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Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

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ABSTRACT

BACKGROUND

Increased levels of the inflammatory biomarker high-sensitivity C-reactive protein predict cardiovascular events. Since statins lower levels of high-sensitivity C-reactive protein as well as cholesterol, we hypothesized that people with elevated high-sensitivity C-reactive protein levels but without hyperlipidemia might benefit from statin treatment.

METHODS

We randomly assigned 17,802 apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher to rosuvastatin, 20 mg daily, or placebo and followed them for the occurrence of the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.

RESULTS

The trial was stopped after a median follow-up of 1.9 years (maximum, 5.0). Rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-reactive protein levels by 37%. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% confidence interval [CI], 0.46 to 0.69; $P < 0.00001$), with corresponding rates of 0.17 and 0.37 for myocardial infarction (hazard ratio, 0.46; 95% CI, 0.30 to 0.70; $P = 0.0002$), 0.18 and 0.34 for stroke (hazard ratio, 0.52; 95% CI, 0.34 to 0.79; $P = 0.002$), 0.41 and 0.77 for revascularization or unstable angina (hazard ratio, 0.53; 95% CI, 0.40 to 0.70; $P < 0.00001$), 0.45 and 0.85 for the combined end point of myocardial infarction, stroke, or death from cardiovascular causes (hazard ratio, 0.53; 95% CI, 0.40 to 0.69; $P < 0.00001$), and 1.00 and 1.25 for death from any cause (hazard ratio, 0.80; 95% CI, 0.67 to 0.97; $P = 0.02$). Consistent effects were observed in all subgroups evaluated. The rosuvastatin group did not have a significant increase in myopathy or cancer but did have a higher incidence of physician-reported diabetes.

CONCLUSIONS

In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events. (ClinicalTrials.gov number, NCT00239681.)

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CURRENT TREATMENT ALGORITHMS FOR the prevention of myocardial infarction, stroke, and death from cardiovascular causes recommend statin therapy for patients with established vascular disease, diabetes, and overt hyperlipidemia.^{1,2} However, half of all myocardial infarctions and strokes occur among apparently healthy men and women with levels of low-density lipoprotein (LDL) cholesterol that are below currently recommended thresholds for treatment.

Measurement of high-sensitivity C-reactive protein, an inflammatory biomarker that independently predicts future vascular events, improves global classification of risk, regardless of the LDL cholesterol level.³⁻⁹ We have previously shown that statin therapy reduces high-sensitivity C-reactive protein levels^{10,11} and that among healthy persons,¹² patients with stable coronary disease,¹³ and those with the acute coronary syndrome,¹⁴⁻¹⁶ the magnitude of the benefit associated with statin therapy correlates in part with the achieved high-sensitivity C-reactive protein level. To date, however, no prospective outcome trial has directly addressed the question of whether apparently healthy persons with levels of LDL cholesterol below current treatment thresholds but with elevated levels of high-sensitivity C-reactive protein might benefit from statin therapy. The primary objective of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) was to investigate whether treatment with rosuvastatin, 20 mg daily, as compared with placebo, would decrease the rate of first major cardiovascular events.

METHODS

TRIAL DESIGN

JUPITER was a randomized, double-blind, placebo-controlled, multicenter trial conducted at 1315 sites in 26 countries (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). The trial protocol was designed and written by the study chair and approved by the local institutional review board at each participating center. The trial data were analyzed by the academic study statistician and the academic programmer. The academic authors vouch for the accuracy and completeness of the data and the analyses.

The trial was financially supported by Astra-Zeneca. The sponsor collected the trial data and monitored the study sites but played no role in

the conduct of the analyses or drafting of the manuscript and had no access to the unblinded trial data until after the manuscript was submitted for publication.

STUDY POPULATION

As described in detail elsewhere,^{17,18} men 50 years of age or older and women 60 years of age or older were eligible for the trial if they did not have a history of cardiovascular disease and if, at the initial screening visit, they had an LDL cholesterol level of less than 130 mg per deciliter (3.4 mmol per liter) and a high-sensitivity C-reactive protein level of 2.0 mg per liter or more. Other requirements for inclusion were a willingness to participate for the duration of the trial, provision of written informed consent, and a triglyceride level of less than 500 mg per deciliter (5.6 mmol per liter).

