

# Rosuvastatin in the Primary Prevention of Cardiovascular Disease Among Patients With Low Levels of Low-Density Lipoprotein Cholesterol and Elevated High-Sensitivity C-Reactive Protein

## Rationale and Design of the JUPITER Trial\*

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Completed randomized trials of statin therapy demonstrate that 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors reduce the risk of myocardial infarction, stroke, and other cardiovascular events among individuals with established coronary disease and overt hyperlipidemia.<sup>1-6</sup> In aggregate, use of statin therapy in these trials has been associated with an approximate 30% reduction in cardiovascular event rates. Largely on the basis of these cholesterol reduction trials, current treatment algorithms from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III endorse the use of statins in secondary prevention and encourage increased use of statins in primary prevention among those with hyperlipidemia and diabetes.<sup>7</sup>

Unfortunately, despite evidence provided by the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS<sup>2</sup>) and the West of Scotland Coronary Prevention Study (WOSCOPS<sup>3</sup>), use of statins for the primary prevention of cardiovascular disease has not been widely adopted in a cost-effective manner. From a clinical perspective, there are several reasons for this slow adoption.

First, almost half of all cardiovascular events occur among apparently healthy men and women who have normal or even low levels of LDL cholesterol (LDL-C). Thus, better screening methods are needed in primary prevention to detect high-risk individuals for whom the number needed to treat (NNT) is small enough to make prophylactic statin therapy cost effective. Second, there has been controversy within the completed clinical trials suggesting that the benefits of statins may extend beyond LDL-C reduction alone. In both the Heart Protection Study of stable high-risk patients<sup>6</sup> and the MIR-ACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) study of patients with acute coronary syndromes,<sup>8</sup> the risk reduction associated with statin therapy was almost identical among those with low as well those with as high levels of LDL-C. Further, statin therapy reduces the risk of stroke, yet LDL-C is not an important risk factor for this disease.<sup>9,10</sup>

### The Role of High-Sensitivity C-Reactive Protein (hsCRP) in Cardiovascular Disease

In an effort to improve vascular risk detection, many physicians screen for hsCRP, an inflammatory biomarker associated with a markedly increased risk of myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death, even among apparently healthy individuals with low levels of LDL-C.<sup>11</sup> To date, more than a dozen large-scale studies demonstrate in aggregate that hsCRP levels are a strong, independent predictor of future vascular events<sup>12-20</sup> and that hsCRP adds prognostic information on risk at all levels of LDL-C, at all levels of the Framingham Risk Score, and at all levels of the metabolic syndrome<sup>15,21-23</sup> (Figure 1). Moreover, hsCRP predicts risk of recurrent coronary events and has important prognostic value in acute coronary ischemia and after coronary interventions.<sup>24-30</sup>

As our understanding that atherothrombosis is fundamentally an inflammatory disease has developed,<sup>31</sup> so too has evidence regarding CRP as a direct participant both in the early initiation of atherosclerotic lesions and in the conversion of stable to unstable plaques. In particular, evidence has recently accumulated that shows CRP to be a direct participant in the atherothrombotic process capable of augmenting the innate inflammatory response, triggering expression of adhesion molecules and monocyte chemoattractant protein-1, attenuating expression of endothelial NO synthase, inducing plasminogen activator inhibitor-1, and having a direct effect on arterial thrombosis<sup>32-37</sup> (Figure 2).

On the basis of these data, an expert panel assembled by the Centers for Disease Control and Prevention and the American Heart Association provided the first guidelines for use of inflammatory biomarkers in clinical practice in January 2003.<sup>38</sup> This report confirmed the importance of hsCRP in clinical risk detection and recommended use of hsCRP as part of global risk prediction, particularly among those deemed at "intermediate risk" by standard risk factors. One of the most important groups likely to benefit from hsCRP evaluation is

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Dr Ridker is listed as a coinventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease.

Guest editor for this article was Joseph Brent Muhlestein, MD, LDS Hospital, Salt Lake City, Utah.

\*Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin.

