In an additional level of regulation, cells initially produce IL-1β in an inactive precursor form, pro-IL-1β, that requires proteolytic cleavage to attain biological activity.

Despite similar activation patterns, IL-1α and IL-1β differ, IL-1β being secreted and circulated systemically, whereas IL-1α largely associates with the plasma membrane of its producing cell and, thus, typically acts in a local contact-dependent fashion. Although many cell types can produce IL-1 family members, monocytes and macrophages, key cells in atherosclerotic plaque biology, produce the bulk of IL-1β. In addition, a complex of intracellular proteins, known as the nucleotide-binding leucine-rich repeat-containing pyrin receptor 3 (NLRP3) inflammasome, activates caspase-1 or IL-1β converting enzyme, the protease that processes mature, active IL-1β from its inactive precursor. Several exogenous “danger signals” trigger the inflammasome including crystalline compounds; for example, activation of the NLRP3 inflammasome by uric acid crystals results in enhanced secretion of IL-1β and the subsequent acute inflammation associated with gout.

Multiple clinical observations support the concept that a net balance of inflammatory activity influenced by relative levels of IL-1 and IL-1Ra contributes to human disease. First, specific amino acid mutations altering the NLRP3 inflammasome can increase secretion of IL-1β and result in a group of autoinflammatory disorders including cryopyrin-associated periodic syndrome (CAPS), neonatal-onset multisystem inflammatory disease, and Muckle-Wells syndrome. 

These conditions respond to treatment with monoclonal antibodies targeted against IL-1β or with exogenous IL-1Ras. Second, rare mutations associated with an absence of IL-1Ra lead to unchecked overexpression of IL-1 and severe systemic inflammation. Relative deficiencies of interleukin-1 receptor antagonist and subsequent moderate to mild imbalances in the IL-1/IL-1Ra system may contribute to a broad range of chronic inflammatory conditions including type 2 diabetes, psoriasis, gout, inflammatory arthritis, and inflammatory bowel disease (Figure 2).

### Interleukin-1 and atherothrombosis

Experimental evidence accumulating over the past quarter century has implicated IL-1 in atherothrombosis. Studies in the early 1980s showed that IL-1 can induce procoagulant activity as well as monocyte and leukocyte adhesion in human vascular endothelial cells. Soon thereafter, both endotoxin and tumor necrosis factors (TNFs) were found to induce IL-1 gene expression in human vascular endothelial cells as well as human vascular smooth muscle cells, identifying a local...
source of this cytokine before monocyte recruitment in the initiation of atherosclerosis. Human atherosclerotic lesions contain both IL-1β and IL-1Ra, and dysregulated balance between such pro- and anti-inflammatory cytokines likely participates importantly in the pathogenesis of atherothrombosis. Animal studies provide consistent support for this hypothesis, including the demonstration of reduced lesions in atherosclerosis-prone mice deficient in either IL-1 or the type I IL-1 receptor. In contrast, IL-1Ra-deficient mice have increased atherogenesis. Interleukin-1 exposure promotes experimental atherogenesis in quantitative analysis of aortic lesion areas in apolipoprotein-E-deficient (apo-E−/−) mice, whereas IL-1Ra administration to apo-E−/− mice reduces fatty lesion formation. Similarly, ablation of the IL-1 receptor inhibits atherosclerosis in apo-E−/− mice inoculated with the common oral cavity bacterium Porphyromonas gingivalis. Studies on pig coronary arteries support a role for IL-1 in arterial hyperplasia, showing increased neointimal formation with periadventitial administration of IL-1 and reduced neointima formation in the presence of IL-1Ra.

Accumulating human studies also support a direct role for IL-1 in atherosclerosis and in rupture prone lesions. Atherosclerotic as compared with normal coronary arteries have increased IL-1β levels, and IL-1Ra concentrations are higher among those with acute coronary syndromes as compared with asymptomatic patients or those with chronic stable coronary disease. Furthermore, among patients with ST-elevation myocardial infarction, elevated levels of IL-1Ra precede increases in markers of myocardial necrosis such as troponin and creatine kinase. Several studies suggest that polymorphism in IL-1Ra associates with the burden of coronary lesions found on angiography, with the incidence of restenosis after coronary stent implantation and with rates of atherosclerotic progression. In patients with rheumatoid arthritis, use of the IL-1Ra anakinra associates with improvement in coronary flow reserve, left ventricular function, and flow-mediated brachial artery dilation (a measure of endothelial vasodilator function), effects that parallel plasma reductions in IL-6, C-reactive protein (CRP), and the vasoconstrictor endothelin-1. Based, in part, on these observations, the MRC-ILA-HEART Study of anakinra is evaluating the effects of IL-1Ra on CRP and other inflammatory biomarkers among patients with non-ST-elevation acute coronary syndromes.