Exclusion criteria were previous or current use of lipid-lowering therapy, current use of postmenopausal hormone-replacement therapy, evidence of hepatic dysfunction (an alanine aminotransferase level that was more than twice the upper limit of the normal range), a creatine kinase level that was more than three times the upper limit of the normal range, a creatinine level that was higher than 2.0 mg per deciliter (176.8 μ mol per liter), diabetes, uncontrolled hypertension (systolic blood pressure >190 mm Hg or diastolic blood pressure >100 mm Hg), cancer within 5 years before enrollment (with the exception of basal-cell or squamous-cell carcinoma of the skin), uncontrolled hypothyroidism (a thyroid-stimulating hormone level that was more than 1.5 times the upper limit of the normal range), and a recent history of alcohol or drug abuse or another medical condition that might compromise safety or the successful completion of the study. Because a core scientific hypothesis of the trial concerned the role of underlying low-grade inflammation as evidenced by elevated high-sensitivity C-reactive protein levels, patients with inflammatory conditions such as severe arthritis, lupus, or inflammatory bowel disease were excluded, as were patients taking immunosuppressant agents such as cyclosporine, tacrolimus, azathioprine, or long-term oral glucocorticoids.

All potentially eligible subjects underwent a 4-week run-in phase during which they received placebo. The purpose of this phase was to identify a group of willing and eligible participants who demonstrated good compliance (defined as the taking of more than 80% of all study tablets) dur-

ing that interval. Only subjects who successfully completed the run-in phase were enrolled.

TRIAL PROTOCOL

Eligible subjects were randomly assigned in a 1:1 ratio to receive either rosuvastatin, 20 mg daily, or matching placebo. Randomization was performed with the use of an interactive voice-response system and was stratified according to center.

Follow-up visits were scheduled to occur at 13 weeks and then 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months after randomization. A closeout visit occurred after study termination. Follow-up assessments included laboratory evaluations, pill counts, and structured interviews assessing outcomes and potential adverse events. Measurements of lipid levels, high-sensitivity C-reactive protein levels, hepatic and renal function, blood glucose levels, and glycated hemoglobin values were performed in a central laboratory. Personnel at each site also contacted their participants midway between scheduled visits to evaluate their well-being and to maintain study participation.

END POINTS

The primary outcome was the occurrence of a first major cardiovascular event, defined as nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes. Secondary end points included the components of the primary end point considered individually — arterial revascularization or hospitalization for unstable angina, myocardial infarction, stroke, or death from cardiovascular causes — and death from any cause.

All reported primary end points that occurred through March 30, 2008, were adjudicated on the basis of standardized criteria by an independent end-point committee unaware of the randomized treatment assignments. Only deaths classified as clearly due to cardiovascular or cerebrovascular causes by the end-point committee were included in the analysis of the primary end point. For the end point of death from any cause, all deaths were included, regardless of whether data were available to confirm the cause of death.

STATISTICAL ANALYSIS

JUPITER was an event-driven trial designed to continue until 520 confirmed primary end points had been documented, to provide a statistical power of 90% to detect a 25% reduction in the rate of

the primary end point, with a two-sided significance level of 0.05. Pretrial estimates of the duration of follow-up and number of participants were based on event rates in earlier prevention trials^{19,20} and were modified to take into account plans to include low-risk groups, including women.

The trial's prespecified monitoring plan called for two interim efficacy analyses with O'Brien-Fleming stopping boundaries determined by means of the Lan-DeMets approach. The stopping boundary was crossed at the first prespecified efficacy evaluation, and on March 29, 2008, the independent data and safety monitoring board voted to recommend termination of the trial. This recommendation took into account the size and precision of the observed treatment benefit, as well as effects on the rates of death and other secondary end points being monitored and on major subgroups. Although the trial ended on March 30, 2008, when the steering committee formally accepted this recommendation, we continued the adverse-event reporting in a blinded manner for each study participant until the date he or she appeared for a formal closeout visit and discontinued therapy.