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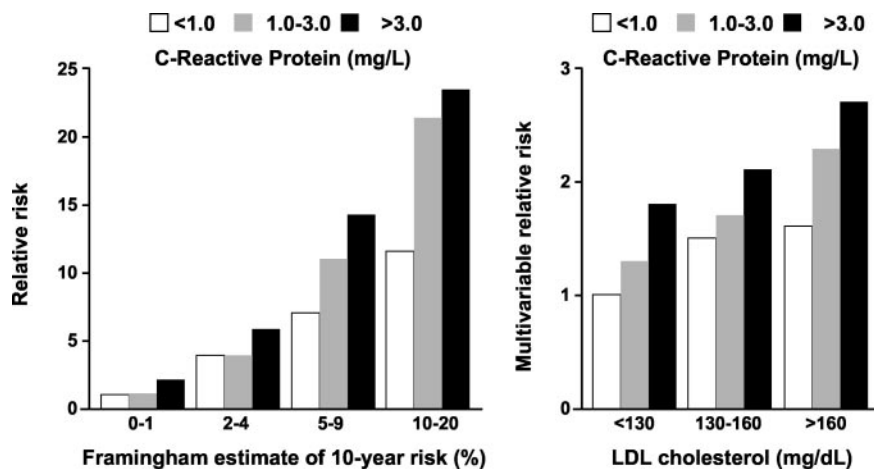


Figure 1. hsCRP adds prognostic information on vascular risk at all levels of LDL-C (right) and at all levels of the Framingham Risk Score (left). Data are derived from Ridker et al.<sup>11,15,21</sup>

composed of those with normal or low levels of LDL-C. As shown in Figure 3 in data from the large-scale Women’s Health Study, apparently healthy individuals with low levels of LDL-C but high levels of hsCRP are at higher absolute risk of future vascular events than are those with high levels of LDL-C but low levels of hsCRP.<sup>15</sup> Such patients, however, are not currently considered for statin therapy, as they have LDL-C levels <130 mg/dL, the current treatment target in primary prevention. Nonetheless, both experimental and clinical studies indicate that statins may have direct anti-inflammatory effects, and it is now established that statins lower hsCRP levels on a population basis.<sup>39–41</sup> Thus, it has been hypothesized that hsCRP screening might provide a method to improve the targeting of statin therapy, particularly among those with low to normal levels of LDL-C.<sup>42</sup>

### hsCRP, Statin Therapy, and the Prevention of Cardiovascular Events

To address this issue, a hypothesis-generating study was recently completed in which hsCRP levels were measured at baseline among 5742 participants enrolled in AFCAPS/TexCAPS, a randomized, double-blind, placebo-controlled trial of lovastatin in the primary prevention of cardiovascular

events conducted among American men and women with average cholesterol levels and below-average HDL cholesterol levels.<sup>43</sup> In that trial, lovastatin allocation was associated with a 37% reduction in the primary clinical end point of fatal or nonfatal myocardial infarction, hospitalization for unstable angina, or sudden cardiac death. However, after measuring baseline hsCRP as well as lipid levels in the AFCAPS/TexCAPS population, several critical observations regarding the efficacy of statin therapy in primary prevention were observed.<sup>43</sup>

First, coronary event rates increased with entry hsCRP levels such that the relative risks from lowest to highest quartiles of baseline hsCRP among those allocated to placebo were 1.0, 1.2, 1.3, and 1.7 ( $P=0.01$ ), an effect that was independent of traditional risk factors included in the Framingham Risk Score.

Second, compared with placebo, allocation to lovastatin in AFCAPS/TexCAPS resulted in a statistically significant reduction in median hsCRP levels at the end of the first year of treatment (95% CI of the median,  $-17.4$  to  $-12.5\%$ ,  $P<0.001$ ); data were consistent with those of other statins.<sup>39–41</sup> As also demonstrated in the Pravastatin INflammation CRP Evaluation (PRINCE),<sup>41</sup> this reduction in hsCRP was not related to the effect of statin therapy on lipid levels.