Moreover, recent studies have shown that the NLRP3 inflammasome crucial for production of active IL-1β responds not only by bacteria, crystalline uric acid, and crystalline pyrophosphate but also to cholesterol crystals and minimally modified LDL cholesterol. This observation further implicates IL-1β in atherogenesis and plaque progression by identifying crystalline cholesterol as an “endogenous danger signal” to trigger IL-1β activation and providing a new link between lipids and inflammation. Furthermore, as IL-1β drives the acute phase response, these new inflammasome data provide a novel unifying causal explanation for why systemic biomarkers of inflammation such as hsCRP or IL-6 are elevated years in advance of acute coronary occlusion. As reviewed elsewhere, IL-1β-induced inflammation in islets of patients with type 2 diabetes also appears mediated through the NLRP3 inflammasome.

Canakinumab as an agent to target IL-1β and potentially reduce cardiovascular event rates and new-onset diabetes: the CANTOS trial

Given the role of IL-1β in atherothrombosis described above, the use of IL-1β inhibition as a possible method to reduce vascular risk has generated considerable interest. Canakinumab is a human monoclonal anti-human IL-1β antibody of the immunoglobin G1/k isotype that is currently indicated for the treatment of IL-1β-driven inflammatory disorders such as CAPS and Muckle-Wells syndrome. Canakinumab binds human IL-1β and, thus, blocks the interaction of this cytokine with its types I and II receptors. In patients with CAPS, rheumatoid arthritis, and type 2 diabetes, IL-1β antagonism with canakinumab produces a rapid and sustained inhibition of the acute phase response resulting in substantial reductions in CRP and IL-6. Furthermore, unlike available TNF-α inhibitors, canakinumab has only marginal effects on lipid levels and, thus, provides a novel method to directly test the inflammatory hypothesis of atherothrombosis by inhibiting inflammation without confounding effects on other pathways implicated in the atherosclerotic disease process. Canakinumab's prolonged effect on the acute phase response permits quarterly dosing using subcutaneous injections. In trials conducted to date, canakinumab has been associated with minimal injection site reactions and few direct side effects, although a small increase in risk of infection is anticipated, reflecting the inhibition of innate immunity achieved through canakinumab therapy. The primary objective of the CANTOS is to determine whether long-term treatment with canakinumab (50, 150, or 300 mg SC every 3 months) as compared with placebo will reduce rates of recurrent cardiovascular events among stable patients with postmyocardial infarction who remain at elevated vascular risk as gauged by increased levels of hsCRP (>2 mg/L) despite usual care, including statin therapy. The trial primary end point will be recurrent major cardiovascular events, defined as nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Secondary objectives of CANTOS include...
determination of the safety and efficacy of long-term canakinumab therapy among patients with postmyocardial infarction on total mortality and on other vascular events including hospitalization for unstable angina requiring revascularization. Furthermore, among those with normal or impaired fasting glucose at the time of randomization, CANTOS will also address whether canakinumab will reduce the incidence of new onset diabetes. This latter secondary hypothesis reflects IL-1β’s implication in autoinflammatory processes related to pancreatic dysfunction, insulin resistance, and diabetes.

Finally, in exploratory prespecified analyses, CANTOS will also address the impact of IL-1β inhibition with canakinumab on the incidence of several clinical conditions known to associate with chronic inflammation including venous thromboembolism, atrial fibrillation, stent thrombosis, hospitalization for congestive heart failure, and macular degeneration. In a series of prespecified biomarker studies, CANTOS will also address the impact of canakinumab on plasma biomarkers of cardiovascular and diabetes risk as well as the effect of canakinumab on nephropathy as assessed by the urinary albumin-to-creatinine ratio in patients with type 2 diabetes or impaired fasting glucose at baseline. The trial protocol also prescribes quality of life and pharmacogenetic evaluations.