All primary analyses were performed on an intention-to-treat basis. Study participation was considered to be complete for any individual participant at the time he or she had an occurrence of the primary end point, had informed consent withdrawn, was unable to be followed further because the study site closed, or had been followed through at least March 30, 2008. The exposure time was calculated as the time between randomization and the first major cardiovascular event, the date of death, the date of the last study visit, the date of withdrawal or loss to follow-up, or March 30, 2008, whichever came first.

Cox proportional-hazards models were used to calculate hazard ratios and 95% confidence intervals for the comparison of event rates in the two study groups. Prespecified subgroup analyses were performed according to the presence or absence of major cardiovascular risk factors.

RESULTS

Between February 4, 2003, and December 15, 2006, a total of 89,890 people were screened for enrollment. Of these, 72,088 were ineligible, including 37,611 (52.2%) with LDL cholesterol levels of 130 mg per deciliter or more and an additional 25,993 (36.1%) with high-sensitivity C-reactive protein lev-

Table 1. Baseline Characteristics of the Trial Participants, According to Study Group.*

Characteristic	Rosuvastatin (N=8901)	Placebo (N=8901)
Age — yr		
Median	66.0	66.0
Interquartile range	60.0–71.0	60.0–71.0
Female sex — no. (%)	3426 (38.5)	3375 (37.9)
Race or ethnic group — no. (%)†		
White	6358 (71.4)	6325 (71.1)
Black	1100 (12.4)	1124 (12.6)
Hispanic	1121 (12.6)	1140 (12.8)
Other or unknown	322 (3.6)	312 (3.5)
Body-mass index‡		
Median	28.3	28.4
Interquartile range	25.3–32.0	25.3–32.0
Blood pressure — mm Hg		
Systolic		
Median	134	134
Interquartile range	124–145	124–145
Diastolic		
Median	80	80
Interquartile range	75–87	75–87
Current smoker — no. (%)	1400 (15.7)	1420 (16.0)
Family history of premature CHD — no. (%)§	997 (11.2)	1048 (11.8)
Metabolic syndrome — no. (%)¶	3652 (41.0)	3723 (41.8)
Aspirin use — no. (%)	1481 (16.6)	1477 (16.6)
High-sensitivity C-reactive protein — mg/liter		
Median	4.2	4.3
Interquartile range	2.8–7.1	2.8–7.2
LDL cholesterol — mg/dl		
Median	108	108
Interquartile range	94–119	94–119
HDL cholesterol — mg/dl		
Median	49	49
Interquartile range	40–60	40–60
Triglycerides — mg/dl		
Median	118	118
Interquartile range	85–169	86–169
Total cholesterol — mg/dl		
Median	186	185
Interquartile range	168–200	169–199
Glucose — mg/dl		
Median	94	94
Interquartile range	87–102	88–102

Table 1. (Continued.)

Characteristic	Rosuvastatin (N = 8901)	Placebo (N = 8901)
Glycated hemoglobin — %		
Median	5.7	5.7
Interquartile range	5.4–5.9	5.5–5.9
Glomerular filtration rate — ml/min/1.73 m ² of body-surface area		
Median	73.3	73.6
Interquartile range	64.6–83.7	64.6–84.1

* To convert values for low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for glucose to millimoles per liter, multiply by 0.05551.

† Race or ethnic group was self-reported.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ A family history of premature coronary heart disease (CHD) was defined as diagnosis of the disease in a male first-degree relative before the age of 55 years or in a female first-degree relative before the age of 65 years.

¶ The metabolic syndrome was defined according to consensus criteria of the American Heart Association and the National Heart, Lung, and Blood Institute.²¹

|| Values for high-sensitivity C-reactive protein are expressed as the average of the values obtained at two screening visits.

els of less than 2.0 mg per liter. Other reasons for exclusion are presented in Figure 1 in the Supplementary Appendix. A total of 17,802 people were randomly assigned to a study group.

BASELINE CHARACTERISTICS

By design, the study population was diverse; 6801 of the 17,802 participants were women (38.2%) and 4485 (25.2%) were black or Hispanic (Table 1). Aspirin was used by 16.6% of participants, and 41.4% had the metabolic syndrome.²¹ In both the rosuvastatin and placebo groups, the median LDL cholesterol level was 108 mg per deciliter (2.8 mmol per liter), the high-density lipoprotein (HDL) cholesterol level was 49 mg per deciliter (1.3 mmol per liter), and the triglyceride level was 118 mg per deciliter (1.3 mmol per liter); the high-sensitivity C-reactive protein level was 4.2 and 4.3 mg per liter in the rosuvastatin and placebo groups, respectively.