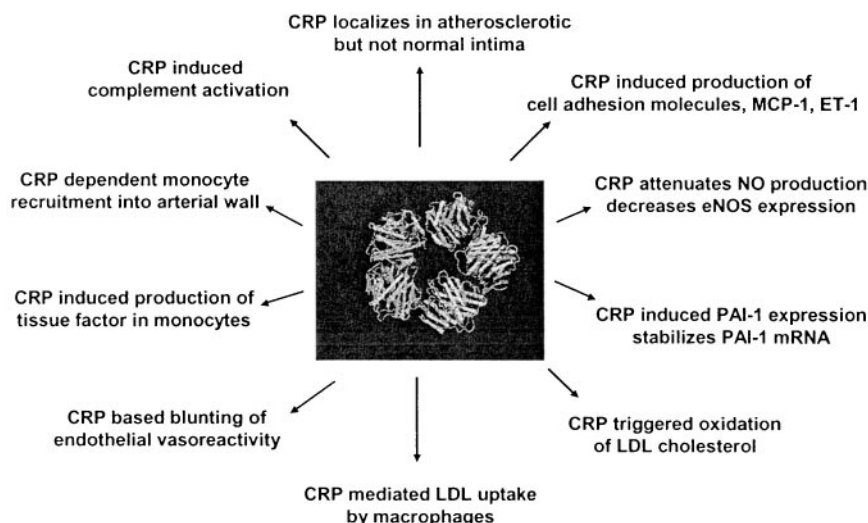
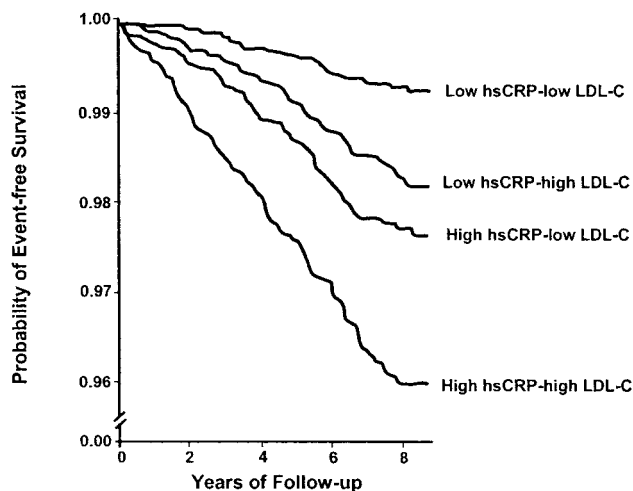


Figure 2. Mechanisms relating C-reactive protein (CRP) to development and progression of the atherothrombotic process. eNOS indicates endothelial NO synthase; ET-1, endothelin-1; MCP-1, monocyte chemoattractant protein-1; and PAI-1, plasminogen activator inhibitor-1.



**Figure 3.** Cardiovascular event-free survival according to baseline levels of LDL-C and hsCRP. Note that those with elevated levels of hsCRP but low LDL-C (the target population for the JUPITER trial) appear at higher vascular risk than those with high LDL-C but low hsCRP. Data are derived from Ridker et al.<sup>15</sup>

Third, and most importantly, there were major differences in the observed efficacy of lovastatin when AFCAPS/TexCAPS participants were stratified into 4 groups on the basis of median LDL-C and median hsCRP levels<sup>43</sup> (Table). As expected, lovastatin was highly effective in preventing first vascular events among participants with elevated levels of LDL-C. However, lovastatin was also highly effective in reducing coronary events among those with low LDL-C levels but who had elevated levels of hsCRP, data that suggest that statin therapy may well have efficacy in the presence of systemic inflammation even in the absence of hyperlipidemia. In fact, the low LDL-C/high hsCRP subgroup in AFCAPS/TexCAPS had a risk of future vascular events just as high as that observed in the subgroups with overt hyperlipidemia. In marked contrast, event rates were low among AFCAPS/TexCAPS participants with low LDL-C and low hsCRP, a subgroup in which there was no evidence that lovastatin reduced the risk of future cardiovascular events. These hypothesis-generating data in primary prevention parallel the data in secondary prevention from the Cholesterol and Recurrent Events (CARE) trial that previously suggested that the benefit of statin therapy was greater among those with elevated hsCRP levels.<sup>24</sup>