Study population

The CANTOS will enroll approximately 17,200 men and women 18 years old and older who (a) have had a documented acute myocardial infarction at least 30 days before randomization, (b) have completed any planned revascularization procedures associated with their initial infarction, and (c) have evidence of systemic inflammation based on an hsCRP >2 mg/L despite the stable use of standard secondary prevention therapies including statins, other lipid-lowering agents, antihypertensives, β-adrenergic blocking drugs, and indicated antiplatelet agents as appropriate.

As the effects of canakinumab on development are unknown, women of child-bearing potential will not be eligible for participation in CANTOS. Furthermore, as canakinumab is an inhibitor of innate immunity, patients with a suspected or known immunocompromised state, those taking another biologic agent that targets the immune system (TNF blockers, anakinra, rituximab, abatacept, tocilizumab), those already taking methotrexate, and those with a history of or at high risk for tuberculosis or HIV-related disease will not be eligible.

Additional exclusion criteria are as follows: multivessel coronary artery bypass surgery within the past 3 years; symptomatic class IV heart failure; uncontrolled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg); uncontrolled diabetes; nephrotic syndrome, renal transplant, or calculated estimated glomerular filtration rate <30 mL/min per 1.73 m²; active or recurrent hepatic disorder including confirmed aspartate aminotransferase/alanine aminotransferase levels >3 times the upper limit of normal or total bilirubin >2 times the upper limit of normal; prior malignancy other than basal cell skin carcinoma; a requirement for live vaccines during the trial period; and history of alcohol or drug abuse or other medical or psychological condition that may compromise successful study completion.

Study design

The overall design of CANTOS is shown in Figure 3. At the initial screening visit (that must take place at least 1 month after the index myocardial infarction or any recent percutaneous revascularization and at least 3 years after any coronary artery bypass graft procedure), informed consent will be sought, a preliminary assessment of subject eligibility will occur, tuberculosis status will be determined, and a fasting blood sample will be obtained for analysis of hsCRP, lipid levels, glucose, hemoglobin A₁c (HbA₁c), and safety measures. For participants who provide additional consent, plasma and buffy coat samples will be stored for future genomic and proteomic analyses related to lipid metabolism, inflammatory function, and canakinumab. A baseline electrocardiogram will be obtained in all trial participants.

Eligible subjects will then return for a randomization visit; at that time, they will be allocated using an interactive voice response system to 1 of 4 therapies: subcutaneous canakinumab 50 mg, subcutaneous canakinumab 150 mg, subcutaneous canakinumab 300 mg, or subcutaneous placebo. These doses will be given to study participants in a blinded manner every 3 months for the study duration. In the 300-mg arm only, an induction dose will also be given 2 weeks after randomization to ameliorate concern regarding potential autoinduction of IL-1β and to achieve greater early suppression of IL-1β-related gene expression in the high-dose arm. Randomization will be stratified to ensure that approximately half of the trial participants are at least 30 days but within 6 months of the index myocardial infarction and that the remaining half are >6 months since the index infarction. Glycemia status will be characterized at trial entry as either normal (HbA₁c <5.7%), prediabetic (HbA₁c, 5.7%-6.4%), or diabetic (HbA₁c >6.5% or fasting glucose >126 mg/dL).

Both active canakinumab and matching placebo will be provided by Novartis (Basel, CH) in prefilled syringes that must be refrigerated before use. After the randomization and 2-week doses are complete, all trial participants will return for an initial safety visit and then on a quarterly basis thereafter. As these quarterly visits, the occurrence of any trial end points or other adverse events will be evaluated; laboratory evaluations of alanine aminotransferase, aspartate aminotransferase, bilirubin, hsCRP, HbA₁c, and glucose obtained; a limited
physical examination performed; and the next trial injection given. Study medication will be discontinued if the patient withdraws consent; becomes pregnant; develops a serious adverse events indicative of hepatitis, liver failure, or jaundice; or develops significant elevations of liver function tests or bilirubin (specific cut points for discontinuation with or without symptoms are provided to investigators in the trial protocol). For any trial participant who did not have diabetes at entry but is found to convert to diabetes as defined by a new elevation of HbA1c or fasting glucose, an additional study visit within 6 weeks will be obtained to formally assess for conversion from prediabetes to type 2 diabetes. All subjects, including those in whom study medication is discontinued, will be followed up for the duration of the trial. Annual electrocardiograms will be obtained and read centrally as a method to systematically detect clinically silent myocardial infarction events and to provide a standardized evaluation for atrial fibrillation and QTc assessment.