COMPLIANCE AND EFFECTS OF ROSUVASTATIN ON LIPIDS AND HIGH-SENSITIVITY C-REACTIVE PROTEIN

At the time the study was terminated, 75% of participants were taking their study pills. Among those assigned to rosuvastatin, the median LDL cholesterol level at 12 months was 55 mg per deciliter (1.4 mmol per liter) (interquartile range, 44 to 72 [1.1 to 1.9]), and the median high-sensitivity C-reactive protein level was 2.2 mg per liter (interquartile range, 1.2 to 4.4) (Table 2). At

the 12-month visit, the rosuvastatin group, as compared with the placebo group, had a 50% lower median LDL cholesterol level (mean difference, 47 mg per deciliter [1.2 mmol per liter]), a 37% lower median high-sensitivity C-reactive protein level, and a 17% lower median triglyceride level ($P < 0.001$ for all three comparisons). These effects persisted throughout the study period. At 12 months, the median HDL cholesterol level was 4% higher in the rosuvastatin group than in the placebo group ($P < 0.001$), but this effect was not present at the time of study completion ($P = 0.34$).

END POINTS

At the time of study termination (median follow-up, 1.9 years; maximal follow-up, 5.0 years), 142 first major cardiovascular events had occurred in the rosuvastatin group, as compared with 251 in the placebo group (Table 3). The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% confidence interval [CI], 0.46 to 0.69; $P < 0.00001$) (Table 3 and Fig. 1). In a test for interaction between the study-group assignment and follow-up time, there was no significant violation of the proportional-hazards assumption.

On the basis of Kaplan–Meier estimates (Fig. 1), the number of patients who would need to be treated with rosuvastatin for 2 years to prevent the occurrence of one primary end point is 95, and

the number needed to treat for 4 years is 31. If 4-year risks are projected over an average 5-year treatment period, as has been commonly done in previous statin trials according to the method of Altman and Andersen,²² the number needed to treat to prevent the occurrence of one primary end point is 25.

Rosuvastatin was also associated with significant reductions in rates of the individual components of the primary trial end point. For the end point of fatal or nonfatal myocardial infarction, event rates were 0.17 and 0.37 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.46; 95% CI, 0.30 to 0.70; $P=0.0002$). The corresponding rates were 0.18 and 0.34 for fatal or nonfatal stroke (hazard ratio, 0.52; 95% CI, 0.34 to 0.79; $P=0.002$), 0.41 and 0.77 for arterial revascularization or unstable angina (hazard ratio, 0.53; 95% CI, 0.40 to 0.70; $P<0.00001$), and 0.45 and 0.85 for the combined end point of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes (hazard ratio, 0.53; 95% CI, 0.40 to 0.69; $P<0.00001$).

In addition, the rates of death from any cause were 1.00 and 1.25 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respec-

tively (hazard ratio for the rosuvastatin group, 0.80; 95% CI, 0.67 to 0.97; $P=0.02$) (Table 3 and Fig. 1). In analyses limited to deaths for which the date of death was known with certainty, there was a similar reduction in the hazard ratio associated with rosuvastatin (0.81; 95% CI, 0.67 to 0.98; $P=0.03$).

SUBGROUP ANALYSES

For the primary end point, there was no evidence of heterogeneity in the results for any subgroup evaluated. Relative hazard reductions in the rosuvastatin group were similar for women (46%) and men (42%) and were observed in every subgroup evaluated, including subgroups according to age, race or ethnic group, region of origin, status with regard to traditional risk factors, and Framingham risk score (Fig. 2). Groups typically