Since publication of the AFCAPS/TexCAPS<sup>43</sup> and CARE<sup>24</sup> trial data for hsCRP, several clinical registries have

corroborated the observation that individuals with elevated hsCRP levels benefit preferentially from the use of statins both among those with angiographically severe coronary disease<sup>44,45</sup> and in the setting of percutaneous coronary interventions and stent placement.<sup>46,47</sup> Moreover, a number of studies have suggested direct anti-inflammatory mechanisms for statin therapy that appear largely independent of LDL reduction.<sup>48–51</sup> One recent study has shown a dose-response relationship between statin therapy and hsCRP reduction that was augmented by the addition of ezetimibe.<sup>52</sup>

For some physicians, these data have been interpreted as evidence that hsCRP screening should be broadly applied and that those with elevated levels of hsCRP should be placed on statin therapy for the primary prevention of cardiovascular events. It is critical to recognize, however, that observations regarding hsCRP in both the AFCAPS/TexCAPS and CARE trials were made on a post hoc basis and that the total number of events within the low LDL-C/high hsCRP strata in each of those studies was small. Thus, a large-scale, prospective, placebo-controlled trial of statin therapy among individuals without overt hyperlipidemia but with evidence of systemic inflammation is needed to directly test this hypothesis.

## The JUPITER Trial

### Study Objectives

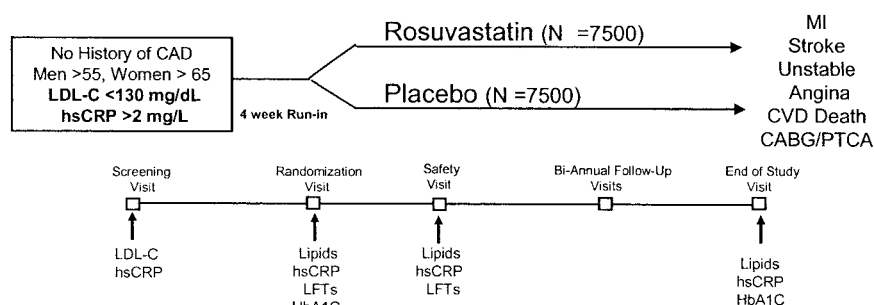
The primary objective of the JUPITER trial is to determine whether long-term treatment with rosuvastatin (20 mg orally per day) will reduce the rate of first major cardiovascular events, defined as the combined end point of cardiovascular death, stroke, myocardial infarction, hospitalization for unstable angina, or arterial revascularization among individuals with LDL-C levels <130 mg/dL (3.36 mmol/L) who are at high vascular risk because of an enhanced inflammatory response as indicated by hsCRP levels  $\geq 2$  mg/L. Secondary objectives of JUPITER are to evaluate the safety of long-term treatment with rosuvastatin in terms of total mortality, non-cardiovascular mortality, and adverse events and to determine whether rosuvastatin reduces the incidence of type 2 diabetes. This latter objective reflects the fact that hsCRP levels also predict the onset of diabetes<sup>53</sup> and that inflammation appears to be a critical link between diabetes and atherothrombosis.<sup>54</sup> Finally, on the basis of observational evidence regarding statins, osteoporosis, and hypercoagulability, the JUPITER trial will also determine whether rosuvastatin reduces the incidence of bone fractures and venous thromboembolic events.<sup>55,56</sup>

### Crude Event Rates, Relative Risks (RR), and the No. Needed to Treat (NNT) Associated With Lovastatin Allocation Among AFCAPS/TexCAPS Participants, According to Baseline Levels of LDL Cholesterol and hsCRP

Study Group	Lovastatin		Placebo		RR	95% CI	NNT*
	N	Rate*	N	Rate*			
Low LDLC/low hsCRP	19/726	0.025	17/722	0.022	1.08	0.56–2.08	...
Low LDLC/high hsCRP	22/718	0.029	37/710	0.051	0.58	0.34–0.98	48
High LDLC/low hsCRP	15/709	0.020	37/711	0.050	0.38	0.21–0.70	33
High LDLC/high hsCRP	29/741	0.038	40/705	0.055	0.68	0.42–1.10	58

\*Event rates and NNT calculated on the basis of 5 patient-years at risk. Data are derived from Ridker et al.<sup>43</sup>

**JUPITER: A Randomized Trial of Rosuvastatin in the Primary Prevention of Cardiovascular Events Among Individuals with Low Levels of LDL-C and Elevated Levels of hsCRP**



**Figure 4.** Overall design of the JUPITER trial. CABG indicates coronary artery bypass graft; CAD, coronary artery disease; CVD, cardiovascular disease; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; LFTs, liver function tests; MI, myocardial infarction; and PTCA, percutaneous transluminal coronary angioplasty.