CANTOS is designed as an event-driven trial with all primary analyses conducted on an intention-to-treat basis. Power estimates are based on the assumption of a sample size of 17,200 randomized participants assigned in a 1:1:1:1.5 allocation ratio between canakinumab 50 mg quarterly, canakinumab 150 mg quarterly, canakinumab 300 mg quarterly, and placebo. Trial completion is anticipated to occur after the accrual of at least 1,400 primary end points. This number of primary end points should provide approximately 90% power to detect the superiority of at least 1 dose of canakinumab compared with placebo, assuming a hazard reduction of 20%. The protocol also prescribes analyses to detect the superiority of the combined canakinumab arms compared with placebo.

The CANTOS was initiated and designed collaboratively by investigators at Novartis and at the Center for Cardiovascular Disease Prevention at the Brigham and Women's Hospital, Harvard Medical School, Boston, MA. A fully independent 5-member Data and Safety Monitoring Board has been established and will review unblinded safety and efficacy data at least twice yearly. A Data and Safety Monitoring Board Charter formally prescribes the frequency of interim efficacy analyses and rules for early trial termination, as approved by all members of this board.

Safety and dosing of canakinumab in the CANTOS trial

Overall, the development program with canakinumab in autoimmune inflammatory, crystal-related, and type 2 diabetes
conditions has demonstrated a favorable safety and tolerability profile as evidenced by a low number of study discontinuations for adverse events, predominantly absent injection site reactions, and no specific target organ toxicity among >2,000 patients exposed to canakinumab to date. As a targeted IL-1β antibody, canakinumab, not surprisingly, has low potential for drug-drug interactions. In studies of patients with type 2 diabetes, canakinumab has not significantly altered lipid profiles.

Because of the mode of action of all inhibitors of the IL-1 pathway, all patients receiving canakinumab have undergone close monitoring for infections. Compared with placebo, canakinumab associates with mildly increased rates of infection, although these have generally been mild to moderate in severity, seldom serious, and either resolved spontaneously or with standard therapy. Nonetheless, as outlined above, all individuals with a history of or at high risk for either tuberculosis or HIV-related disease will not be eligible for CANTOS nor will any individuals with chronic infections or the need for other systemic anti-inflammatory therapies. Drug-induced autoimmune syndromes, observed with other anticytokine agents and caused by potential immune modulation, have not been observed with canakinumab. To date, antibodies to canakinumab (immunogenicity) have not been detected.

Canakinumab doses for the CANTOS trial were selected based on clinical data in other inflammatory conditions, safety, effects on IL-1β, and effects on several clinical biomarkers of inflammation (hsCRP, IL-6, and fibrinogen). The additional dose provided 2 weeks after randomization in the 300-mg arm is designed to ameliorate concern regarding potential autoinduction of IL-1β and to achieve greater early suppression of IL-1β-associated gene expression. The selected dose range of 50, 150, and 300 mg quarterly showed optimal balance between safety, tolerability, efficacy on surrogate biomarkers, and effectiveness in other inflammatory conditions.

What will CANTOS teach us?
The CANTOS will be the first randomized trial to formally address the inflammatory hypothesis of atherothrombosis. Specifically, CANTOS will evaluate in an innovative event-driven protocol whether IL-1β inhibition over prolonged periods. Thus, if successful, CANTOS could not only affirm the inflammatory hypothesis of atherothrombosis but also provide an entirely novel cytokine-based therapy for the secondary prevention of cardiovascular disease and new-onset diabetes.

Disclosures
The CANTOS is a trial sponsored by Novartis and was initiated and designed by investigators at the Center for Cardiovascular Disease Prevention at Brigham and Women’s Hospital, Harvard Medical School, in collaboration with Novartis. Drs Thuren and Zalewski are employees of Novartis. Drs Ridker and Libby have received research grant support from Novartis. Dr Ridker is listed as a co-inventor on patents held by the Brigham and Women’s Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to Siemens and AstraZeneca. The authors are solely responsible for the design of this study and for the drafting and editing of this paper and its final contents.

References