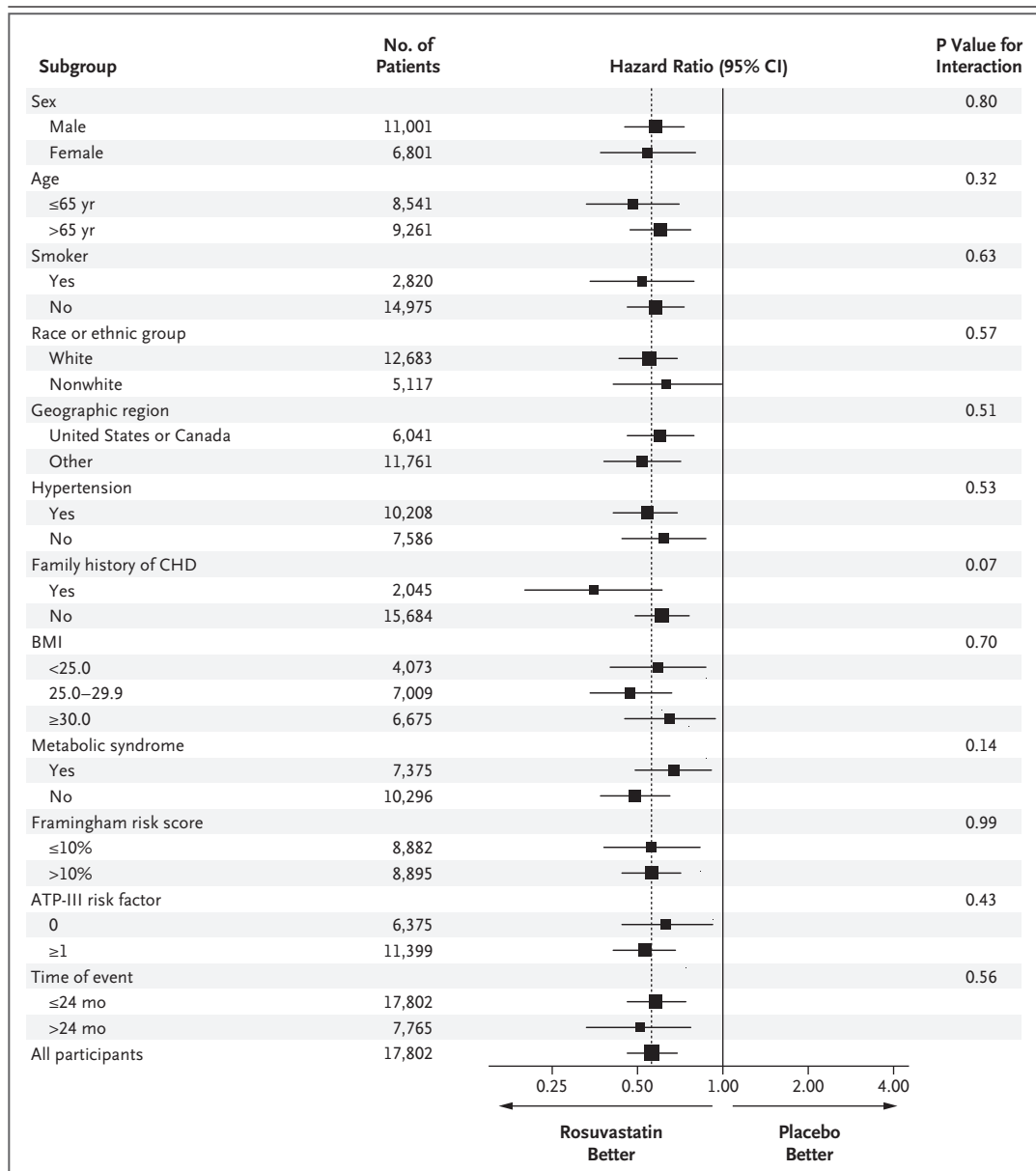


Figure 2. Effects of Rosuvastatin on the Primary End Point, According to Baseline Characteristics.