### Study Population

The JUPITER trial will enroll up to 15 000 men age 55 years and older and women age 65 years and older, who, on initial screening, are found to have hsCRP  $\geq 2$  mg/L, LDL-C  $< 130$  mg/dL, and triglycerides  $< 500$  mg/dL (5.65 mmol/L), and who have no history of myocardial infarction, stroke, arterial revascularization, or coronary risk equivalent as defined by current NCEP guidelines. Additional exclusion criteria are as follows: current use of statins or other lipid-lowering therapies, including fibrates, niacin, and bile-acid sequestrants; known hypersensitivity to statin therapy; current use of postmenopausal oral hormone therapy; current use of immunosuppressants; active liver disease or elevated liver enzymes (alanine aminotransferase [ALT]  $> 2$  times upper limit of normal [ULN]); creatine kinase [CK]  $> 3$  times ULN; diabetes mellitus (fasting serum glucose  $> 126$  mg/dL [7.0 mmol/L], or use of insulin or oral hypoglycemic agent); uncontrolled hypertension (systolic or diastolic blood pressure  $> 190$  or 100 mm Hg, respectively); history of cancer, except nonmalignant skin cancer, within the past 5 years; uncontrolled hypothyroidism (thyroid-stimulating hormone  $> 1.5$  above ULN); chronic inflammatory conditions such as severe arthritis, lupus, or inflammatory bowel disease; history of alcohol or drug abuse within the past year; and serious medical or psychological conditions that may compromise successful study participation.

### Study Design

The overall design of the JUPITER trial is shown in Figure 4. At the initial screening visit, informed consent will be sought, a preliminary assessment of subject eligibility will occur, and a fasting blood sample will be obtained for analysis of hsCRP and lipid levels. At a second screening visit, a physical examination and medical history focusing on cardiovascular risk factors will be conducted, and fasting blood and urine samples will be collected for further lipid analysis, hematologic indices, creatinine, thyroid-stimulating hormone, ALT, CK, glucose, and hemoglobin A<sub>1c</sub>. For participants who provide additional consent, plasma and buffy coat samples will be stored for future genomic and proteomic analyses relating to lipid metabolism, inflammatory function, and statin therapy. Eligible subjects will then be enrolled in a 4-week prerandomization run-in period designed to ensure a

group of study participants capable of long-term protocol compliance.

Following the run-in period, participants will be randomly assigned to either oral rosuvastatin (20 mg/d; supplied as CRESTOR by AstraZeneca [Wilmington, Del]) or placebo for a period of 3 to 4 years, the estimated time needed to accrue the 520 cardiovascular end points on which the study is powered. The dose of rosuvastatin selected should result in  $\approx 50\%$  reductions in LDL cholesterol<sup>57</sup> as well as a substantial reduction in hsCRP.

All study participants will visit the clinic sites for evaluation at 3 and 6 months after randomization and thereafter at 6-month intervals for the duration of follow-up. At these visits, staff will dispense study medication; assess compliance with pill taking, the use of concomitant medications, and the development of major illnesses, study end points, or adverse effects; and collect fasting blood and urine samples to evaluate changes in lipid and inflammatory parameters and to monitor safety. Study medication will be discontinued among subjects who develop myopathy (CK  $> 10$  times ULN and muscle aches or weakness) or a persistent elevation in ALT ( $> 3$  times ULN on 2 consecutive tests). Subjects whose blinded LDL-C levels rise to  $\geq 130$  mg/dL during the study will be counseled to adopt lifestyle changes recommended by the NCEP. If, after 3 months, LDL-C levels remain elevated and the calculated Framingham Risk Score exceeds 10% despite lifestyle changes, investigators will be encouraged to consider lipid-lowering therapy with bile-acid sequestrants or cholesterol-absorption inhibitors for those subjects. However, if the responsible study physician believes statin therapy is indicated, the study medication will be discontinued and open-label statin therapy will be initiated. All subjects in whom study medication is discontinued will be followed for the duration of the trial and included in data analyses.