The primary end point was the combination of nonfatal myocardial infarction, nonfatal stroke, arterial revascularization, hospitalization for unstable angina, or confirmed death from cardiovascular causes. The relative hazard ratios for rosuvastatin as compared with placebo are shown, with the size of each black square proportionate to the number of participants who had an occurrence of the primary end point in the subgroup; the horizontal lines indicate 95% confidence intervals. The dashed vertical line indicates the overall relative risk reduction for the complete trial cohort. Also shown are the P values for the test of an interaction between the primary end point and the categories within each subgroup. For the ordinal variables, interaction tests considered a trend across the subgroup categories with integer scores applied to these categories. Data were missing for some participants in some subgroups. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. CHD denotes coronary heart disease. The metabolic syndrome was defined according to 2005 consensus criteria of the American Heart Association and the National Heart, Lung, and Blood Institute.²¹ ATP-III risk factors refer to major risk factors, other than increased age, according to the Adult Treatment Panel III of the National Cholesterol Education Program. Race or ethnic group was self-reported.

Table 4. Monitored Adverse Events, Measured Laboratory Values, and Other Reported Events of Interest during the Follow-up Period.*

Event	Rosuvastatin (N = 8901)	Placebo (N = 8901)	P Value
Monitored adverse events			
Any serious adverse event — no. (%)	1352 (15.2)	1377 (15.5)	0.60
Muscular weakness, stiffness, or pain — no. (%)	1421 (16.0)	1375 (15.4)	0.34
Myopathy — no. (%)	10 (0.1)	9 (0.1)	0.82
Rhabdomyolysis — no. (%)†	1 (<0.1)	0	—
Newly diagnosed cancer — no. (%)	298 (3.4)	314 (3.5)	0.51
Death from cancer — no. (%)	35 (0.4)	58 (0.7)	0.02
Gastrointestinal disorder — no. (%)	1753 (19.7)	1711 (19.2)	0.43
Renal disorder — no. (%)	535 (6.0)	480 (5.4)	0.08
Bleeding — no. (%)	258 (2.9)	275 (3.1)	0.45
Hepatic disorder — no. (%)	216 (2.4)	186 (2.1)	0.13
Laboratory values‡			
Creatinine, >100% increase from baseline — no. (%)	16 (0.2)	10 (0.1)	0.24
Glomerular filtration rate at 12 mo — ml/min/1.73 m ²			0.02
Median	66.8	66.6	
Interquartile range	59.1–76.5	58.8–76.2	
Alanine aminotransferase >3× ULN on consecutive visits — no. (%)	23 (0.3)	17 (0.2)	0.34
Glycated hemoglobin at 24 mo — %			0.001
Median	5.9	5.8	
Interquartile range	5.7–6.1	5.6–6.1	
Fasting glucose at 24 mo — mg/dl			0.12
Median	98	98	
Interquartile range	91–107	90–106	
>Trace of glucose in urine at 12 mo — no. (%)	36 (0.5)	32 (0.4)	0.64
Other events			
Newly diagnosed diabetes (physician-reported) — no. (%)	270 (3.0)	216 (2.4)	0.01
Hemorrhagic stroke — no. (%)	6 (0.1)	9 (0.1)	0.44

* Data were missing for some patients for some events.

† The single case of rhabdomyolysis occurred after closure of the trial.

‡ To convert values for creatinine to micromoles per liter, multiply by 88.4. To convert values for glucose to millimoles per liter, multiply by 0.05551. ULN denotes upper limit of the normal range.

erally reported a 20% reduction in vascular risk for each 1 mmol per liter (38.7 mg per deciliter) of absolute reduction in the LDL cholesterol level,^{24,25} an effect that would have predicted a proportionate reduction in the number of events in our study of approximately 25%. However, the reduction in the hazard seen in our trial, in which enrollment was based on elevated high-sensitivity C-reactive protein levels rather than on elevated LDL cholesterol levels, was almost twice this magnitude and revealed a greater relative benefit than that

found in most previous statin trials (see Fig. 2 in the Supplementary Appendix).

In this trial, myopathy, hepatic injury, and cancer did not occur more frequently with rosuvastatin than with placebo, despite the fact that LDL cholesterol levels below 55 mg per deciliter were achieved in half the participants receiving rosuvastatin (and LDL cholesterol levels below 44 mg per deciliter in 25%). Since the median follow-up of subjects was 1.9 years, we cannot rule out the possibility that the rate of adverse events might

increase in this population during longer courses of therapy. However, no such increase was detected in an analysis of participants who continued to receive treatment for 4 or more years.