### Data Analysis, Power, and Trial Organization

The primary end point under study is the first occurrence of a major cardiovascular event defined as cardiovascular death, stroke, myocardial infarction, hospitalization for unstable angina, or arterial revascularization. Secondary end points are total mortality, noncardiovascular mortality, diabetes mellitus, venous thromboembolic events, bone fractures, and discontinuation of the study medication because of adverse

effects. All primary analyses will be on an intention-to-treat basis. Event rates for the rosuvastatin and placebo groups will be compared using the proportional-hazards regression model to adjust for variable length of follow-up.

Power estimates are based on the assumption of a mean follow-up of 3.5 years, a placebo event rate of 1.5 per 100 patient-years at risk, and a net attrition rate of 5% per year. Given a sample size of 15 000, the power of the trial to detect a 25% reduction in risk of major vascular events associated with rosuvastatin exceeds 90%.

The JUPITER trial was designed as an investigator-initiated protocol from the Center for Cardiovascular Disease Prevention at the Brigham and Women's Hospital, Harvard Medical School, Boston, Mass.<sup>42</sup> Members of the JUPITER Steering Committee are listed in Appendix A.

A fully independent 5-member Data and Safety Monitoring Board has been established and will review unblinded safety data at least twice yearly. Frequency of interim efficacy analyses and rules for early trial termination have been prespecified and approved by all members of this board (listed in Appendix B).

### What Will the JUPITER Trial Teach Us?

The JUPITER trial has been carefully designed to address a critical unanswered question regarding inflammation, statins, and atherothrombosis, as follows: Will statin therapy prevent first-ever cardiovascular events among those with LDL-C <130 mg/dL, but who are nonetheless at increased vascular risk because of elevated levels of hsCRP? This issue is of exceptional clinical importance, as half of all vascular events occur among those with normal or even low levels of LDL-C. Within the United States alone, as many as 25 to 30 million adults fall into this potentially high-risk category. Thus, a strong positive finding from JUPITER will dramatically affect public health and prevention and would provide a clear rationale for much broader use of statin therapy for the primary prevention of cardiovascular events than currently endorsed. On the other hand, a negative finding would also be of great importance, as it would direct the use of scarce prevention resources to other nonstatin methods for coronary risk reduction.

By using rosuvastatin, JUPITER will also be addressing whether aggressive LDL-C reduction<sup>57</sup> has efficacy in primary prevention among those with relatively low LDL-C levels. However, because JUPITER is evaluating an agent that dramatically lowers LDL-C as well as hsCRP, the JUPITER trial will not directly answer whether CRP reduction alone leads to reduced vascular risk. This hypothesis will require testing of agents with targeted vascular anti-inflammatory effects that lack proven beneficial effects such as LDL-C reduction.

Initial site recruitment for the JUPITER trial within the United States and Canada began in mid-2003. Further information on the JUPITER trial can be obtained at [www.JUPITERstudy.com](http://www.JUPITERstudy.com) or by calling (888) 660-8254.

### Appendix A: JUPITER Steering Committee (United States and Canada)

Paul M Ridker, Harvard Medical School (Study Chairman)  
Antonio Gotto, Weill Medical College of Cornell University

Jacques Genest, McGill University  
Peter Libby, Harvard Medical School  
James Willerson, University of Texas  
James Blasetto, Astra-Zeneca (nonvoting)

### Appendix B: JUPITER Independent Data and Safety Monitoring Board

Rory Collins, Oxford University (Chair)  
Gervasio Lamas, Miami Heart Institute  
Douglas Vaughan, Vanderbilt University  
Sidney Smith, University of North Carolina  
Kent Bailey, Mayo Clinic  
Robert J Glynn, Harvard Medical School (nonvoting)

### Acknowledgments

The JUPITER trial is being funded by AstraZeneca (Wilmington, Del). Dr Ridker receives research grant support from the National Heart, Lung, and Blood Institute (Bethesda, Md); the American Heart Association (Dallas, Tex); the Doris Duke Charitable Foundation (New York, NY); and the Donald W. Reynolds Foundation (Las Vegas, Nev).

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