We did detect a small but significant increase in the rate of physician-reported diabetes with rosuvastatin, as well as a small, though significant, increase in the median value of glycated hemoglobin. Increases in glucose and glycated hemoglobin levels, the incidence of newly diagnosed diabetes, and worsening glycemic control have been reported in previous trials of pravastatin, simvastatin, and atorvastatin.^{26,27} However, systematic protocol-specified measurements showed no significant difference between our two study groups in fasting blood glucose levels or glycosuria during the follow-up period. Therefore, although the increase in the rate of physician-reported diabetes in the rosuvastatin group could reflect the play of chance, further study is needed before any causative effect can be established or refuted. Physicians' reports of diabetes were not adjudicated by the end-point committee, and careful evaluation of participants' records will be needed to better understand this possible effect.

Potential limitations of our study merit consideration. First, we did not include people with low levels of high-sensitivity C-reactive protein in our trial, since our hypothesis-generating analysis of high-sensitivity C-reactive protein in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)¹² showed extremely low event rates and no evidence that statin therapy lowered vascular risk among persons who had neither hyperlipidemia nor elevated high-sensitivity C-reactive protein levels. Thus, a trial of statin therapy involving people with both low cholesterol and low high-sensitivity C-reactive protein levels would have been not only infeasible in terms of statistical power and sample size but also highly unlikely to show a benefit.

Second, since the trial was stopped early by the independent data and safety monitoring board after a median follow-up of less than 2 years, the effect of longer-term therapy should be considered. We verified that the assumption of proportional hazards was not violated during the follow-up period, and we found a robust benefit of rosuvastatin in analyses restricted to events occurring more than 2 years after randomization. These findings, as well as the demonstration that rates of hospitalization and arterial revascularization

were reduced by 47% within a 2-year period, suggest that the strategy tested could be cost-effective. The strategy also could reduce the demand for imaging tests in asymptomatic populations. On the other hand, our trial evaluated the use of rosuvastatin for the prevention of first cardiovascular events; therefore, the absolute event rates are lower than would be expected among patients with a history of vascular disease, a fact that should be taken into account in considering whether the use of statin therapy among those with low LDL cholesterol levels but elevated high-sensitivity C-reactive protein levels would be cost-effective if applied widely.

With regard to the inflammatory hypothesis of atherothrombosis, our trial involved an agent that is highly effective at reducing levels of both cholesterol and high-sensitivity C-reactive protein. In previous work, achieving low levels of both LDL cholesterol and high-sensitivity C-reactive protein appears to have contributed to the clinical benefit of statin therapy.¹²⁻¹⁶ Given the recognition that atherothrombosis is in some respects a disorder of innate immunity,²⁸ we hope the data presented here spur the further development of targeted antiinflammatory drugs as potential vascular therapeutic agents and lead to innovative trials that can directly address whether the inhibition of inflammation by agents other than statins can reduce rates of vascular events.²⁹

In conclusion, in this randomized trial of apparently healthy men and women who did not have hyperlipidemia but did have elevated levels of high-sensitivity C-reactive protein, the rates of a first major cardiovascular event and death from any cause were significantly reduced among the participants who received rosuvastatin as compared with those who received placebo.

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APPENDIX

Committee and board members for JUPITER were as follows: **Steering Committee** — P.M. Ridker (principal investigator and trial chair), F.A.H. Fonseca, J. Genest, A.M. Gotto, Jr., J.J.P. Kastelein, W. Koenig, P. Libby, A.J. Lorenzatti, B.G. Nordestgaard, J. Shepherd, J.T. Willerson; **Clinical Coordinating Center** — P.M. Ridker (chair), E. Danielson, R.J. Glynn, J.G. MacFadyen, S. Mora (Brigham and Women's Hospital, Boston); **Study Statistician** — R.J. Glynn; **Independent Data and Safety Monitoring Board** — R. Collins (chair), K. Bailey, B. Gersh, G. Lamas, S. Smith, D. Vaughan; **Clinical End Point Committee** — K. Mahaffey (chair), P. Brown, D. Montgomery, M. Wilson, F. Wood (Duke University, Durham NC). The site investigators are listed in the Supplementary Appendix.

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